Antiepileptic Drugs

Combination Therapy and Interactions
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Antiepileptic Drugs
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This book reviews the use of antiepileptic drugs focussing on the interactions between these drugs, and between antiepileptics and other drugs. These interactions can be beneficial or can cause harm. The aim of this book is to increase awareness of the possible impact of combination pharmacotherapies. Pharmacokinetic and pharmacodynamic interactions are discussed supported by clinical and experimental data. The book consists of five parts covering the general concepts and advantages of combination therapies, the principles of drug interactions, the mechanisms of interactions, drug interactions in specific populations or in patients with co-morbid health conditions, concluding with a look at the future directions for this field of research. The book will be of interest to all who prescribe antiepileptics to epileptic and non-epileptic patients, including epileptologists, neurologists, neuropediatricians, psychiatrists and general practitioners.
Contents

List of contributors ix
Foreword Giuliano Avanzini xiii
Foreword Torbjörn Tomson xv
Acknowledgements xvii

Part I Introduction 1

1 Combination therapy of diseases: general concepts 3
   Emma Mason and Philip A. Routledge

2 Combination therapy with antiepileptic drugs: potential advantages and problems 16
   Richard H. Mattson

3 Pharmacogenetic aspects 26
   Matthew C. Walker, Michael R. Johnson and Philip N. Patsalos

Part II Pharmacokinetic interactions 45

4 Pharmacokinetic principles and mechanisms of drug interactions 47
   Philip N. Patsalos

5 Predictability of metabolic antiepileptic drug interactions 57
   Edoardo Spina, Emilio Perucca and Rene Levy

6 Influence of food and drugs on the bioavailability of antiepileptic drugs 93
   Carlos A. Fontes Ribeiro

7 Interactions between antiepileptic drugs 111
   Bernhard Rambeck and Theodor W. May

8 Interactions between antiepileptic and non-antiepileptic drugs 139
   Jerzy Majkowski and Philip N. Patsalos
# Contents

<table>
<thead>
<tr>
<th>Part III</th>
<th>Pharmacodynamic interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Pharmacodynamic principles and mechanisms of drug interactions</td>
</tr>
<tr>
<td></td>
<td>Blaise F. D. Bourgeois</td>
</tr>
<tr>
<td>10</td>
<td>Methods for assessing pharmacodynamic interactions</td>
</tr>
<tr>
<td></td>
<td>Blaise F. D. Bourgeois</td>
</tr>
<tr>
<td>11</td>
<td>Experimental studies of pharmacodynamic interactions</td>
</tr>
<tr>
<td></td>
<td>Stanislaw J. Czuczwar</td>
</tr>
<tr>
<td>12</td>
<td>Clinical studies of pharmacodynamic interactions</td>
</tr>
<tr>
<td></td>
<td>John R. Pollard and Jacqueline French</td>
</tr>
<tr>
<td>13</td>
<td>Clinical studies of pharmacodynamic interactions between antiepileptic drugs and other drugs</td>
</tr>
<tr>
<td></td>
<td>Gaetano Zaccara, Andrea Messori and Massimo Cincotta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part IV</th>
<th>Drug interactions in specific patient populations and special conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Antiepileptic drug interactions in children</td>
</tr>
<tr>
<td></td>
<td>Olivier Dulac, Elizabeth Rey and Catherine Chiron</td>
</tr>
<tr>
<td>15</td>
<td>Antiepileptic drug interactions in the elderly</td>
</tr>
<tr>
<td></td>
<td>Jeannine M. Conway and James C. Cloyd</td>
</tr>
<tr>
<td>16</td>
<td>Antiepileptic drug interactions in pregnancy</td>
</tr>
<tr>
<td></td>
<td>Mark S. Yerby</td>
</tr>
<tr>
<td>17</td>
<td>Antiepileptic drug interactions in handicapped and mentally retarded patients</td>
</tr>
<tr>
<td></td>
<td>Matti Sillanpää</td>
</tr>
<tr>
<td>18</td>
<td>Antiepileptic drugs and sex steroids</td>
</tr>
<tr>
<td></td>
<td>Richard H. Mattson</td>
</tr>
<tr>
<td>19</td>
<td>Antiepileptic drug interactions in patients requiring psychiatric drug treatment</td>
</tr>
<tr>
<td></td>
<td>Michael R. Trimble and Marco Mula</td>
</tr>
<tr>
<td>20</td>
<td>Antiepileptic drugs in non-epileptic health conditions: possible interactions</td>
</tr>
<tr>
<td></td>
<td>Jerzy Majkowski</td>
</tr>
<tr>
<td>21</td>
<td>Drug monitoring in combination therapy</td>
</tr>
<tr>
<td></td>
<td>Walter Fröschler</td>
</tr>
</tbody>
</table>
Contents

22 Cognitive side-effects due to antiepileptic drug combinations and interactions 403
   Albert P. Aldenkamp, Mark de Krom, Irene Kotsopoulos and Jan Vermeulen

Part V Conclusions and future perspectives 419

23 Selection of drug combinations in clinical practice: current and future perspectives 421
   Jerzy Majkowski

24 Future research: an experimental perspective 441
   Rob A. Voskuyl, Daniel M. Jonker and Fernando H. Lopes da Silva

25 Future research: a clinical prospective 458
   Carlos A. Fontes Ribeiro

Index 475
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It is my special pleasure to introduce this book about the principles on which to base combination antiepileptic drug (AED) therapy and its related problems.

As reviewed in the excellent opening chapter by Mason and Routledge, therapeutic strategies involving the combination of different drugs are currently used to treat hypertension, infectious diseases and cancer in an attempt to enhance efficacy, reduce unwanted side effects and decrease the probability of developing resistance. However, their disadvantages may exceed their benefits. First of all, drug toxicity may actually be increased by combination therapy as a result of negative pharmacodynamic interactions and the increased probability of idiosyncratic reactions. Secondly, the management of combination therapy is complicated by pharmacokinetic interactions. Thirdly, the risks of non-compliance and medication error are significantly greater with a multiple drug regimen.

How these general concepts apply to pharmacological antiepileptic therapy is dealt with by the most authoritative specialists in the first three parts of the book, which give considerable space to pharmacokinetic and pharmacodynamic interactions, while the fourth part develops these questions further with special regard to the patients’ age, associated health problem (neurological or general), and sexual life (contraception, pregnancy, etc.). The reader is thus guided in understanding the rationale for combining AEDs, and made aware of the caveats that need to be taken into account.

In an ideal situation, we should consider AED combinations in such a way as to ensure that each pharmacological ingredient targets a specific epileptogenic mechanism. Unfortunately, our current understanding of the basic mechanisms of epileptogenesis and drug activity is still too limited to make such rational polypharmacy feasible. However, the favourable effects of some combinations based on traditional or newly developed AEDs (or both) is documented in the literature and here critically reviewed. This information is relevant and important when choosing the drug combinations to be prescribed to patients failing to respond to single drug regimens on the basis of exploiting the potential synergies of different drugs.

It is worth noting that the availability of newly developed AEDs has made multiple drug regimens increasingly frequent in clinical practice because, until the
efficacy and tolerability of a given new drug are fully understood it would be inappropriate (and in many instances illegal) to use it as a first choice monotherapy. A good knowledge of the advances and drawbacks of combination therapy is essential for the everyday use of new AEDs.

Appropriate attention is given to the pharmacogenetic aspects underlying the variables that may influence AED responses and interaction profiles, such as metabolism, pharmacokinetics and pharmacodynamics, and there is a critical discussion of the usefulness and pitfalls of genetic screening. Pharmacogenetics and pharmacogenomics are currently seen as speculative perspectives, but it is worth bearing in mind that it is already possible to characterize individuals on the basis of the polymorphisms of genes encoding drug metabolic enzymes, even though the relevance of this approach to the clinical use of combination therapy has not yet been assessed.

This book will stimulate new thoughts and ideas, and I am sure that all of its readers will learn something even about what at first glance may seem familiar subjects. For instance, although I was of course aware that most drug formulations contain multiple ingredients, it had not occurred to me that this makes the very concept of monotherapy rather relative as the active principle may make up as little as 8% of a tablet’s weight, with the rest consisting of coating and binding agents, fillers, dyes, preservatives, and solubilising and disintegrating ingredients which, however rarely, may give rise to dose-related or idiosyncratic reactions in susceptible subjects.

In summary, this book will provide readers an updated account of the state of the art and an appraisal of the exciting perspectives of an important aspect of pharmacological antiepileptic therapy. The editors (Jerzy Majkowski, Blaise Bourgeois, Philip Patsalos and Richard Mattson) wrote some of the critical chapters themselves, but also gathered a highly authoritative group of other scientists in order to cover the field comprehensively. In thanking them for this, I wish the book the success it deserves.

Giuliano Avanzini
President of the International League Against Epilepsy
Foreword

Drug interactions may be regarded as a stimulating challenge by the pharmacologist but by the physician responsible for management of the patient, interactions are often considered cumbersome and a vexing factor complicating treatment. Drug interactions are particularly common in the treatment of patients with epilepsy. Although monotherapy has been the favoured treatment strategy for the last 25 years or so, up to 50% may not achieve satisfactory seizure control while on the first drug they have been prescribed. A high proportion of these patients will eventually end up taking a combination of different antiepileptic drugs. Until now, the selection of drug combinations has more often been the result of chance or the physician’s individual preferences rather than being rational or evidence-based. Given the long duration of epilepsy treatment, most patients will frequently be prescribed drugs for other conditions too. Conventional antiepileptic drugs have been among the most prone to pharmacokinetic interactions, and pharmacodynamic interactions occur whenever two drugs are used together. For all these reasons, the topic of combination therapy and drug interactions is of great importance and up-to-date knowledge is an essential basis for a rational approach to the pharmacological treatment of people with epilepsy.

The editors of the current book on *Antiepileptic drugs: combination therapy and interactions* have managed to gather an international group of experts to cover these and related issues in a comprehensive volume. The reader is provided the relevant general background, along with in-depth coverage of pharmacokinetic and pharmacodynamic interactions as well as interactions in specific patient populations. It is made clear that while pharmacokinetic interactions in most cases are negative, recent advances in our understanding of drug metabolism enable us to predict and avoid adverse interactions. Drug level monitoring can help us manage those interactions that cannot be avoided. Pharmacodynamic interactions are not always adverse. Some are advantageous, improving the therapeutic index, and could be exploited to the benefit of our patients. This volume, which should be of interest to all physicians engaged in the treatment of patients with epilepsy, shows how far we have advanced from the level where interactions could be regarded as just an
unwieldy factor complicating pharmacotherapy. Instead, the data provided will hopefully serve as a platform for more rational and effective therapeutic strategies in the future for epilepsy patients in need of combination therapy.

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J. Majkowski, B.F.D. Bourgeois, P.N. Patsalos and R.H. Mattson
Part I

Introduction
Combination therapy of diseases:
general concepts

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Many drugs are excellent when mingled and many are fatal

Homer 950 EC

Historical aspects

Combination therapy has been used since therapeutics was first practiced. The physician or asu of Mesopotamia in 1700 BC used combinations of several plants, minerals and animal products in concoctions, salves and fomentations (Lyons and Petrucelli, 1987). We know little of the efficacy or toxicity of these combined medications. However, the Babylonian code of Hammurabi states that a doctor who causes the death of a patient or loss of an eye should lose his hands. It would not have been surprising if such stringent punishments encouraged the use of a large number of non-toxic (and possibly non-efficacious) medicines. At least this would have ensured that the physician could continue to be able to mix his own preparations.

Since many early drugs were of plant origin, the use of single herbal preparations containing many potentially active ingredients resulted in combination therapy, albeit often unknowingly. Thus cannabis, advocated by the Red Emperor (Shen Nung) around 2800 BC contains around 30 cannabinoid compounds, and debate still rages today as to whether cannabis has greater therapeutic efficacy than single cannabinoid therapy (e.g. with delta-9 tetrahydrocannabinol) in certain medical conditions. Traditional Chinese medicines continue to be used regularly by up to half the population of China (Encyclopaedia Britannica, 1999), and contain several constituents prescribed in individualized doses in a bespoke fashion. The patient takes these ingredients home and boils them in a soup, before consuming the broth.

In 1753, the Scottish physician and sailor, James Lind described one of the first controlled trials of drug therapy in history, which he had performed 6 years earlier. He administered a combination treatment for scurvy containing nutmeg, garlic mustard seed, rad. raphan, balsam of Peru and gum myrrh to two sailors for 6 days.
It is not surprising that the sailors who improved most were not these two individuals, but two others given another ‘combination therapy’ – two oranges and a lemon (Lind, 1753)! The deliberate combination of medicines continued to be practiced right through into the nineteenth and twentieth centuries, although not embraced by all physicians.

William Withey Gull (1816–1890) particularly condemned prescriptions containing multiple drugs. He was a passionate advocate of the scientific basis of medicine and stated that ‘The road to a clinic goes through the pathologic museum and not through the apothecary’s shop’. Drug combinations were often contained in medicines, the contents of which were kept secret from the patient. Dr Pierce’s Pleasant Purgative Pills were said to combine the active principles of several unspecified vegetable compounds which ‘in some inexplicable manner, gradually changed certain morbid conditions of the system, and established a healthy condition instead’ (Pierce, 1891). Dr Pierce did not patent his proprietary medicines as ‘cure-alls’, but others did patent theirs, since there was little or no government regulation of ingredients or need to verify claims of therapeutic efficacy. It was not until 1938, a year after 105 people died due to an elixir of sulfonamide made up of 70% diethylene glycol that the US government legislation was introduced to ensure labeling of all ingredients and prevention of false claims of efficacy (Routledge, 1998a).

The issue of toxicity of ingredients, which still occurs today (Stephens, 1998) is a reminder that most formulations of medicines contain several ingredients, some of which may rarely cause either dose-related (Type A) or idiosyncratic (Type B) toxicity in certain susceptible individuals. Thus, the active principle may constitute as little as 8% of the weight of a typical tablet, and the remainder may include coating and binding agents, fillers, dyes, preservatives, solubilizing and disintegrating agents (Freestone, 1969). To this extent, combination therapy with several compounds occurs when only one medicine is prescribed, although the other ingredients are inactive in most individuals. However, changes to the formulation may affect bioavailability, and were responsible for an outbreak of phenytoin (diphenylhydantoin) toxicity in Australia when lactose was substituted for calcium sulfate as an excipient (Tyrer et al., 1970).

A scientific basis for the value of combination therapy was established in the 1940s. Waksman had discovered streptomycin as the first compound to be effective in the treatment of tuberculosis (Waksman, 1949). Indeed the efficacy of streptomycin in tuberculosis was the subject of the first published randomized controlled trial in medicine (Medical Research Council (MRC), 1948). It was soon realized that streptomycin monotherapy required the use of large doses, which could cause significant toxicity. The emergence of streptomycin resistance was also soon recognized, and combination therapy was seen to be a possible answer to this serious problem. Thus a trial of para-aminosalicylic acid and streptomycin in pulmonary tuberculosis
found a reduction in streptomycin resistance from 67% in the streptomycin-only group to 10% in those treated with both agents concomitantly (MRC, 1950).

It soon became clear that similar principles applied to the treatment of malignant cells as to slow-growing pathogenic bacteria such as *Mycobacterium tuberculosis*. This led not only to the use of combination chemotherapy of cancer according to specific principles shown in Table 1.1 (Muggia and Von Hoff, 1997). The first three of these principles are generally applicable to combination therapy in other conditions, although some exceptions will be highlighted in this chapter. Before discussing the possible advantages and disadvantages of combination therapy, it is important to define and discuss two terms that have been used in this context, sometimes interchangeably.

**Polypharmacy**

The term polypharmacy has been in use in medicine for around 40 years. One of the first occasions on which it was used was in the context of multiple drug administration versus hypnosis for surgical patients (Bartlett, 1966). This early paper did not make any suggestion that polypharmacy was a bad practice, but a subsequent review of polypharmacy in America highlighted the potential problems that polypharmacy could produce (Hudson, 1968). Indiscriminate polypharmacy has been identified as a major medical problem in some developing countries and a challenge for the World Health Organisation’s action program on essential drugs (Hogerzeil et al., 1993).

The strict definition of the word in *The New Shorter Oxford Dictionary* (1993) is ‘the use of several drugs or medicines together in the treatment of disease’. However this initially rather non-judgemental definition is immediately qualified with the rider ‘frequently with the suggestion of indiscriminate, unscientific or excessive prescription’. Other authors have assumed that the administration of an excessive number of drugs is implicit in the definition (*Online Medical Dictionary*, 1997). This has led to the use of the term rational polypharmacy to distinguish the appropriate use of drug combinations from indiscriminate use of several medicines concurrently (Kalviainen et al., 1993; Reus, 1993; Wolkowitz, 1993). Thus

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**Table 1.1 Principles for the development of chemotherapeutic regimens in oncology**

| 1 | Each single agent should have activity against the disease |
| 2 | The agents should have different mechanisms of action |
| 3 | The agents should have non-overlapping toxicity profiles |
| 4 | The regimen should combine cell cycle specific and cell cycle non-specific agents |
Polypharmacy tends to be a pejorative term for excessive irrational drug use, although the drugs may be being used for a range of medical conditions rather than for a single disease.

**Polytherapy**

The first record of the use of this term listed on Medline was just over 20 years ago (1978) in the context of epilepsy management (Deisenhammer and Sommer, 1978). Since then it has been used predominantly in this therapeutic area, and largely by German, Italian, Spanish and French authors. It has not entered general use in the UK, where combination therapy is generally the preferred term for use of more than one drug for the same condition. The definition in the Online Medical Dictionary is ‘A therapy that uses more than one drug’. It thus differs from polypharmacy in that it normally refers to the use of drugs for the same medical condition rather than for a group of existing medical conditions. In the following discussion, we will treat the term polytherapy as synonymous with combination therapy, a term that is more widely accepted across the spectrum of therapeutics and throughout Europe and the USA.

**Epidemiology of combination therapy**

Although, around 10% of the general population take more than one prescribed medicine, the incidence of combination therapy is even greater in the elderly, in females and in those who have had recent hospital admission (Nobili et al., 1997; Teng Liaw, 1997). Stewart and Cooper reviewed a number of studies and concluded that patients aged over 65 years use on average 2–6 prescribed medications and 1–3.4 non-prescribed medications (Stewart and Cooper, 1994).

The effects of multiple drug administration on the incidence of adverse drug reactions were first studied by May and co-workers in 10518 patients hospitalized on a general medical service during a 5-year period (May et al., 1977). Their data suggested a disproportionately increased risk of adverse drug reactions for patients, the more drugs they were receiving. A significant proportion of these adverse drug reactions were due to adverse interactions between two or more co-prescribed agents.

In a case-control study by Hamilton and co-workers (who over the 3-year period 1993–1995 studied more than 157,000 patients in the USA) the drug combination most often associated with hospital admission was angiotensin converting enzyme (ACE) inhibitors co-prescribed with potassium replacement therapy. Combinations with inhibitors of drug metabolism (particularly macrolide antibiotics such as erythromycin) formed the next most frequent group of agents associated with increased hospitalization (Hamilton et al., 1998).
Advantages of combination therapy

Efficacy can be enhanced by combination therapy

One of the first indications that the use of more than one agent could be more effective than the use of either agent as monotherapy was in the treatment of severe infections (e.g. bacterial endocarditis) with combinations of penicillin and an aminoglycoside (Wilson et al., 1978). It later became clear that this synergism was achieved by a dual action on bacterial growth. Penicillins inhibited cell wall synthesis while the aminoglycoside inhibited protein synthesis. Synergism was also demonstrated between loop diuretics and thiazides, since each acted at a different site on the nephron to reduce sodium and water reabsorption. This combination (e.g. frusemide and metolazone) is still used to produce diuresis in resistant congestive cardiac failure. Thus combination therapy normally involves the use of two or more drugs with different mechanism of action, and therefore normally from different drug classes.

The effects of some drug combinations are merely additive rather than synergistic. Nevertheless, the combination produces more efficacy than the use of each single agent alone and this can be of therapeutic benefit. Patients may now leave hospital after acute myocardial infarction on a beta-blocker, ACE inhibitor, antiplatelet agent (e.g. aspirin) and lipid lowering agent (e.g. statin), all having been shown individually to provide secondary preventive benefit in this situation. In heart failure, ACE inhibitors, beta-blockers and spironolactone have been shown to reduce mortality when added to standard therapy. Ischemic heart disease, heart failure and hypertension are heterogeneous diseases with multiple mechanisms contributing to their pathogenesis. It is therefore not surprising that more than one mechanism of action (and therefore more than one drug) may be needed to treat the underlying problems. In addition, several of these chronic diseases result in multiple end-organ damage and several drugs may be needed to treat the multiple pathologies associated with them.

Monotherapy is effective in only around 50% of hypertensive patients, but efficacy can be increased to around 80% with the judicious use of combination therapy (Mancia et al., 1996). The need for combination therapy is also demonstrated by the hypertension optimal treatment (HOT) study. Depending on the target blood pressure, up to 74% of patients needed more than one drug to achieve the required blood pressure (Hansson et al., 1998; Opie, 1998). It is also interesting to note that in this study, patients randomized to acetylsalicylic acid had significantly reduced rates of major cardiovascular events. Thus combined antihypertensive and antiplatelet therapy is valuable, even though these drugs are producing their beneficial effects in completely different ways.

Anticonvulsant drugs are also thought to have a range of different mechanisms of action, but that the same principles should also apply. Even with carefully instituted
and monitored monotherapy, only 70–80% of patients will achieve satisfactory control of their epilepsy (Jallon, 1997) so that combination therapy may be an option that should be considered.

**Combination therapy may help to reduce the incidence and/or severity of adverse drug reactions**

Dose-related (Type A) adverse drug reactions are thought to make up around 75% of all adverse drug reactions (Routledge, 1998b). Combinations of medicines with different spectra of adverse drug reactions may therefore allow reduction of dose of each compound to levels that are less likely to produce clinically relevant toxicity. This principle (i.e. that the agents should have non-overlapping toxicity) is one of the underlying reasons for the general use of combination chemotherapy in cancer (Muggia and Von Hoff, 1997). In the case of tuberculosis, the use of triple and quadruple antituberculous chemotherapy has allowed some potentially toxic agents (e.g. ethambutol and pyrazinamide) to be used at lower and therefore safer doses than previously. This approach has also allowed shorter treatment courses, thus reducing duration of exposure to risk of toxicity. In hypertension combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent adverse effects.

**Combination therapy can prevent the development of resistance**

The experience of treatment of tuberculosis indicated that combination therapy might help to prevent the emergence of resistant bacteria. Chambers and Sande (1996) have elegantly argued that if spontaneous mutation were the major mechanism by which bacteria acquired antibiotic resistance, combination chemotherapy should be effective. They illustrate their argument with the example of a microorganism that has a frequency of development of resistance to one drug of $10^{-7}$ and to a second drug of $10^{-6}$. In this case, the probability of independent mutation of resistance to both drugs in a single cell would be the product of the two frequencies (i.e. $10^{-13}$) making the likelihood of development of resistance extremely small. Such arguments clearly apply to other situations such as oncology where the development of resistance can otherwise limit drug efficacy. They are less relevant to the treatment of other diseases.

**Disadvantages of combination therapy**

**The evidence for the benefits of combined therapy is often poor**

At the beginning of the last century, therapeutics was based more on the experience of others, rather than on firm evidence. Thus Wilson was able to state that
although many remedies had been tried and were still in favor for the treatment of epilepsy, the only ones that have any effect are the bromides of potassium, sodium and ammonium. It is interesting to note that 'the best results seem to follow the administration of all three in a combined dose' (Wilson, 1912).

In diabetes, the benefits of combination therapy with a biguanide (e.g. metformin) and sulfonylurea (e.g. glibenclamide), in patients with Type 2 (non-insulin-dependent) diabetes who are inadequately controlled with either agent alone, have been claimed for 40 years. The mechanism of action of these two drug classes is different. Biguanides such as metformin (which first became available in Europe in 1957), work by increasing the action of insulin in peripheral tissues and reducing hepatic glucose output due to inhibition of gluconeogenesis. Sulfonylureas act primarily by potentiating glucose-stimulated insulin release from functioning pancreatic islet beta-cells (O’Meara et al., 1990), although studies of insulin secretion at the same plasma glucose concentrations before and during long-term sulfonylurea therapy have shown increased beta-cell sensitivity to glucose and continuously augmented insulin secretion (Gerich, 1989). However, the evidence for combined therapy sulfonylurea/biguanide was relatively sparse for many years, and rested largely on a single non-randomized observational trial of 108 sulfonylurea failures (Clarke and Duncan, 1965). It was only 30 years later that controlled trials confirmed the benefits of this combination of agents (Hermann et al., 1994; DeFronzo, 1995).

In his article on rational polypharmacy in epilepsy, Richens points out that few randomized placebo-controlled studies have been undertaken to compare the relative merits of monotherapy and combination therapy with respect to seizure control (Richens, 1995). Evidence-based medicine should play an important role in the therapeutics of epilepsy, as it has increasingly done in other areas of disease management.

**Toxicity may be greater with combination therapy than monotherapy**

One of the principles of combination therapy in cancer is that the agents should have non-overlapping toxicity. Clearly this is not always possible, even in oncology, since many anti-cancer drugs share similar toxicity profiles (e.g. myelotoxicity). It may also be difficult to achieve in other therapeutic areas.

It is possible that combination therapy is a risk factor in the production of sudden unexpected death in epilepsy, although the use of more than one drug may just reflect the severe unstable nature of the epilepsy in such individuals (Nilsson et al., 2001). It is also possible that combination therapy is associated with greater risk of anticonvulsant embryopathy in infants exposed to anticonvulsant drugs in utero, (control frequency 8.5%, monotherapy 20.6%, combination therapy 28.0%) so that the risks from each agent in this situation may be additive (Holmes et al., 2001).

Non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of arthritis can increase the risk of peptic ulcer by around four-fold in patients aged
65 years or older (Griffin et al., 1991). Corticosteroids are also used in some patients with arthritis, particularly rheumatoid arthritis. Piper and colleagues, using the same design and patient database as Griffin, showed that the estimated relative risk for the development of peptic ulcer disease among current users of oral corticosteroids (but not NSAIDs) was 1.1 (i.e. a 10% increase in risk). However, patients concurrently receiving corticosteroids and NSAIDs had a risk for peptic ulcer disease that was 15 times greater than that of non-users of either drug (Piper et al., 1991).

Similarly, compared with non-users of either drug, the relative risk of hemorrhagic peptic ulcer disease among current users of both anticoagulants and NSAIDs was 12.7 (95% confidence interval, 6.3–25.7)(Shorr et al., 1993). However, the prevalence of NSAID use among anticoagulant users was 13.5%, the same as in those who were not using anticoagulants. Thus toxicity of drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone.

Enhanced toxicity of drug combinations may sometimes be due to pharmacokinetic interaction. Herpes Zoster infections are not uncommon in immunocompromised patients, and anti-viral agents may be required. Unfortunately 19 people with cancer and Herpes Zoster died in Japan in 1993 because of fluoro-pyrimidine toxicity, caused by the inhibition of 5-fluorouracil metabolism by the metabolite of a new anti-viral agent, sorivudine. Sixteen of the deaths occurred after the drug had been licensed, illustrating that not all drug interactions may be recognized before marketing and widespread exposure to the offending combination of agents occurs (Watabe, 1996).

In 1997, Mibefradil (Posicor) was marketed in the USA and Europe for the treatment of hypertension and angina as an exciting new molecule that selectively blocked T-calcium channels (Frishman, 1997). It was already known before marketing that mibefradil inhibited the metabolism of three potentially toxic agents, astemizole, cisapride and terfenadine. Soon further clinically significant interactions with cyclosporin and tricyclic antidepressants were being reported. It was known that mibefradil could inhibit the action of cytochrome P450 3A4 and thus reduce the clearance of other drugs that were metabolized by this enzyme. In December 1997, because of seven reports of statin-induced rhabdomyolysis in patients receiving simvastatin and mibefradil, lovastatin and simvastatin were added to the list of those that should never be co-administered with mibefradil. This was of particular importance, since hypertension and hypercholesterolemia are important and often co-existing risk factors for ischemic heart disease.

Finally, as a result of the number of serious interactions, the manufacturers announced the withdrawal of mibefradil from the market in 1998; almost exactly a year after the drug had been given marketing approval (Po and Zhang, 1998). Recently Wandel and co-workers have used a human intestinal cancer-derived cell which expresses P-glycoprotein to show that mibefradil is not only a substrate for
P-glycoprotein, but may well be a potent inhibitor of this efflux pump mechanism (Wandel et al., 2000). Thus its combined effects on CYP3A and P-glycoprotein could explain the magnitude of the effect of its interactions with other drugs. Thus the clinical significance of potential interactions may not be fully realized until after marketing.

**Combination therapy may be associated with increased risk of non-compliance (non-concordance)**

Compliance with therapy is an essential prerequisite of obtaining the benefits of the drugs. The use of combination therapy means that the patient has to take more tablets, unless the drugs have been formulated in a combined preparation. If two drugs are being used in combination, the dose of each should be adjusted to achieve optimal benefit. Thus, patient compliance is essential, yet more difficult to achieve. If patients perceive that they are being overmedicated, they self-report that their compliance falls (Fincke et al., 1998). Polypharmacy may thus result in poor compliance, which may itself result in failure of therapy. This mechanism has been reported to be a problem in individuals with epilepsy (Lambie et al., 1981), and an important factor precipitating admission to hospital for seizure (Lambie et al., 1986).

To obviate the problem of multiple medication use, many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient. In the USA, a fixed-dose combination of drugs is considered a ‘new drug’ and as such must be approved by the Food and Drug Administration (FDA) before it can be marketed, even though the individual drugs are available for concurrent use. To be approved, certain conditions must be met. Either the two drugs must act to achieve a better therapeutic response than either drug alone (e.g. many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (e.g. a diuretic that promotes the urinary excretion of K⁺ combined with a K⁺-sparing diuretic) (Nies and Spielberg, 1996).

**Combination therapy may be associated with an increased risk of medication error**

Misuse of medications is a major cause of morbidity and mortality. Patients’ medication bottles and their reported use of medications were compared with physicians’ records of outpatients in Boston, Massachusetts. Discrepancies were present in 239 patients (76%). The 545 discrepancies in these patients were the result of patients taking medications that were not recorded (n = 278 [51%]); patients not taking a recorded medication (n = 158 [29%]) and differences in dosage (n = 109 [20%]). Older age and polypharmacy were the most significant correlates of discrepancy (Bedell et al., 2000).
Conclusions

Combination therapy is an essential therapeutic tool, although one that can all too often be misused, to the detriment of the patient. The efficacy of many treatment schedules can be enhanced by combination therapy, and this approach may help to reduce the incidence and/or severity of adverse drug reactions. In cancer and anti-infective chemotherapy, combination therapy can prevent or at least delay the development of resistance.

However there is often a dearth of robust evidence for the benefits of certain drug combinations. Increased toxicity, sometimes as a result of direct interaction, is also a possibility. Finally combination therapy may be associated with an increased risk of non-compliance (non-concordance). A good working knowledge of the pharmacology of the drugs prescribed, and the potential for interaction is an important part of obtaining the benefits of combination therapy and minimizing toxicity. In addition, the risk of medication error in patients on multiple medicines means that physicians should check medication lists with patients carefully. Since patients are major stakeholders in the prescribing process, they should be encouraged to engage in a ‘prescribing partnership’. They can help in the monitoring of therapy by alerting physicians, pharmacists and other healthcare professionals to problems that occur, especially when new drugs are introduced or doses of existing agents are changed (Seymour and Routledge, 1998).

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Combination therapy with antiepileptic drugs: potential advantages and problems

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Rationale for combination therapy

Antiepileptic drug (AED) treatment of epilepsy to prevent or minimize recurrent epileptic seizures begins with the use of a single agent as monotherapy. The primary reason why two or more drugs are used together is the failure of monotherapy to control the seizures. Depending on the type of seizures and epilepsy syndrome, control may be complete or very poor. In adult-onset seizures control varies between 35% and 60% for partial seizures and 10% and 20% higher for tonic–clonic seizures after 1-year follow-up (Mattson et al., 1985, 1992, 1996; Richens et al., 1994; Heller et al., 1995; Kwan and Brodie, 2000). The long-term response is less favorable for some patients because breakthrough seizures occur over time although others enter remission (Richens et al., 1994; Heller et al., 1995). Seizures associated with idiopathic generalized epilepsies are usually more easily controlled.

When seizures continue despite increasing doses of the initial AED to the maximum that can be tolerated, a second drug is usually added to the first in an effort to achieve better control. In those patients with particularly refractory seizures/epilepsy, three and even four AEDs are occasionally employed. The overall indications for and selection of combined therapy as well as the associated problems encountered are issues of importance.

When initial monotherapy fails to provide adequate seizure control despite being optimally given, an alternative AED is added and, when possible, is titrated up gradually. Dose increases are made as tolerated and as needed to obtain control. The intent is to taper the first AED to again achieve monotherapy. If addition of a second drug fails, another is recommended as an alternate until it is clear that control cannot be achieved with use of a single agent. In actual practice it is common for the second AED to be added without tapering of the first. At times, the patient may be unwilling to change the medical regimen if complete or significantly...
improved control has been achieved with a combination of two or more AEDs for fear of a recurrent seizure with all the attendant medical and social complications.

**Background**

The use of combination therapy for management of medical or psychiatric problems extends far back, even before the time when pharmacodynamically active products became available. When Locock and later others used bromides for treatment of seizures, they often combined multiple agents, although only bromides ultimately proved effective. Turner (1907) stated 'perhaps the drug most frequently used as a substitute for, or as an adjuvant to, the bromides is *borax* (sodium biborate). Others included belladonna, zinc salts and opium. Similarly, when Hauptmann (1912) first introduced phenobarbital (PB), it was often used in combination with the bromides. This pattern has persisted with virtually every new AED introduced. The addition was usually made to improve seizure control. After the introduction of phenytoin (PHT), Yahr and colleagues (1953) reported that PHT was more successful than PB but the combination produced the best control of seizures in patients not controlled by either alone. Indeed, a product became available from Parke-Davis known as phelantin that contained 100 mg of dilantin and 32 mg of PB. New onset patients could be put on the combination without ever trying monotherapy. The lack of dosing flexibility together with studies by Reynolds and co-workers (1981) as well as Schmidt (1983) in the early 1980s emphasized that monotherapy was as effective as polytherapy in the majority of patients and was associated with fewer adverse effects. A shift to the use of monotherapy followed and has remained the accepted principle to the present time.

**Potential advantages of combination therapy**

It is assumed that combined AEDs work to increase efficacy (Table 2.1) either by an additive and/or synergistic effect or by achieving infra-additive adverse effects (Bourgeois and Dodson, 1988; Chapter 9, this book) allowing a higher dose to be administered. Unfortunately, more often such combinations add adverse effects at the same time and fail to improve the overall outcome or success.

<table>
<thead>
<tr>
<th>Table 2.1 Advantages for combinations of AEDs</th>
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<td>Broader spectrum</td>
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<td>Additive efficacy</td>
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<td>Complementary mechanisms</td>
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<td>Decreased adverse effects</td>
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<td>Counteracting adverse effects</td>
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Different seizure types
Combination therapy is clearly indicated when two or more seizure types exist that fail to respond to any one agent. For example, until the introduction of valproate (VPA) with its broad spectrum of action it was necessary to combine both an anti-absence drug, ethosuximide, with another AED effective against tonic–clonic seizures, such as PB or PHT, for patients with generalized idiopathic epilepsy having both seizure types. With the introduction of new AEDs since the 1990s, many of which have broad-spectrum efficacy, the need for such combination therapy is less frequent.

Different antiepileptic mechanisms
The concept of rational polytherapy is based on the realization that most AEDs have different mechanisms and act, at least in part if not primarily, at one site to produce an anti-seizure effect. PHT, for example, has well defined effects at the sodium channel to block high-frequency discharge of action potentials. PB has an action at the gamma amino butyric acid (GABA)-A receptor enhancing chloride flux. This effect increases hyperpolarization leading to inhibition of neuronal depolarization. This concept of combining complementary mechanisms is ‘rational’ and, as noted below, is one of the most commonly used. Similar principles would favor other combinations such as PHT or other AEDs active at the sodium channel (carbamazepine, CBZ; lamotrigine, LTG) with GABA-active drugs such as barbiturates, vigabatrin (VGB) or tiagabine (TGB). Combinations might also include drugs whose mechanism is unclear or unknown (VPA; levetiracetam, LEV), or multiple (topiramate, TPM; felbamate, FBM). By this reasoning it would not be rational to combine AEDs with similar mechanism such as PHT with CBZ or oxcarbazepine (OXC) with CBZ. However, some evidence (below) suggests these latter combinations may be effective. As with all combinations, the actual evidence favoring ‘rational’ polytherapy is lacking and the concept remains theoretical.

Additive efficacy/infra-additive adverse effects
A third reason for combined AED therapy is to achieve infra-additive adverse effects and equal or better efficacy. By selecting AEDs with different adverse effect profiles, it might be expected that efficacy would be additive while adverse effects would remain tolerable. For example, dose-related adverse effects of CBZ often first appear as dizziness or visual dysfunction (blurring or diplopia) whereas PB causes sedation and cognitive compromise as doses increase. In theory, giving modest doses of both drugs should provide additive efficacy while keeping the AED levels sufficiently low to remain under the threshold for tolerability problems. In contrast, monotherapy doses increased to achieve comparable efficacy would usually double the adverse effects. Other combinations can be readily considered using this logic.
Counteracting adverse effects

A fourth potential advantage of combination therapy is to add efficacy at the same time using AEDs with counteracting adverse effects. For example, combining TPM with VPA would utilize a drug causing weight loss with one causing weight gain. The help in ameliorating tremor by TPM would also decrease this side effect of VPA.

Pharmacoeconomic benefits

Although combination therapy usually adds to the cost of drugs, it can be theorized that a combination of PB with low doses of any other AED would be less expensive than high doses of any other drug even in monotherapy due to the very low cost of PB. Another potentially less costly combination is the use of low dose VPA with LTG. The relatively less costly VPA markedly inhibits LTG clearance, making it possible to give a half or less of LTG, the more expensive drug, and achieve comparable LTG blood levels to what would be obtained if giving double the dose as monotherapy.

Evidence of benefits of combination therapy versus monotherapy

Although many theoretical advantages can be proposed for combination therapy as noted above, it must be emphasized that there is no evidence to prove a benefit. That is not to say there is no benefit. It only emphasizes that there is a need for evidence. The only prospective, randomized, double-blind comparison between monotherapy and combination AED treatment was been carried out and published by Deckers and colleagues (2001). They compared CBZ monotherapy to VPA combined with CBZ in patients with new onset epilepsy. Doses were selected to reflect comparable ‘drug loads’ and were intended to be low. Adverse effects were the primary outcome. No significant difference was found for adverse effects (or control) although withdrawals showed a trend favoring combination therapy. Unfortunately, the number of patients entered (130) was too small to detect possible clinically meaningful differences. Although this design using new onset epilepsy patients is of interest, it is not the setting in which combination therapy is commonly employed. It might be a concept to consider when initiating therapy despite the many reasons to avoid combinations as noted below.

In fact, combination therapy is almost always selected when monotherapy has failed to control seizures in a more refractory population. No prospective efficacy studies have been conducted comparing monotherapy to combinations of AEDs in patients not controlled on monotherapy when titrated to maximally tolerated doses.

The typical clinical trial design for licensing of a new AED adds an investigational AED to a regimen of one or more drugs that failed monotherapy. All approved new
AEDs have demonstrated improved control by some efficacy outcome measure. However, compared to the placebo control groups, the add-on investigational group has always been associated with more adverse effects. In addition, the designs do not increase doses of pre-study medication in the placebo group to an amount producing comparable amounts of adverse effects. If improved efficacy could still be detected in such a setting, it would be strong evidence for greater effect for combination therapy.

A prospective combination trial was attempted in the original Veterans Administration (VA) study comparing CBZ, PB, PHT and primidone (PRM). Patients failing acceptable control on monotherapy despite maximally tolerated doses on initial or a second alternate drug were randomized to a two-drug combination. Unfortunately only 89 patients entered this protocol and had a 1-year follow-up. Nine of the patients (11%) were fully controlled. Although this is a small number, it provided evidence of increased efficacy. However, a quantitative measure of adverse effects (Cramer, 1983) showed scores higher than the monotherapy groups, suggesting better control came at least in part at the cost of more side effects.

In an often cited abstract Hakkarainen (1980) reported the results of a group of 100 patients randomized to either CBZ or PHT. After a year of treatment one half were controlled. Those failing were crossed to the other drug for the next year and another 17% came under control. Those still not controlled were placed on the combination and another 15% achieved remission. This work was never published in full text to allow scrutiny of the methods and results. A limitation of interpreting studies such as those above to show efficacy of combination therapy is the fact that some spontaneous remission occurs in epilepsy and inclusion of a parallel group maintained on monotherapy would be needed to demonstrate a true difference.

Evidence that AED combinations are more effective than monotherapy also can be inferred from the repeated observations that testing of new AEDs for regulatory approval is carried out by showing efficacy of an added drug compared to placebo as add-on to failed treatment with one or more drugs. However, such trials inevitably show more adverse effects of some type than the placebo group. Other observations suggesting added efficacy of AED combinations are common in epilepsy monitoring units. In an effort to record events on CCTV/EEG, AEDs are commonly reduced sequentially. The occurrence of attacks after one or more drugs is removed and another continues to be administered implies the drug removed was contributing to seizure control.

Potential problems with combined AEDs

Problems with combination AED therapy are given in Table 2.2.
Additive adverse effects

Add-on trials for licensing of all the new AEDs have demonstrated a statistically significant improvement in the percentage of patients achieving a 50% or greater reduction in seizures compared to placebo. Although this seems to provide clear evidence of better control with use of combined agents, virtually all trials reveal more adverse effects in the arm with an add-on drug than in the placebo arm. It is likely that drug combinations with similar adverse effects of central nervous system type are more likely to become poorly tolerated. For example, adding LTG to CBZ in clinical trials caused dizziness in 38% of patients, an additive adverse effect common to both AEDs, whereas when studied as monotherapy only 8% reported dizziness. The increased side effects may be difficult to attribute to any of a combination of drugs.

In addition to increased additive or supra-additive adverse effects from pharmacodynamic mechanisms, CBZ and LTG in combination were found to have similar dose-related central nervous system (CNS) side effects and often caused dizziness, ataxia, and visual complaints when used together. Similarly LTG and VPA often increase tremor well above what is seen in monotherapy.

Pharmacokinetic interactions

All the older AEDs (CBZ, PB, PRM, PHT, VPA) are associated with potentially clinically important interactions when used in combination (Perucca et al., 2002). VPA inhibits PB, PRM and CBZ epoxide metabolism leading to increased blood levels with associated side effects. VPA also inhibits the clearance of LTG at times, leading to rapid elevation of LTG levels and increased risk of a hypersensitivity reaction. PB, PRM and PHT induce the clearance of CBZ and VPA such that the elimination half-life of these drugs is approximately half of what is found when the drugs are given as monotherapy. Unless more frequent dosing is given (with increased chance of non-compliance), or extended release formulations are used, peak and trough effects can lead to swings from side effects to insufficient control. Similar effects result when these inducing drugs are combined with some of the newer AEDs (LTG; TPM; zonisamide, ZNS). These problems are sufficient that the

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<td>Increased adverse effects</td>
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<td>Pharmacokinetic interactions</td>
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<td>New active metabolites</td>
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<td>Choice of combination</td>
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text, *Antiepileptic Drugs* (Levy *et al*., 2002), devotes a chapter to this topic for each of the AEDs.

**Active metabolites**

Combinations of AEDs may produce pharmacodynamically active metabolites not present in clinically relevant concentrations when drugs are used as monotherapy. These include the conversion of PRM to PB in much greater proportion when co-administered with PHT. The consequence is that giving PRM in such a combination essentially means the PRM is little more than a more costly pro-drug for PB. CBZ is metabolized into the 10–11 epoxide (CBZ-E), a pharmacodynamically active product. The quantities are usually sufficiently low to be of minimal clinical effect when CBZ is used as monotherapy. When PHT is co-administered, the conversion to CBZ-E is enhanced. If VPA is combined with CBZ, inhibition of CBZ-E hydrolase occurs and levels of the CBZ-E may rise to clinically meaningful amounts. These changes may contribute to efficacy and, perhaps more importantly, to side effects.

VPA given in moderate dose is primarily metabolized to the 2-ene derivative in the mitochondria. When used at higher doses, and especially if co-administered with enzyme-inducing drugs such as PB or PHT, significant metabolism occurs in the hepatic CYP 450 system causing omega oxidation and producing putatively hepatotoxic and teratogenic products.

**Selection of AED combinations**

The principles that are used in selection of an added drug are different mechanisms and/or different adverse effects expectation, with the goal of an overall greater efficacy without a parallel increase in intolerable adverse effects. However, it must be re-emphasized that no clinical data from controlled randomized studies exist to address this theoretical issue. CBZ, LTG, or PHT, sodium channel active drugs having primarily vestibulo-cerebellar dose-related adverse effects, should be an appropriate combination with GABA-active drugs such as VGB or TGB with adverse effects of sedation or cognitive type.

CBZ, LTG, and PHT work at least in part by action at the sodium channel to prevent rapid neuronal firing and seizure spread. VGB or TGB act to increase GABA inhibitory effect and presumably provide different and complementary action. Some support of this concept was reported in the study of Tanganelli and Regestra (1996) in a comparative trial of CBZ or VGB alone or in combination. Although this is a ‘rational’ combination, it implies that we understand the mechanism by which the AEDs work. CBZ and PHT are both thought to function by preventing rapid firing due to action at the sodium channel. Consequently, combining both drugs should not be useful if the first was maximally given. In fact, however, this ‘non-rational’
Combination therapy with antiepileptic drugs

Combination has been effective in clinical practice going back to early reports by Troupin and Hakkarainen (Dodrill and Troupin, 1977; Hakkarainen, 1980). Similar experience has shown that the combination of two closely related AEDs, CBZ and OXC may prove more effective than either used alone (Barcs et al., 2000).

Problems with the process of combining AEDs

When a decision is made to add a second or third AED after monotherapy has failed an adequate trial, the decision needs to be made not only what drug should be selected but also how the drug should be given. Questions arise concerning initial dose, titration rate and target dose. Clinical responses of achieving seizure control or, more frequently, limitations of tolerability are the main guidelines. Adverse effects may appear as the second (or third) AED is titrated up. It is unclear whether the escalation of the add-on drug should be slowed/reversed or whether the baseline drug dose should be decreased to allow higher doses of the add-on AED. The adverse effects may be attributed erroneously to the add-on AED. For example, sedation was often observed when VPA was combined with PB. Evidence made clear that the side effect often was due to marked elevation of PB levels as a consequence of inhibition of PB metabolism by VPA rather than a direct effect of VPA.

Expense

Combinations of AEDs may double the cost of using monotherapy with a few exceptions mentioned above. In some cases combining an enzyme-inducing drug such as PHT with CBZ or VPA increases the clearance, often requiring a much larger dose to achieve blood levels comparable to those achieved with monotherapy. An even greater expense can be incurred by combining one of these older enzyme-inducing drugs with one of the costlier new AEDs, LTG, OXC, TPM or ZNS.

Summary

The failure of monotherapy to prevent seizures in 20–60% of patients (depending on seizure and epilepsy type) has led to combinations of AEDs to achieve better control. Although persuasive evidence indicates such treatment may improve control, the benefit is usually modest and adverse effects are almost always increased for both pharmacokinetic and pharmacodynamic reasons. No adequate randomized prospective clinical trials have compared combination of AED treatment with monotherapy in either new onset or refractory epilepsy. The absence of evidence does not mean combination therapy is not helpful, but until such evidence becomes available, treatment decisions unfortunately must be based on Level III and IV evidence.
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**Combination therapy with antiepileptic drugs**
Pharmacogenetic aspects

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Introduction

Pharmacogenetics and pharmacogenomics are fields which show how the genetic make-up of an individual can influence drugs effects. In epilepsy it is one part of a number of influences that determine drug responsiveness. Other contributors are age, sex, concomitant medication, other illnesses and cause and type of epilepsy. The cause and type of epilepsy may have a complex interaction with the genetics of drug response, as the genes that contribute to epilepsy can directly affect drug responsiveness (see below), and epilepsy itself may influence genetic expression. The observation that inherited differences can affect drug disposition, adverse effects and responsiveness is not new. The observation that there are slow metabolizers of phenytoin was made in the 1960s (Kutt et al., 1964), and later this was noted to be an inherited familial trait (Vasko et al., 1980; Vermeij et al., 1988).

The human genome project will undoubtedly revolutionize the practice of medicine. The relatively small number of human genes (approximately 30 000–40 000; International Human Genome Sequencing Consortium, 2001) and the growth of rapid sequencing technology has brought the possibility of complete genome screening closer to reality. Variation in these genes, environmental factors, and their joint interactions determine our individual response to drugs. Human genetic variation mostly consists of single nucleotide polymorphisms (SNPs) and small insertion or deletion (INDELS) polymorphisms. Over 1.4 million SNPs were identified in the initial sequencing of the human genome (International SNP Map Working Group, 2001). Most of these lie in non-coding regions of the genome, with fewer (approximately 60 000) identified within exons (coding regions of the genes). Between any two genomes there are an estimated 2.3 million variants and on a population level, up to 10 million variant positions with a frequency of more than 1%. Due to linkage disequilibrium, certain patterns of SNPs within a gene are found within specific populations (Salisbury et al., 2003), which may enable a reduction in the number of SNPs that need to be genotyped in order to screen for
Pharmacogenetic aspects

the association of variability in a gene with disease and drug response. Although technology has advanced, in many instances tests of the gene product (e.g. enzyme activity) rather than for the gene itself may be cheaper, more reliable and more relevant (see review by Streetman et al., 2000).

Genetic polymorphisms can influence antiepileptic drug (AED) responses and, during polytherapy, their interaction profile by influencing metabolism, central nervous system penetration, pharmacodynamics and adverse events. We will consider the evidence for each of these in turn before reviewing the use and pitfalls of genetic screening.

Metabolism

Lipophilic drugs cannot be easily eliminated from the body, and thus are biotransformed to more hydrophilic compounds that are then easily excreted. This biotransformation involves either modification of functional groups (phase I) or conjugation with hydrophilic moieties (phase II). Both of these systems are under extensive genetic control. Most of our presently available AEDs are metabolized by the cytochrome P450 (CYP) system. The CYP system consists of a number of different enzymes, and the classification of these, adopted in 1996, was into CYP{number}{letter}{number}*{number} groups (Nelson et al., 1996). The first number groups into families which have greater than 40% protein sequence homology, the subsequent letter into subfamilies that have greater than 55% homology, the second number into members of subfamilies that are encoded by a particular gene, and the number following the ‘*’ represents specific alleles of that gene. Four isoenzymes (CYP3A4, CYP2D6, CYP2C9 and CYP1A2) are known to be responsible for the metabolism of 95% of all drugs, and there are extensive pharmacogenetic polymorphisms for each of the enzymes. Three isoenzymes (CYP2C9, CYP2C19 and CYP3A4) are of particular importance in relation to AED metabolism and interactions (Rendic and Di Carlo, 1997). Indeed the two enzymes that have received the most attention have been CYP2C9 and CYP2C19. CYP2C9 is the dominant enzyme in the metabolism of phenytoin, and the two alleles CYP2C9*2 and CYP2C9*3 have impaired enzymatic activity compared to CYP2C9*1 (Aithal et al., 1999); those with either a CYP2C9*2 or CYP2C9*3 allele need a phenytoin dose that is 30% lower than those who have only CYP2C9*1 (van der Weide et al., 2001). Due to impaired enzymatic activity, those patients with a CYP2C9*2 or CYP2C9*3 allele are more likely to experience metabolic interactions during combination therapy with phenytoin and an interacting drug (Meyer, 2000). CYP2C19 is also involved in the metabolism of phenytoin, but to a lesser degree and consequently CYP2C19 polymorphism has less of an effect on phenytoin metabolism and its propensity to interact with concomitant drugs. CYP2C19 is, however, the dominant enzyme in the
metabolism of phenobarbitone, and CYP2C19 allelic variation has been associated with decreased metabolism and also an increased propensity for metabolic interactions. Decreased metabolism is especially common in the Japanese population where 8% of patients with epilepsy may be poor phenobarbitone metabolizers (Mamiya et al., 2000) and may be more prone to metabolic interactions.

Like CYP-mediated reactions, glucuronidation processes are susceptible to inhibition and induction.

Phase II metabolism is also subject to genetic variation. Uridine glucuronyl transferases (UGTs) are a family of enzymes that catalyze the process of glucuronidation and comprise two distinct families, UGT1 and UGT2, with eight isoenzymes identified in each family. The UGT1A4 isoenzyme plays an important role in the glucuronidation of lamotrigine (Green et al., 1995), whereas the isoenzyme isoforms catalyzing the glucuronide conjugation of valproic acid have not yet been elucidated. Patients with Gilbert’s syndrome (unconjugated hyperbilirubinaemia due to a mutation in a gene coding for UGT) have over 30% lower clearances and higher half-lives for lamotrigine when compared to healthy volunteers (Posner et al., 1989). Certain drug interactions with lamotrigine can be explained by the glucuronidation pathway, such as the reduction of lamotrigine serum concentrations by oral contraceptives (Sabers et al., 2001) and the potential reductions in olanzapine glucuronidation by lamotrigine (Linnet, 2002). Such interactions are likely to be affected by polymorphisms and mutations in the genes coding for UGT, although this remains to be tested.

Genotyping to determine drug metabolism probably has a limited role in epilepsy for two main reasons:

1. for many AEDs, there is not a clear relationship between plasma concentrations and efficacy/adverse events;
2. AEDs are titrated up slowly and concomitant blood level monitoring often gives an accurate idea if patients are slow or fast metabolizers.

This contrasts with the now commonly used screening of children for thiopurine S-methyltransferase deficiency before beginning mercaptopurine treatment for acute lymphoblastic leukemia (McLeod and Siva, 2002). In these cases the children are given acute courses of a drug whose efficacy and side-effect profile is closely related to plasma concentrations. An exceptional use for genotyping for drug metabolism may come into use for AEDs which have potential metabolites that are toxic (see below), and geneotyping may prove useful in predicting drug–drug interactions.

Central pharmacokinetics

The point of action for AEDs is the brain, and so AEDs have to be able to cross the blood–brain barrier. Transport proteins regulate the flux of drugs across the
blood–brain barrier. Many of these proteins belong to the ATP-binding cassette family of membrane transporters of which P-glycoprotein is the most extensively studied (Lee et al., 2001; Sisodiya, 2003). P-glycoprotein at the blood–brain barrier limits the accumulation of specific drugs in the central nervous system by transporting the drugs out of the brain. The role of such transporters in epilepsy remains uncertain (Sisodiya, 2003). This is partly because there is at present no consensus on which AEDs are transported by these proteins (see, for example Potschka et al., 2001 and Owen et al., 2001). Nevertheless, upregulation of these proteins is associated with drug resistant epilepsy in both humans and animal models (Sisodiya, 2003). Furthermore, a specific SNP in the gene encoding P-glycoprotein, ABCB1, has a strong association with AED resistance (Siddiqui et al., 2003). This SNP is in a non-coding portion of the gene and thus its functional significance is uncertain – it is probable that it is associated with a separate functional SNP in an exon (Siddiqui et al., 2003). This raises a problem with the use of SNPs in order to determine biological function, as they could be associated with SNPs elsewhere in the gene or even on other genes and thus unless a change of function of the gene product is demonstrated, such SNPs should only be used as biological markers as they may not be causal. The use of such markers for drug resistance could be useful for determining early referral for surgery, the spectrum of drug responsiveness or even the use of concomitant blockers of such transporters. In addition, the finding that carbamazepine may inhibit P-glycoprotein, albeit at high concentrations (Weiss et al., 2003), raises the possibility that certain AED interactions could be explained by competitive inhibition of these drug transporters. In such instances, polymorphisms could determine the degree to which such interactions occur.

**Pharmacodynamics**

There is, at present, scant human evidence that genotype contributes to AED responsiveness, despite considerable evidence that receptor and channel subtypes determine drug pharmacodynamics. Genes that determine the type of epilepsy can influence drug pharmacodynamics by two specific mechanisms. First the epilepsy type and the pathophysiological substrate of the epilepsy could influence drug pharmacodynamics and secondly a genetic mutation could lead to both a channel that is ‘responsible’ for the epilepsy and also particularly sensitive/resistant to specific drugs. Thus, the first of these influences can be illustrated by the idiopathic generalized epilepsies which are largely genetically determined. Despite the likelihood that there are many genes determining the subtype and expression of these epilepsies, they are characterized by seizures with similar pathophysiological substrates. Thus absence seizures are generated within a recurrent loop between the thalamus and neocortex, and their generation is dependent upon oscillatory
behavior mediated by gamma amino butyric acid (GABA) receptors, GABA receptors, T-type calcium channels and glutamate receptors (Crunelli and Leresche, 2002). One hypothesis is that hyperpolarization of the thalamocortical neurons in the thalamus mediated by GABAergic inhibition leads to activation of T-type calcium currents which open on neuronal depolarization, resulting in repetitive spiking that activates neurons in the neocortex which in turn stimulate the thalamic reticular nucleus leading to GABAergic inhibition of the thalamocortical (relay) neurons, and so the cycle continues (Danober et al., 1998; Huguenard, 1999).

The pathophysiological substrates of absence seizures lead to specific pharmacodynamic actions that may largely be independent of the genetic defects underlying the generation of such seizures. Within this circuit, clonazepam preferentially inhibits the thalamic reticular neurons, perhaps due to the higher expression of α3-containing GABA receptors (Browne et al., 2001). Ethosuximide, a drug whose main action may be on T-type calcium channels, has a specific action on absence seizures. Drugs that increase ambient GABA, such as tiagabine and vigabatrin, and GABA receptor agonists can hyperpolarize thalamocortical neurons and so can have a pro-absence effect (Danober et al., 1998). Also certain other drugs such as carbamazepine and phenytoin can worsen absence seizures; the mechanism of this is unknown, but does not seem to be a class effect, as lamotrigine, a drug that also inhibits sodium channels (see below) has an antiabsence effect (Frank et al., 1999).

That genes that determine specific epilepsies could also influence drug responsiveness has been well documented recently. Autosomal dominant frontal lobe epilepsy is an epilepsy that can result from a mutation in the gene for the α4 subunit of the nicotinic receptor. How this mutation results in the epilepsy remains a topic for speculation, but an interesting observation is that this mutation also renders the receptor more sensitive to carbamazepine (Picard et al., 1999), and this tallies with clinical experience as carbamazepine is a very effective treatment in this disorder. A note of caution needs to be raised here: a mutation of a specific channel does not necessarily mean that drugs acting at that channel are more likely to be effective. Thus benign neonatal convulsions result from mutations in KCNQ2 and KCNQ3 potassium channels (these channels make up the M potassium current – a potassium current that is ‘switched off’ by muscarinic receptor activation; Tatulian et al., 2001). A facile interpretation is that drugs that act at these potassium channels are likely to be most effective in this epilepsy, and such a drug exists; retigabine (Tatulian et al., 2001). Yet one could equally expect drugs that act at muscarinic receptors to be effective, and with further thought, and the realization that epilepsy is a network phenomenon that involves a multitude of receptors and channels, one could predict the efficacy of drugs acting at quite separate targets. In fact this epilepsy responds very well to a range of conventional AEDs. Nevertheless certain genetic defects could prevent the efficacy of certain drugs. An interesting
finding is that of a mutation of the γ subunit of the GABA_A receptors underlying absence epilepsy with febrile seizures in a large family (Wallace et al., 2001). This mutation, along with other mutations in the same subunit, possibly results in seizures by decreasing the function of GABA_A receptors containing this subunit (Baulac et al., 2001; Bianchi et al., 2002). Yet this mutation also renders the receptors benzodiazepine insensitive, and thus possibly makes this a benzodiazepine-resistant epilepsy (Wallace et al., 2001).

Genetic differences could also affect the channels to which specific drugs are targeted, and may be independent of those genes that are contributing/determining the epilepsy. Voltage-dependent sodium channels and GABA_A receptors are two of the main targets for presently available AEDs, and the effect of drugs on these targets is subtype dependent. Since drug action is critically dependent on subunit composition, it is easy to appreciate how genetic polymorphisms could have a strong influence on drug effects. We will use these two targets as illustrations of how genetic differences can influence drug effects, and how those genes that determine the epilepsy syndrome could similarly affect drug responsiveness.

Voltage-gated sodium channels are responsible for the rising phase of the action potential in excitable cells and membranes, and are thus critical for action potential generation and propagation (Catterall, 2000). The sodium channel exists in three principle conformational states:

1. at hyperpolarized potentials the channel is in the resting closed state;
2. with depolarization the channels convert to an open state that conducts sodium ions;
3. the channel then enters a closed, non-conducting, inactivated state, this inactivation is removed by hyperpolarization.

In this manner, depolarization results in a transient inward sodium current that rapidly inactivates.

The sodium channel consists of a 260-kDa α subunit that forms the sodium selective pore. This α subunit consists of four homologous domains (I–IV) that each consist of six α-helical transmembrane segments (S1–6). The highly charged S4 segments are responsible for voltage-dependent activation. A ‘hinged lid’ consisting of the intracellular loop connecting domains III and IV that can only close following voltage-dependent activation provides the mechanism of inactivation (Catterall, 2000).

In the central nervous system, the α subunit is associated with two auxiliary β subunits (β1 and β2) that influence the kinetics and voltage dependence of the gating. There are at least 10 different sodium channel isoforms (Na_v1.1–1.9 and Na_x). Five of these isoforms are present in the central nervous system – Na_v1.1–1.3, Na_v1.5 (in the limbic system) and Na_v1.6; these isoforms have some functional differences
that are of physiological importance. Certain receptor subtypes, such as Na\textsubscript{v}1.6 are more prone to late openings following a depolarization that can lead to persistent sodium currents that can contribute to burst firing. Sodium channels are additionally modulated by protein phosphorylation, which can affect the peak sodium current, and the speed and voltage dependence of channel inactivation (Catterall, 2000).

Many drugs including certain anesthetics and antiarrhythmics exert their therapeutic effect by preferential binding to the inactivated state of the sodium channel (Catterall, 2000). This has two effects: first to shift the voltage dependence of inactivation towards the resting potential (i.e. the channels become inactive at lower membrane potentials), and secondly to delay the return of the channel to the resting, closed conformation following hyperpolarization. Phenytoin, lamotrigine and carbamazepine have a similar mode of action (Lang \textit{et al.}, 1993; Kuo, 1998). All bind in the inner pore of the sodium channel, and their binding is mutually exclusive (Kuo, 1998). There are, however, differences in the fashion in which drugs interact with adjacent amino acids that can partly explain drug specific effects (Ragsdale \textit{et al.}, 1996; Liu \textit{et al.}, 2003); AEDs perhaps have more complex interactions with surrounding amino acids than do local anesthetics (Liu \textit{et al.}, 2003), and will have their effects modified by a greater number of possible polymorphisms. Indeed, mutations of single amino acids affect the binding of individual drugs to different degrees, indicating that these drugs interact in an overlapping, but non-identical, manner with a common receptor site (Ragsdale \textit{et al.}, 1996). Sodium channels from patients with refractory temporal lobe epilepsy may be selectively resistant to carbamazepine (Remy \textit{et al.}, 2003).

There are other drugs such as valproate that inhibit rapid repetitive firing (McLean and Macdonald, 1986), but act at a different site from the site on which carbamazepine, lamotrigine and phenytoin act (Xie \textit{et al.}, 2001). Thus there could be single amino acid substitutions that would affect sodium channel inhibitors (but not necessarily all drugs acting on that channel), and also amino acid substitutions that could result in resistance to specific drugs.

\textit{GABA\textsubscript{A}} receptors are the target for a number of AEDs since alterations in \textit{GABA\textsubscript{A}} receptor-mediated transmission have been implicated in the pathogenesis of epilepsy. \textit{GABA\textsubscript{A}} receptors are mainly expressed post-synaptically in the brain (pre-synaptic \textit{GABA\textsubscript{A}} receptors have been described within the spinal cord). \textit{GABA\textsubscript{A}} receptors are constructed from five of at least 16 subunits, grouped in seven classes: $\alpha$, $\beta$, $\gamma$, $\delta$, $\sigma$, $\varepsilon$ and $\pi$ (Mehta and Ticku, 1999). This permits a vast number of putative receptor isoforms. The subunit composition determines the specific effects of allosteric modulators of \textit{GABA\textsubscript{A}} receptors, such as neurosteroids, zinc and benzodiazepines (Mehta and Ticku, 1999). Importantly the subunit composition of \textit{GABA\textsubscript{A}} receptors expressed in neurons can change during epileptogenesis, and these changes influence the pharmacodynamic response to drugs (Brooks \textit{et al.}, 1998). \textit{GABA\textsubscript{A}}
receptor activation results in the early rapid component of inhibitory transmission. Since GABA<sub>A</sub> receptors are permeable to chloride and, less so, bicarbonate, the effects of GABA<sub>A</sub> receptor activation on neuronal voltage are dependent on the chloride and bicarbonate concentration gradients across the membrane (Macdonald and Olsen, 1994). In neurons from adult animals, the extracellular chloride concentration is higher than the intracellular concentration resulting in the equilibrium potential of chloride being more negative than the resting potential. Thus GABA<sub>A</sub> receptor activation results in an influx of chloride and cellular hyperpolarization. This chloride gradient is maintained by a membrane potassium/chloride co-transporter, KCC2 (Rivera et al., 1999). Absence of this transporter in immature neurons results in a more positive reversal potential for chloride, and thus GABA<sub>A</sub> receptor activation in these neurons produces neuronal depolarization (Ben-Ari et al., 1994; Rivera et al., 1999). Under these circumstances GABA<sub>A</sub> receptors can mediate excitation rather than inhibition. Thus the expression of KCC2 could influence the response to drugs acting at GABA<sub>A</sub> receptors, and importantly the expression of KCC2 can be modified by epileptogenesis. Thus, polymorphisms in genes that do not directly code for the GABA<sub>A</sub> receptor could influence the pharmacodynamic response of drugs acting on this receptor.

Benzodiazepines are specific modulators of GABA<sub>A</sub> receptors and act at GABA<sub>A</sub> receptors that contain an α1, α2, α3 or α5 subunit in combination with a γ subunit (Mehta and Ticku, 1999). Drugs acting at the benzodiazepine site have different affinities for the different α subunit-containing GABA<sub>A</sub> receptors, and this specificity can affect pharmacodynamic response (McKernan et al., 2000). This is due perhaps to the varied distribution of these receptors in the brain. Thus the α1 subunit-containing receptors seem to have mainly a sedative effect, and are perhaps responsible for this side effect of benzodiazepines (McKernan et al., 2000). This may also explain why zolpidem, a drug that has great affinity for GABA<sub>A</sub> receptors containing the α1 subunit has marked sedative effects and weak anticonvulsant efficacy (Crestani et al., 2000). More selective ligands could thus result in benzodiazepine agonists that have less sedative effect and greater anticonvulsant potential. Importantly, single amino acid substitutions rendering certain subunits insensitive to benzodiazepines can thus radically alter the profile of these drugs. Importantly, a mutation in the γ subunit has been found to underlie a specific epilepsy syndrome in some families, and this mutation renders the GABA<sub>A</sub> receptors benzodiazepine insensitive. It is likely that a range of polymorphisms in the GABA<sub>A</sub> receptor are likely to underlie the range of clinical responses to these drugs (adverse effects, efficacy, tolerance etc.). Even drugs that are less selective than benzodiazepines (e.g. barbiturates) still show some preference for certain GABA<sub>A</sub> receptor subtypes.

The manner by which polymorphisms and receptor expression can affect drug interactions is an unexplored area, but it is easy to speculate that certain
pharmacodynamic interactions are receptor subtype dependent. For example, the enhancement of the action of tiagabine (increasing extracellular GABA) on GABA_A receptors by a benzodiazepine would require the presence of benzodiazepine-sensitive GABA_A receptors, and the extent of such an interaction could thus be determined by polymorphisms and mutations in specific receptor subunits.

**Adverse events**

The spectrum of adverse events may also depend upon receptor and channel polymorphisms, but most of these are likely to be dose related and inconsequential. There is unlikely to be a role for screening for these. There are, however, serious adverse events with AED use that may benefit from pharmacogenetic screening. Pharmacogenetic screening of serious adverse events that result from drug metabolites is potentially a powerful application. Felbamate has three primary metabolites, 2-hydroxy, 3-hydroxy, and monocarbamate metabolites (Kapetanovic et al., 1998). The monocarbamate metabolite is eventually metabolized to a carboxylic acid (3-carbamoyl-2-phenylpropanoic acid), which is the major metabolite of felbamate in humans (Kapetanovic et al., 1998). Metabolism of the monocarbamate metabolite can also result in the formation of a reactive aldehyde, atropaldehyde that could be responsible for aplastic anemia and hepatic damage associated with this drug. Enzymatic defects in the metabolism of the monocarbamate metabolite may result in the overproduction of atropaldehyde, or defects in the conjugation of atropaldehyde with glutathione (and thus detoxification) could lead to its accumulation; screening for these defects could result in identification of those who are susceptible to the serious adverse effects of felbamate, and could result in the wider use of a potentially very effective drug. Many adverse effects such as rash have an immunological basis, and these are frequently associated with human leukocyte antigen (HLA) type, providing a possible method of screening for other idiopathic adverse events. The association with HLA does not always indicate an immunological basis as HLA-determining genes on chromosome 6 can be in linkage disequilibrium with other genes (i.e. the occurrence of a specific HLA type may increase the chance of a specific polymorphism in a neighboring but distinct gene) (see, for example Pirmohamed et al., 2001).

There could also be a place for screening for chronic adverse events. Reduced folate levels have been associated with chronic AED treatment. A possible consequence of this is hyperhomocysteinaemia. Hyperhomocysteinaemia is associated with vascular disease and so a prediction would be that AED therapy, through reducing folate levels, would increase homocysteine levels and result in an increase in cardiovascular disease. This could explain the increased incidence of cardiovascular disease in patients with epilepsy. Such associations have been described,
and indeed it has been noted that patients receiving phenytoin and carbamazepine, who are homozygous for the thermolabile genotype of methylenetetrahydrofolate reductase gene (MTHFR), are at significant risk of hyperhomocysteinaemia (Yoo and Hong, 1999). Similarly gum hypertrophy with phenytoin is a problem that may occur in up to 50% of the patients treated with phenytoin. In cats the main metabolite of phenytoin, \( p \)-hydroxyphenol-5-phenylhydantoin (\( p \)-HPPH), has been shown to induce gingival overgrowth (Hassell and Page, 1978), and it may be that those who produce higher concentrations of \( p \)-HPPH (i.e. the fast metabolizers) have a higher incidence of gum hypertrophy. Undoubtedly there are other genetic factors at play that may affect fibroblasts and gingival inflammation (Seymour et al., 1996).

Lastly there may be strong genetic determinants in AED teratogenicity. Defects in detoxification pathways such as epoxide hydrolase, which detoxifies epoxides, have been implicated in increasing the risk of fetal malformations. One of the oxidized products of phenytoin is an arene oxide (epoxide). It has been proposed that these arene oxide metabolites can covalently bind to cell macromolecules, resulting in cell death, hypersensitivity and even birth defects (Spielberg et al., 1981; Strickler et al., 1985). A defect in epoxide hydrolase has been proposed to increase the risk of fetal malformations (Strickler et al., 1985; Buehler et al., 1990). Furthermore developmental homeobox genes may play an important role, as it has been shown that certain mutations result in an increased chance of valproate-associated malformations in mice (Faiella et al., 2000).

The predisposition to the formation of toxic metabolites, and an enhanced susceptibility to the adverse effects of these metabolites will undoubtedly lead to enhanced toxicity with specific drug combinations. Conversely, there may be certain drug combinations that could be protective in that they may reduce the serum concentrations of responsible metabolites. Identification of relevant polymorphisms may help tailor AED therapy and drug combinations in pregnant women.

**Misconceptions about the use of genetic tests**

We have shown above that genetic polymorphisms may have a profound effect on drug responsiveness and drug interactions. How useful will genetic testing be? The purpose of a diagnostic test is to provide increased certainty of the presence or absence of a disease. Pharmacogenetic tests are performed in an attempt to predict the therapeutic or adverse consequences of a drug in an unexposed individual. As such, they are screening tests not diagnostic tests and whilst screening tests may have health benefits, the harm that can result from inappropriate tests or their inappropriate interpretation is well documented (Sackett, 1991; Grimes and Schulz, 2002). Here we review the utility of genetic testing to predict drug response
(pharmacogenetics) in the context of the intrinsic epidemiological constraints on genetic tests. We do not consider other important aspects of genetic testing including ethical, legal and social implications (Rothstein and Epps, 2001).

The principles of screening tests are best considered by means of an example. Consider an hypothetical genetic test for predicting the risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in response to lamotrigine. The precise risk of SJS/TEN following lamotrigine use is unknown. Such data are uncertain because of an inability to control for confounding, low risk and (relatively) small numbers of exposed individuals. Observational studies by prescription event monitoring in general practice, however, suggest an approximate risk of 0.1/1000 patient months of exposure, with most cases occurring in the first 2 months of use (Mackay et al., 1997; Rzany et al., 1999). Suppose we have a genetic test for identifying patients at risk of SJS/TEN with lamotrigine that has sensitivity 95% and specificity 99%. Intuitively one might consider this an ‘excellent’ test, but how will such a test perform in clinical practice?

The effectiveness of a screening test can be evaluated using a $2 \times 2$ table that relates test result to drug outcome. The ability of our hypothetical test to discriminate those at risk of SJS/TEN from those not at risk is illustrated in Table 3.1. Table 3.1 shows how the four indices of a test’s validity, sensitivity, specificity and positive and negative predictive value are calculated. For the clinician, who wishes to predict the probability of a patient developing SJS/TEN with lamotrigine, the key index is the positive predictive value (PPV – the probability of the disease given a positive test result). In the example cited (Table 3.1), it can be seen that although

<table>
<thead>
<tr>
<th>Test (T)</th>
<th>Disease outcome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>D+</td>
</tr>
<tr>
<td>T+</td>
<td>19</td>
</tr>
<tr>
<td>T−</td>
<td>1</td>
</tr>
</tbody>
</table>

The background risk of SJS or TEN with lamotrigine is estimated at 2 in 10 000 (see text). $D+$: presence; $D-$: absence of SJS/TEN following 100 000 hypothetical exposures. $T$ refers to a + or − test result.

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<table>
<thead>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>D+</td>
<td>D−</td>
</tr>
<tr>
<td>Sensitivity (probability of $T+$ in people with $D+$):</td>
<td>19/20 = 0.95</td>
<td></td>
</tr>
<tr>
<td>Specificity (probability of $T-$ in people without $D-$):</td>
<td>98980/99980 = 0.99</td>
<td></td>
</tr>
<tr>
<td>PPV (probability of $D+$ in people with $T+$):</td>
<td>19/1019 = 0.02</td>
<td></td>
</tr>
<tr>
<td>NPV (probability of of $D-$ in people with $T-$):</td>
<td>98980/98981 = 0.99999</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1 Discriminative value of genetic test ($T$) for drug outcome ($D$)
the test has both high sensitivity (95%) and high specificity (99%), the predictive value of a positive test result (PPV) is only 2%. Although the probability of SJS/TEN following a positive test result has risen substantially from 2 in 10 000 to 2 in 100, it remains the case that 98% of patients testing positive will not develop SJS/TEN. This example illustrates how, in low prevalence settings, even good tests may have low predictive value. Thus, for a test with a sensitivity 95% and a specificity 99%, PPV only exceeds 90% when prior risk exceeds 1 in 11 (Figure 3.1). If prior risk is not considered when interpreting the result of the test, a positive result might deny some epilepsy patients the opportunity of an appropriate treatment.

The above discussion illustrates how the probability of a specific drug outcome after a screening test is dependent on prior risk. Knowledge of prior risk is therefore critical for interpreting the result of a screening test. Yet, even for serious adverse drug reactions (ADRs), an accurate estimate of prior risk may not be available. Co-medication, co-morbidity, age, sex, weight, duration of treatment, renal and liver function, under- and over-reporting as well as misdiagnosis all confound the accurate assessment of prior risk. Moreover, in routine clinical practice the dependency of test performance on prior risk is frequently under-appreciated, resulting in badly interpreted test results (Johnson et al., 2001). Without accurate prevalence data, the clinical utility of a predictive genetic test will have to be determined by prospective randomized controlled trial. Yet methodology for the evaluation of new diagnostic techniques remains poorly defined, it is less advanced than that relating to the assessment of new therapies and there are no formal standards for the acceptance of new diagnostic procedures (Knottnerus, 2002).
The predictive value of a pharmacogenetic test can also be viewed from a genetic epidemiological perspective. Whilst some have argued that genetic testing will be widely used to predict a person’s probability of developing a disease, others have pointed to limitations based on the low magnitude of relative risk and incomplete penetrance associated with various genotypes in the general population (Holtzman and Marteau, 2000; Vineis et al., 2001). Using simple epidemiological principles, Holtzman and Marteau (2000) demonstrated that under most conditions, common genotypes associated with common human diseases will have little predictive power. We can apply similar principles when considering the potential for pharmacogenetic tests to yield clinically useful predictive value. The PPV of a test for a genetic susceptibility factor (this might denote the alleles that a person possesses at a single gene locus on homologous chromosomes or a complex genomic profile) is a function of the frequency of the genetic factor in the population, its relative risk and the prevalence of the drug outcome (Lilienfeld and Lilienfeld, 1980; Khoury et al., 1985; Holtzman and Marteau, 2000). This can be appreciated if we consider a gene test (or genomic profile) for a drug response (adverse or therapeutic) with a prior risks prevalence of 1 in 100 and 1 in 10 (Table 3.2). Thus the drug response of interest may occur in persons with a specific genotype \(G\) as well as in persons without that genotype \(1G\). Individuals without the specific genotype may still experience the drug response of interest due to locus and allelic heterogeneity, environmental variation and/or stochastic factors.

If \(r+\) is the risk associated with exposure to genotype, and \(r-\) the risk associated with non-exposure, then the relative risk for the drug response conferred by the susceptibility phenotype \(R = r+/r-\). The prevalence of the drug response \(D\) will include cases that arise from exposure to the genotype \(G \times r+\) as well as cases that arise from unrelated mechanisms \((1G \times r-)\). Substituting PPV for \(r+\), this can be re-written as:

\[
D = G \times \text{PPV} + (1 - G) \times \text{PPV}/R
\]

which, solved for

\[
\text{PPV} = DR \times 100/(R - 1) + 1 \quad \text{(expressed as a %)}
\]

The PPV of a test based on a genetic susceptibility factor can now be estimated across a range of \(D, R\) and \(G\) values. Table 3.2 lists PPV across a range of \(G\) and \(R\) values for a drug response with a prevalence of 1 in 100 and 1 in 10. For an outcome with prior risk of 1 in 100, it can be seen that only when the frequency of the susceptibility factor is low, and the genotype relative risk is high, will PPV be high. Whilst this ‘Mendelian’ situation may account for some drug responses, it seems just as likely that genotypes will confer lower relative risk for a specific drug response and thus lower PPV. Where the prevalence of the outcome of interest is lower (as, for example
Pharmacogenetic aspects

Table 3.2 PPV of a screening test for a genetic susceptibility factor (genotype) for a drug response (adverse or therapeutic) with a prior risk of 1 in 100 and 1 in 10

<table>
<thead>
<tr>
<th>Genotype frequency</th>
<th>Genotype relative risk</th>
<th>PPV: 1 in 100 (%)</th>
<th>PPV: 1 in 10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.001</td>
<td>2.0</td>
<td>5.0</td>
<td>9.9</td>
</tr>
<tr>
<td>0.01</td>
<td>2.0</td>
<td>4.8</td>
<td>9.2</td>
</tr>
<tr>
<td>0.1</td>
<td>1.8</td>
<td>3.6</td>
<td>5.3</td>
</tr>
<tr>
<td>0.3</td>
<td>1.5</td>
<td>2.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

in the risk of SJS/TEN with lamotrigine), then PPV will be even lower. Of course, where the outcome is more prevalent (e.g., 1 in 10 exposures, Table 3.2), then PPV will be higher. In this situation, whilst there may be no point in testing people if the prevalent outcome is a beneficial drug response, there may be value in identifying people without genetic susceptibility to a prevalent harmful response.

What is clear, at the moment however, is that there is a lack of data on which to base predictions regarding the potential utility of pharmacogenetic testing. Epidemiological considerations such as those above highlight that if genetic tests for drug outcomes (therapeutic or adverse) are to become widely used, they will need to be validated, easy to use, unambiguous, and provide a significant improvement over current clinical practice. Physicians are used to working within established risk scenarios, and may not adapt easily to genetically altered benefit–risk trade-offs. Clinical and cost effectiveness of pharmacogenetic tests may need to be established in prospective randomized trials and their use may require new professional standards of testing and test interpretation. The degree to which pharmacogenetic tests become integrated into routine clinical practice will be determined as much by epidemiological constraints as the important legal, ethical, social and commercial aspects of genetic testing.

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Part II

Pharmacokinetic interactions
Pharmacokinetic principles and mechanisms of drug interactions

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The National Society for Epilepsy, Chalfont St Peter, UK

Introduction

In recent years, many of the fundamental principles and concepts of pharmacokinetics have emerged from studies with antiepileptic drugs (AEDs). Pharmacokinetics describes how a drug is absorbed, distributed, metabolized, and ultimately excreted from the body. These characteristics will determine not only the ease of clinical use of the drug (e.g. how it is prescribed) and whether or not a patient will comply with its prescription, but also the pharmacokinetics of a drug has a direct impact on a drug’s efficacy. During combination therapy with AEDs and indeed with AEDs and other drugs, there is potential for interference in pharmacokinetic processes and these interactions can be of major clinical significance. In this chapter, we review the various pharmacokinetic principles that are important to drug interactions and relate these to the major mechanisms of drug interactions.

Mechanisms of drug interactions

There are two basic types of drug interaction, pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are associated with changes in drug disposition, which are readily measured in that changes in drug concentrations in plasma occur. These interactions, which in fact can be associated with a change in plasma concentration of either the drug or its metabolite(s) or both, involve a change in the absorption, distribution, or elimination of the affected drug and account for most known interactions (Patsalos and Perucca, 2003a). Pharmacodynamic interactions are also important but are less well recognized and occur between drugs that have similar or opposing pharmacological mechanisms of action. These interactions take place at the cellular level where drugs act, leading to additive, supra-additive, or infra-additive effects in relation to a therapeutic
response or drug toxicity. Pharmacodynamic interactions are not associated with any change in the plasma concentration of either drug and are reviewed in detail in Chapter 9.

As pharmacokinetic interactions can occur during any stage of drug disposition (i.e. during absorption, distribution, metabolism, or elimination) these stages are discussed in greater detail below.

**Absorption**

Absorption is the entry of drug molecules into the systemic circulation via the mucous membranes of the gut or lungs, via the skin, or from the site of an injection. Although drug interactions with AEDs are rare during absorption, such interactions can be important in some cases. For example, when phenytoin is ingested with certain nasogastric feeds, it is thought to bind to constituents of the feeding formulas to form insoluble complexes that cannot be absorbed (Bauer, 1982; Hatton, 1984; Worden et al., 1984). Therefore, phenytoin absorption is impaired. Another example is that of antacids which have been shown to reduce the absorption of some AEDs (e.g. phenytoin, phenobarbitone, carbamazepine, and gabapentin) by decreasing the acidity of the stomach (Patsalos and Perucca, 2003b).

Another, useful, interaction is that with activated charcoal which both impairs drug absorption and adsorbs drug secreted into the intestine. This interaction is exploited clinically to hasten the elimination of phenobarbitone, phenytoin, and carbamazepine in overdose patients (Neuvonen et al., 1978; Neuvonen and Elonen, 1980; Mauro et al., 1987; Weichbrodt and Elliot, 1987).

In recent years, evidence has accumulated that transporters, particularly P-glycoprotein, may play an important role in the gastrointestinal absorption of many drugs (Lin and Yamazaki, 2003), including digoxin (Hoffmeyer et al., 2000) and cyclosporine (Fricker et al., 1996; Lown et al., 1997). Whether P-glycoprotein contributes to the gastrointestinal absorption of AEDs is unknown. As the distribution of P-glycoprotein varies significantly across the gastrointestinal tract, its role and contribution to drug absorption may vary for different drugs (Cox et al., 2002). Furthermore, the expression of P-glycoprotein in many tissues, including the gut, is subject to inhibition and induction by co-administered drugs, and many inhibitors and inducers of the cytochrome P450 (CYP) isoenzyme CYP3A4 may inhibit or induce P-glycoprotein activity (Wacher et al., 1995; Jette et al., 1996; Schuetz et al., 1996; Verschraagen et al., 1999). Therefore, overall, based on these observations, it cannot be excluded that some AED interactions currently ascribed to other mechanisms could in fact be mediated by modulation of P-glycoprotein function at the level of drug absorption or distribution. This possibility needs to be investigated.
Distribution

Distribution is the movement of drug molecules between the various water, lipid, and protein compartments in the body, including the movement of drugs to their sites of action, metabolism, and elimination. Interactions involving the distribution of drugs are difficult to ascertain. For example, during combination therapy with vigabatrin and phenytoin, phenytoin plasma concentrations are reduced by approximately 30%. Although the mechanism of this interaction is unknown, it is thought to involve an effect on phenytoin distribution (Tonini et al., 1992).

Drug distribution is affected by protein binding in the circulation and the primary proteins to which drugs bind are albumin and α-glycoprotein, with albumin being by far the most important in relation to AEDs. Since the non-protein-bound drug concentration is that that is available for distribution in the body in general, and in relation to AEDs for distribution into the brain, and is pharmacologically active, plasma protein binding is important. Therefore, interactions involving competition between two drugs for plasma-protein-binding sites may affect drug distribution. However, these interactions are only important for drugs which are highly protein bound (>90%), and among AEDs, only phenytoin, valproic acid, diazepam, and tiagabine have this characteristic (Perucca, 2001; Table 4.1).

Competition of drugs for albumin binding sites depends on both the affinity and the concentration of the two drugs. Drugs with lower affinity and lower concentration will be displaced. The most commonly occurring plasma-protein-binding displacement interaction involving AEDs is the displacement of phenytoin by valproic acid (Patsalos and Lascelles, 1977a; Perucca et al., 1980). As the free fraction of phenytoin increases, total systemic clearance also increases, leading to a decline in total phenytoin concentration. Unbound (pharmacologically active) drug concentrations are dependent on drug dose and hepatic intrinsic clearance. Therefore, although at steady state a displacement interaction may transiently increase the unbound concentration of phenytoin, the concentration should return to its pre-interaction value, assuming there has not been any alteration in hepatic intrinsic clearance (e.g. due to concurrent inhibition). Thus, although typically this interaction results in a fall in total phenytoin concentration while the concentration of free, pharmacologically active, phenytoin is usually unaltered (Tsanaclis et al., 1984), in some patients a modest rise in free phenytoin concentration may actually be seen, due to a concomitant inhibition of phenytoin metabolism by valproic acid (Patsalos and Lascelles, 1977b). Awareness of this interaction is important for interpretation of plasma drug concentration measurements since in this setting the “therapeutic” range of total plasma phenytoin concentrations is shifted towards lower values and therapeutic and toxic effects will occur at total drug concentrations lower than usual. Patient management may best be guided by monitoring free unbound phenytoin concentrations (Patsalos, 2001, 2002).
Tolbutamide and phenylbutazone also interact with phenytoin by simultaneously displacing phenytoin from its protein-binding site and inhibiting its metabolism (Tassaneeyakul et al., 1992). Thus, the same precautions described above for valproic acid would also apply.

AEDs that are not protein bound (Table 4.1; ethosuximide, gabapentin, levetiracetam, and vigabatrin) would not be susceptible to protein-binding displacement interactions.

Distribution of AEDs from the blood compartment to the brain is very necessary for a successful therapeutic outcome. There is evidence that the efflux of some AEDs, including carbamazepine, felbamate, lamotrigine, phenobarbitalone, and phenytoin, across the blood–brain barrier is mediated by p-glycoprotein (Potschka and Loscher, 2001; Potschka et al., 2001, 2002; Rizzi et al., 2002). Furthermore, p-glycoprotein overexpression in brain tissue may limit the penetration of AEDs to

### Table 4.1 Some pharmacokinetic characteristics the various AEDs

<table>
<thead>
<tr>
<th>AED</th>
<th>% bound</th>
<th>Undergoes metabolic transformation</th>
<th>Undergoes renal elimination</th>
<th>Elimination half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>75</td>
<td>Yes</td>
<td>No</td>
<td>16–24</td>
</tr>
<tr>
<td>Clobazam</td>
<td>85</td>
<td>Yes</td>
<td>No</td>
<td>10–58</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>85</td>
<td>Yes</td>
<td>No</td>
<td>19–40</td>
</tr>
<tr>
<td>Diazepam</td>
<td>98</td>
<td>Yes</td>
<td>No</td>
<td>24–48</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>40–60</td>
</tr>
<tr>
<td>Felbamate</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>13–23</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>5–9</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>56</td>
<td>Yes(^d)</td>
<td>No</td>
<td>22–38</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0</td>
<td>Yes(^e)</td>
<td>Yes</td>
<td>6–8</td>
</tr>
<tr>
<td>Oxcarbazepine(^b)</td>
<td>40</td>
<td>Yes</td>
<td>Yes</td>
<td>5–30</td>
</tr>
<tr>
<td>Phenobarbitalone</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>80–100</td>
</tr>
<tr>
<td>Phenytoin(^c)</td>
<td>90</td>
<td>Yes</td>
<td>No</td>
<td>7–42</td>
</tr>
<tr>
<td>Primidone</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>8–12</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>98</td>
<td>Yes</td>
<td>No</td>
<td>5–8</td>
</tr>
<tr>
<td>Topiramate</td>
<td>15</td>
<td>Yes</td>
<td>Yes</td>
<td>19–25</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>90</td>
<td>Yes</td>
<td>No</td>
<td>8–18</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>5–7</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>57–68</td>
</tr>
</tbody>
</table>

\(^a\)Values relate to patients co-administered with non-interacting drugs.

\(^b\)Refers to the mono-hydroxy metabolite of oxcarbazepine.

\(^c\)Dose or plasma concentration dependent.

\(^d\)Refers to glucuronide metabolite of lamotrigine.

\(^e\)Metabolism is non-hepatic.
their sites of action and may be a mechanism of pharmacoresistance in epilepsy (Sisodiya, 2003). Therefore, the possibility exists that AEDs may compete for transport across the blood-brain barrier via p-glycoprotein mechanisms.

**Metabolism**

Metabolism is the most important mechanism of elimination and accounts for the majority of clinically relevant drug interactions with AEDs. By far the most important system for AED metabolism is that involving the CYP system (e.g. carbamazepine, phenobarbitone, phenytoin, tiagabine, topiramate, zonisamide, and felbamate). However, metabolic pathways such as conjugation involving uridine glucuronyl transferases (UGTs) (e.g. lamotrigine and valproic acid) and β-oxidation (e.g. valproic acid) are also important.

CYP enzymes are a major component of the mixed function oxidase system that is located in the smooth endoplasmic reticulum of the cells of almost all tissues. The highest concentrations of CYP enzymes are found in the liver and four of these isoenzymes (CYP3A4, 50%; CYP2D6, 25%; CYP2C9, 15%; CYP1A2, 5%) are known to be responsible for the metabolism of 95% of all drugs (Spatzenegger and Jaeger, 1995). Furthermore, 50–70% of all drugs might be substrates for CYP3A4 and three isoenzymes (CYP3A4, CYP2C9 and CYP2C19) are of particular importance in relation to AED interactions (Rendic and Di Carlo, 1997). CYP3A4 and CYP2C9, which are responsible for the metabolism of carbamazepine and phenytoin respectively, are susceptible to induction and inhibition by many compounds and carbamazepine is capable of inducing its own metabolism (autoinduction) via its action on the CYP3A4 isoenzyme. If two drugs are metabolized by, or act upon, the same isoform of CYP, then drug interactions are more likely. Phenobarbitone, primidone, phenytoin, and carbamazepine are inducers of CYP isoenzymes, whereas valproate is an inhibitor (Mather and Levy, 2000).

The UGT family of enzymes are involved in the catalysis of glucuronidation processes and comprise two distinct families, UGT1 and UGT2. To date eight isoenzymes have been identified in each family. The glucuronidation of lamotrigine is by the UGT1A4 isoenzyme, whereas the isoenzyme isoform catalysing the glucuronide conjugation of valproic acid has not yet been identified (Green et al., 1995). Glucuronidation processes, just like those mediated by CYPs, are susceptible to inhibition and induction.

Of all AEDs, phenytoin has the greatest propensity to interact. Phenytoin binds loosely to CYP isoenzymes and consequently it is easily displaced from its binding sites by other drugs. Consequently, its metabolism is readily inhibited. Furthermore, the fact that the metabolism of phenytoin is saturable makes phenytoin particularly susceptible to problematic interactions. As the metabolism of phenytoin is
primarily via the isoenzyme CYP2C9 (responsible for approximately 80% of the metabolism of phenytoin) whilst the isoenzyme CYP2C9 contribution is limited (responsible for the remaining 20%) the clinical significance of an interaction will very much depend on which isoenzyme is involved. Thus, amiodarone, which interacts with CYP2C9, will have a greater effect on the plasma concentration of phenytoin compared with cimetidine, which interacts with CYP2C19.

By far the most important pharmacokinetic interactions with AEDs are those which are related to induction or inhibition of drug metabolism (Anderson, 1998; Patsalos and Perucca, 2003a). Enzyme inhibition is the phenomenon by which a drug or its metabolite(s) blocks the activity of one or more drug-metabolizing enzymes resulting in a decrease in the rate of metabolism of the affected drug. This, in turn, will lead to increased plasma concentrations of the affected drug and, possibly, clinical toxicity. Inhibition is usually competitive in nature and dose dependent, and tends to begin as soon as sufficient concentrations of the inhibitor are achieved, with significant inhibition being often observed within 24 h after addition of the inhibitor (Anderson, 1998). However, the time scale of the maximal pharmacological potentiation consequent to an inhibitory interaction depends on the elimination half-life of the affected drug with potentiation of drug activity occurring more quickly if the drug has a short half-life. As a rule, a new steady-state plasma concentration will be achieved at a time that is equivalent to five half-life values of the affected drug (Figure 4.1). For example, lamotrigine has a half-life

![Figure 4.1](image-url)
value of approximately 1.5 days, and therefore its maximal pharmacological potentiation occurs 7.5 days later (Table 4.1). In contrast, the maximal pharmacological potentiation of phenobarbitone will occur 20 days later because its half-life is longer (approximately 4 days). If drug interactions result in an increased plasma concentration of a drug or its active metabolite, then the patient may experience toxicity and side effects, in which case it may be necessary to reduce the dose of the affected drug. However, in some patients, an increase in plasma drug concentration may actually enhance the therapeutic response, particularly if the concentration was previously sub-therapeutic. An extended half-life may also mean that the frequency of dosing can be reduced, which may actually help to improve compliance.

Enzyme induction, which is the consequence of an increase in the synthesis of CYP isoenzymes in the liver and in other tissues resulting in an increase in enzyme activity, becomes apparent more slowly than that of inhibition (Perucca et al., 1984; Su et al., 1998). The elevated enzyme activity, in turn, results in an increase in the rate of metabolism of drugs, which are substrates of those isoenzymes, leading to a decrease in plasma concentration of the affected drug. In this setting the pharmacological effect of the drug will be reduced. However, if the affected drug has a pharmacologically active metabolite (e.g. the epoxide of carbamazepine), induction can result in increased metabolite concentration and seizure control may continue to be effective, but the possibility of an increase in drug toxicity is also greater. A further example involves the induction of disopyramide and amiodarone by enzyme-inducing AEDs whereby formation of an active metabolite complicates dosage requirements after induction has occurred (Aitio et al., 1981; Nolan et al., 1990). As enzyme induction requires synthesis of new enzymes, the time course of induction is dependent on the rate of enzyme synthesis and degradation and the time to reach steady-state concentrations of the inducing drug. Thus, the time course of induction is usually dose dependent and gradual (Perucca, 1987; Patsalos et al., 1988).

It should be remembered that both enzyme induction and enzyme inhibition are reversible processes and that upon the removal of an interacting drug, drug dosage re-adjustments will be necessary.

AEDs that are not subject to hepatic metabolism (gabapentin, levetiracetam, and vigabatrin) would not be susceptible to metabolic interactions (Table 4.1).

**Elimination**

Elimination is the removal of drug molecules from the body by excretion, usually by the kidneys, or by biotransformation/metabolism (primarily CYPs), mainly in the liver. Excretion is important for water-soluble drugs and the water-soluble metabolites of lipid-soluble drugs. Conjugation by UGT isoenzymes usually results in the production of pharmacologically inactive and less lipid-soluble metabolites, which
are often excreted in the urine or in the bile. Although drug interactions affecting renal excretion are rare with AEDs, AEDs that undergo extensive renal elimination in unchanged form may be susceptible to interactions affecting the excretion process, particularly when the latter involves active transport mechanisms or when the ionized state of the drug is highly sensitive to changes in urine pH (Bonate et al., 1998). For example, probenecid increases the plasma concentration of penicillin by competing for the same active transport system in the kidneys and consequently reduces the renal excretion of penicillin (Hansten, 1998). Also, agents which cause alkalinization of urine, reduce the reabsorption of phenobarbitone from the renal tubuli and consequently enhance its elimination (Powell et al., 1981). The latter interaction is exploited therapeutically in severe cases of barbiturate intoxication. It should be borne in mind that although vigabatrin, gabapentin, levetiracetam, topiramate and felbamate are renally excreted, it has not been established whether or not this occurs by active transport systems (Table 4.1). Nevertheless, other drugs that are similarly excreted could potentially interact with these AEDs.

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Predictability of metabolic antiepileptic drug interactions

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Principles of drug metabolism

Many drugs are lipid soluble, weak organic acids or bases that are not readily eliminated from the body, being reabsorbed into the blood from the glomerular filtrate. Metabolic processes are necessary to convert a drug into one or more metabolites which are chemically different from the parent compound, but generally more polar and water soluble, facilitating their excretion in urine or bile. Although metabolism usually results in inactivation or detoxification, many drug metabolites have pharmacological activity. Metabolites may occasionally be much more active than the parent compound (which then may be designated as a prodrug), they may exert effects similar to or different from those of the parent molecule, or they may be responsible for toxic effects (Perucca and Richens, 1995). When metabolites are active, termination of their action occurs by further biotransformation or by direct excretion of the metabolite in urine or bile.

The chemical reactions involved in the biotransformation of drugs are catalyzed by various enzyme systems and are conventionally divided into phase I (functionalization) and phase II (conjugation) biotransformation reactions, which may occur in series. Phase I reactions involve the addition of a polar functional group (e.g. a hydroxyl group) or the deletion of a non-polar alkyl group (e.g. N-demethylation) by oxidation, reduction, or hydrolysis. In phase II or conjugation reactions, the drug or the phase I metabolite are covalently attached to a water-soluble endogenous substrate (e.g. glucuronic acid, acetic acid, sulfate, amino acids or glutathione), usually resulting in an inactive, easily excretable compound.

The liver is usually the main organ responsible for phase I and phase II reactions, but other organs such as the gastrointestinal tract, the kidney, the lungs, the brain, the blood, the skin and the placenta may also contribute to metabolism. In the hepatocyte, phase I oxidative enzymes are located almost exclusively in the smooth
endoplasmic reticulum, along with the phase II enzyme, glucuronyltransferase. Other phase II enzymes responsible for conjugation reactions are found predominantly in the cytoplasm.

**Major drug-metabolizing enzymes**

Knowledge of the main enzyme systems involved in the biotransformation of antiepileptic drugs (AEDs) is essential for understanding the principles and mechanisms of metabolically based drug interactions involving these drugs.

**The cytochrome P450 system**

The cytochrome P450 (CYP) system constitutes a superfamily of isoenzymes that are responsible for the oxidative metabolism of many endogenous (e.g. steroids, prostaglandins and fatty acids) and exogenous compounds (e.g. many drugs). These isoenzymes are haemoproteins located in the membranes of the smooth endoplasmic reticulum in the liver and in many extrahepatic tissues (Guengerich, 1997a), and they are subdivided into families, subfamilies and isoenzymes according to a nomenclature system based on amino acid sequence homology (Nelson et al., 1996). Each enzyme is designated with the root CYP followed by a first Arabic number indicating the ‘family’ (>40% sequence identity within family members), a capital letter designating the ‘subfamily’ (>59% sequence identity within subfamily members), and a second Arabic number representing individual isoenzymes. The major CYP enzymes involved in drug metabolism in humans belong to families 1, 2 and 3, which together represent approximately 70% of the total CYP content in human liver (Shimada et al., 1994). The most important isoforms playing a major role in the biotransformation of therapeutic agents are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, and these will be discussed in more detail below. Each CYP isoform is a specific gene product and possesses a characteristic but relatively broad spectrum of substrate specificity. Different CYP isoforms may display overlapping substrate specificities.

There is a large variability in the expression and activity of these isoenzymes, which may lead to interindividual differences in drug exposure. Such a variability results from genetic, pathophysiological and environmental factors, including concomitant administration of other drugs. A number of genes coding for CYP isoforms have variant alleles resulting from mutations, and these mutations can result in enzyme variants with higher, lower or no activity, or in the very absence of the enzyme. The existence of mutated alleles in at least 1% of the population is referred to as genetic polymorphism (Meyer, 1994). The CYP polymorphisms that have the greatest clinical implications are CYP2D6, CYP2C9 and CYP2C19.
In recent years, the major CYP isoenzymes have been characterized at the molecular level and their different substrates, inhibitors and inducers have been identified (Rendic and Di Carlo, 1997). As indicated in Table 5.1, the majority of AEDs are metabolized by CYP enzymes and some may also inhibit or induce, to varying degrees, one or more of these isoforms. The activity of CYP enzymes can be evaluated in vitro and in vivo. In vitro studies provide a screening method for evaluating drug affinities as substrates, inhibitors or inducers. In vivo studies include phenotyping and/or genotyping tests. Phenotyping tests are based upon administration of a single dose of a probe compound to an individual, followed by measurement of urinary or plasma concentrations of the test compound and its major metabolite(s). The ratio of parent drug/metabolite (metabolic ratio, MR) is used as a measure of the activity of the enzyme responsible for the formation of that metabolite. Genotyping is performed by using polymerase chain reaction (PCR)-based assays and restriction fragment length polymorphism (RFLP) analyses and allows detection of allelic variants for the genes coding for the polymorphic enzymes.

CYP1A2

CYP1A2 accounts for approximately 13% of total hepatic CYPs and represents the primary enzyme responsible for the metabolism of many drugs, including phenacetin, paracetamol, tacrine, theophylline, caffeine, clozapine and olanzapine (Miners and McKinnon, 2000). Although CYP1A2 has not been found to play a major role in the metabolism of any AED, it does contribute to a minor extent to carbamazepine metabolism (Patsalos et al., 2002). Phenacetin and theophylline are frequently used as in vitro probes for CYP1A2, and caffeine is also widely used as a marker for CYP1A2 activity in vivo. Though CYP1A2 activity does not seem to be polymorphically distributed, it shows large interindividual variability.

Furafylline and α-naphtoflavone are potent selective inhibitors of CYP1A2 and, therefore, may be used in vitro to evaluate the contribution of this isofrom in drug-metabolizing pathways. Fluvoxamine is also a potent, but not selective, inhibitor of CYP1A2. The activity of CYP1A2 is induced by polycyclic aromatic hydrocarbons (including those found in charcoal-broiled foods and cigarette smoke), rifampicin, omeprazole and, possibly, by phenobarbital, phenytoin and carbamazepine (Guengerich, 1997a). Two polymorphisms have been reported which seem to enhance the inducibility of CYP1A2 (Nakajima et al., 1999; Sachse et al., 1999), but the clinical implications of this observation have not been clarified.

CYP2C9 and CYP2C19

The human CYP2C subfamily, which accounts for approximately 20% of total CYPs expressed in human liver, includes at least four members: CYP2C8, CYP2C9, CYP2C18 and CYP2C19 (Rettie et al., 2000). The relative contributions of these
### Table 5.1 Substrates, probe drugs, inhibitors and inducers of the major CYP isoforms involved in drug metabolism

<table>
<thead>
<tr>
<th>Isoenzymes</th>
<th>Substrates</th>
<th>Probe drugs</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Antidepressants: amitryptiline, clomipramine, imipramine, fluvoxamine, mirtazepine</td>
<td>In vitro</td>
<td>Furafylline</td>
<td>Cigarette smoke</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics: clozapine, olanzapine, haloperidol</td>
<td>Phenacetin O-deethylation</td>
<td>α-naphtoflavone</td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Methylxanthines: theophylline, caffeine</td>
<td>Theophylline 8-hydroxylation</td>
<td>Fluvoxamine</td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td>Miscellaneous: phenacetin, paracetamol, tacrine, tamoxifen, R-warfarin</td>
<td>In vivo</td>
<td>Ciprofloxacin</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caffeine</td>
<td>Clarithromycin</td>
<td>Phenytoin</td>
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<td></td>
<td>Charcoal-broiled meat</td>
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<tr>
<td>CYP2C9</td>
<td>AEDs: phenytoin, phenobarbital</td>
<td>In vitro</td>
<td>Sulfaphenazole</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>NSAIDs: diclofenac, ibuprofen, naproxen, piroxicam, celecoxib</td>
<td>Phenytin p-hydroxylation</td>
<td>Amiodarone</td>
<td>Barbiturates</td>
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<td></td>
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<td>Fluconazole</td>
<td>Phenytoin</td>
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<td>S-(\textit{S})-warfarin hydroxylation</td>
<td>Miconazole</td>
<td>Carbamazepine</td>
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<td>Tolbutamide</td>
<td>Valproic acid</td>
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<td>Diclofenac, Losartan</td>
<td>Fluoxetine</td>
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<td>S-warfarin</td>
<td>Fluvastatin</td>
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</tr>
<tr>
<td>CYP2C19</td>
<td>AEDs: S-mephenytoin, methylphenobarbital, phenytoin, diazepam</td>
<td>In vitro</td>
<td>Omeprazole</td>
<td>Rifampicin</td>
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<td>Antidepressants: amitryptiline, clomipramine, imipramine, citalopram, moclobemide</td>
<td>S-mephenytoin</td>
<td>Ticlopidine</td>
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<td>4'-hydroxylation</td>
<td>Fluvoxamine</td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td></td>
<td>In vivo</td>
<td>Felbamate</td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td></td>
<td>S-mephenytoin</td>
<td>Topiramate (weak)</td>
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<tr>
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<td></td>
<td>Omeprazole</td>
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<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Antidepressants: amitryptiline, clomipramine, imipramine, desipramine, nortriptyline, fluoxetine, paroxetine, fluvoxamine, citalopram, venlafaxine, mianserine, mirtazepine</td>
<td>In vitro</td>
<td>Quinidine</td>
<td>No inducer known</td>
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<td></td>
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<td>Dextrometorphan</td>
<td>Propafenone</td>
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<td></td>
<td>O-demethylation</td>
<td>Thioridazine</td>
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<td></td>
<td></td>
<td>Debrisoquine</td>
<td>Perphenazine</td>
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<td>Category</td>
<td>Examples</td>
<td>Metabolism</td>
<td>Inducer</td>
<td>Interactions</td>
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<td>-------------------------------</td>
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<td>Antipsychotics</td>
<td>thioridazine, perphenazine, fluphenazine,</td>
<td>4-hydroxylation</td>
<td>Debrisoquine</td>
<td>Ketoconazole, Rifampicin, St. John’s wort, Glucocorticoids^a</td>
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<td>haloperidol, risperidone, clozapine,</td>
<td>Bufuralol 1’-hydroxylation</td>
<td>Fluoxetine</td>
<td>Oxcarbazepine, Topiramate^a</td>
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<td>olanzapine, chlorpromazine</td>
<td>In vivo</td>
<td>Paroxetine</td>
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<td>timolol, pindolol</td>
<td>Sparteine</td>
<td>Haloperidol</td>
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<td>Metoprolol</td>
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<td>In vitro</td>
<td>Disulfiram</td>
<td>Isoniazid</td>
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<td>CYP2E1</td>
<td>Ethanol, halotane, dapsone, isoniazid,</td>
<td>Chlorzoxazone 6-hydroxylation</td>
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<td>chlorzoxazone, felbamate, phenobarbital</td>
<td>In vivo</td>
<td>Itraconazole</td>
<td>Barbiturates</td>
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<td>CYP3A4</td>
<td>AEDs: carbamazepine, ethosuximide,</td>
<td>Midazolam 1’-hydroxylation</td>
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<td>Phenytoin</td>
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<td>tiagabine, zonisamide, some benzodiazepines</td>
<td>Erythromycin N-demethylation</td>
<td>Erythromycin</td>
<td>St. John’s wort</td>
</tr>
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<td>(e.g. alprazolam, midazolam, triazolam)</td>
<td>Testosterone 6β-hydroxylation</td>
<td>Troleandomycin</td>
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<td>Antidepressants</td>
<td>amitryptiline, clomipramine, imipramine,</td>
<td>In vivo</td>
<td>Troperidol</td>
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<td>sertraline, nefazodone, mirtazepine</td>
<td>Nefedipine</td>
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<td>cyclosporine, tacrolimus, erythromycin,</td>
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<td>clarithromycin, tamoxifen, amiodarone,</td>
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<td>quinidine, itraconazole, ketoconazole,</td>
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<tr>
<td></td>
<td>indinavir, ritonavir</td>
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^a Weaker or tissue-selective inducers.
isoforms to total CYP2C content in human liver are about 60% for 2C9, 35% for 2C8, 4% for 2C18 and 1% for 2C19. Of these isoforms, CYP2C9 and CYP2C19 seem to be the most important for drug metabolism, although CYP2C8 should not be neglected as it contributes to the metabolism of carbamazepine (Kerr et al., 1994). As CYP2C9 and CYP2C19 show a 91% identity in amino acid sequence, many substrates of CYP2C9 are also metabolized, at least in part, by CYP2C19.

CYP2C9 plays an important role in the oxidation of many drugs, including phenytoin, phenobarbital, S-warfarin, tolbutamide, losartan, fluvastatin and many non-steroidal anti-inflammatory agents such as diclofenac, ibuprofen and piroxicam (Perucca and Richens, 1995; Guengerich, 1997a). CYP2C9 is polymorphically expressed in humans. To date, three different allelic variants have been identified, that code for enzymes with different catalytic activity (Miners and Birkett, 1998). The frequencies of the defective alleles CYP2C9*2 and CYP2C9*3 vary between 8% and 12% and 3% and 8%, respectively among Whites, but they are somewhat lower in Orientals and black Africans. Subjects carrying two mutated alleles for CYP2C9*3 lack almost completely CYP2C9 activity, and, therefore, are unable to metabolize important CYP2C9 substrates such as phenytoin and S-warfarin (Brandolese et al., 2001). While sulfaphenazole is the prototypic inhibitor for CYP2C9, other inhibitors include valproic acid, amiodarone, fluconazole and miconazole.

CYP2C19 is involved to a significant extent in the biotransformation of methylphenobarbital, phenytoin, omeprazole, proguanil, citalopram and tricyclic antidepressants (demethylation reactions) (Guengerich, 1997a). However, the prototype substrate for this isoform is the S-enantiomer of mephenytoin, which undergoes p-hydroxylation at position 4 on its aromatic ring. The exclusive participation of CYP2C19 in this metabolic pathway is the basis for the use of S-mephenytoin as an in vitro and in vivo probe for CYP2C19 activity. CYP2C19 also exhibits an important genetic polymorphism. The frequency of the poor metabolizer (PM) phenotype varies from approximately 3% in Whites to 12–25% in many Asian populations, while in black Africans PM frequencies vary between 4% and 7% (Goldstein, 2001). The major defective alleles responsible for the PM phenotype are CYP2C19*2, the most common among Whites and Orientals, and CYP2C19*3, found at a frequency of about 12% among Orientals, but almost absent among Whites. The activity of CYP2C19 may be inhibited by felbamate, omeprazole, ticlopidine, fluvoxamine and, possibly, topiramate.

Inducers of the activity of CYP2C isoforms include barbiturates, phenytoin, carbamazepine and rifampicin.

**CYP2D6**

Although expressed at low levels (2% of hepatic CYPs) compared with other human CYPs, CYP2D6 plays an important role in the biotransformation of a large
number of drugs (Zanger and Eichelbaum, 2000). To date, however, none of the major AEDs has been found to be metabolized to a significant extent by CYP2D6.

Debrisoquine, sparteine, dextromethorphan and desipramine have been validated as probe drugs for CYP2D6. This enzyme exhibits an important genetic polymorphism. PMs lack CYP2D6 activity and represent approximately 3–10% of Whites, but only 1–2% of Orientals (Evans et al., 1980). Among extensive metabolizers (EMs), the catalytic activity varies largely, and a subgroup of subjects with extremely high enzyme activity have been classified as ultrarapid metabolizers (UMs) (Johansson et al., 1993). The CYP2D6 gene is extremely polymorphic with more than 70 allelic variants described so far (Bertilsson et al., 2002). Three major mutated alleles, CYP2D6*3, CYP2D6*4 and CYP2D6*5, account for 90–95% of the PM alleles in Whites, and CYP2D6*4 is the most common allele associated with the PM phenotype in Whites (allele frequency of about 21%). CYP2D6*4 is almost absent in Orientals, which may account for the low incidence of PMs in these populations. On the other hand, the high frequency (up to 50%) of the CYP2D6*10 allele among Orientals, and its absence among Whites, may explain the slightly lower CYP2D6 activity found in Oriental EMs compared to Whites. The frequency of the CYP2D6*5 allele, with deletion of the entire CYP2D6 gene, is about 4–6% and is similar in different ethnic populations. Individuals heterozygous for the defect alleles have lower enzyme activity than homozygous EMs. On the other hand, alleles with duplication or multiduplication of a functional CYP2D6*2 gene are associated with an increased CYP2D6 activity: the frequency of this condition varies from 1–2% in Swedes to up to 7–10% in Spaniards and Southern Italians (Bertilsson, 2002).

Quinidine, fluoxetine, paroxetine and different phenothiazines are potent inhibitors of CYP2D6. In contrast to all other CYPs involved in drug metabolism, CYP2D6 does not appear to be inducible, an important consideration in predicting interactions caused by AEDs.

CYP2E1

CYP2E1, which represents approximately 7% of total human hepatic CYPs, is of greater importance in toxicants' metabolism than in drug metabolism (Raucy and Carpenter, 2000). CYP2E1 is responsible for the metabolism of ethanol, halotane and dapsone, and plays a minor role in the oxidative biotransformation of felbamate and phenobarbital. Chlorzoxazone has been suggested as probe drug for CYP2E1. CYP2E1 activity is inhibited by disulfiram and is induced by ethanol and isoniazid.

CYP3A4

The CYP3A subfamily, which includes the isoforms 3A4, 3A5 and 3A7, is the most abundant in human liver, accounting for approximately 30% of total CYP content.
CYP3A4 is the predominant isoform in adults, is present both in the liver and in the small intestine, and participates in the biotransformation of more than 50% of all eliminated by metabolism drugs (Wrighton and Thummel, 2000). CYP3A4 is the primary enzyme responsible for the metabolism of carbamazepine, ethosuximide, tiagabine and zonisamide, and it is also involved in the biotransformation of felbamate (Perucca and Richens, 1995). Other drugs primarily metabolized by this isoform include immunosuppressants (e.g. cyclosporin and tacrolimus), triazolobenzodiazepines (e.g. alprazolam, midazolam and triazolam), non-sedating antihistamines (e.g. terfenadine and astemizole), calcium antagonists (e.g. diltiazem, verapamil, nifedipine and other dihydropyridines), cholesterol lowering drugs (e.g. simvastatin and lovastatin), antiarrhythmics (e.g. amiodarone and quinidine), and several steroids (e.g. cortisol, ethinylestradiol and levonorgestrel). Index reactions for CYP3A4 activity in vitro include midazolam and triazolam 1- and 4-hydroxylation, nifedipine dehydrogenation and testosterone 6β-hydroxylation. Cortisol, nifedipine, erythromycin and midazolam have been used as in vivo probes.

The hepatic and enteric location of CYP3A4 makes it well suited to play a significant role in first-pass (or presystemic) drug metabolism. Furthermore, the considerable overlap in substrate selectivity and tissue localization of CYP3A4 and P-glycoprotein, an intestinal transport protein located in the small bowel, has led to the hypothesis that this transporter and enzyme pair act as a co-ordinated barrier against xenobiotics at the intestinal level (Schuetz et al., 1996). Although CYP3A4 drug-metabolizing activity varies more than 20-fold among individuals, it has a unimodal distribution and does not appear to be subject to genetic polymorphism. Its wide interindividual variability is caused, at least in part, by modulation of CYP3A4 activity by many environmental compounds, including dietary constituents and medications.

Compounds that inhibit CYP3A4 activity includeazole antimycotics (e.g. ketoconazole and itraconazole), macrolide antibiotics (e.g. erythromycin and troleandomycin), HIV protease inhibitors (e.g. ritonavir and indinavir), nefazodone and some of the furanocoumarin dimers found in grapefruit juice (Guengerich, 1997b). The hepatic and, possibly, the intestinal CYP3A4 isoforms are induced by glucocorticoids (e.g. dexamethasone), rifampicin, phenobarbital, phenytoin and carbamazepine. Felbamate, oxcarbazepine and topiramate appear to exert a selective inducing effect on CYP3A4 activity, at least in some tissues. Recent studies indicate that CYP3A5 can account for more than 50% of total CYP3A hepatic and jejunal content in 30% of Whites and 50% of African Americans. This behavior has been associated with the CYP3A5*1 wild-type allele (Lamba et al., 2002). Such individuals will exhibit more variability in clearance of CYP3A substrates and more variability in drug interactions since CYP3A5 appears less inhibitable than CYP3A4.
Epoxide hydrolases

Epoxide hydrolases (EHs) belong to the group of hydrolytic enzymes which also includes esterases, proteases, dehalogenases and lipases. EHs catalyze a specialized form of hydrolysis, called hydration, where water is added to a compound without causing its cleavage into separate components (Omcienski, 2000). These enzymes hydrate epoxides and arene oxides to dihydrodiol and diol-epoxide metabolites.

Many epoxide intermediates, formed during oxidation of xenobiotics and endogenous substances, are reactive electrophilic species that may act as critical initiators of cellular damage through protein and RNA adduction as well as genetic mutation. Through inactivation of epoxides, EHs are usually implicated in detoxification processes, although in certain instances they may be involved in bioactivation. Five classes of EHs have been described: (a) cholesterol oxide hydrolase; (b) hepxylin A₃ hydrolase; (c) leukotriene A₄ hydrolase; (d) soluble EH; and (e) microsomal EH.

Microsomal EH catalyzes the trans-addition of water to a broad range of epoxides and arene oxides derived from xenobiotics, resulting in the formation of dihydrodiol products. This enzyme exhibits a broad-substrate specificity and plays a role in the metabolism of some AEDs. Phenobarbital, phenytoin and carbamazepine, in particular, are metabolized by CYP isoenzymes to epoxide intermediates, which have been implicated in idiosyncratic adverse drug reactions and teratogenicity. Since these epoxide intermediates can be substrates for microsomal EH, it has been hypothesized that EH enzymatic status may modulate the individual susceptibility to adverse drug reactions (Lindhout, 1992).

Unlike other epoxides, the 10,11-epoxide metabolite of carbamazepine is chemically stable and retains anticonvulsant activity. The clearance of this metabolite is controlled by microsomal EH activity. In vitro and in vivo interaction studies with carbamazepine-10,11-epoxide have indicated that valpromide, valnoctamide and, to a lesser extent, valproic acid are inhibitors of microsomal EH (Kerr et al., 1989; Pisani et al., 1993). Another AED, progabide, has been reported to inhibit microsomal EH both in vivo and in vitro (Kroetz et al., 1993). The activity of microsomal EH may be moderately induced by phenobarbital, phenytoin and carbamazepine.

Uridine diphosphate-glucuronosyltransferases

Uridine diphosphate (UDP)-glucuronosyltransferases (UDPGTs) are a subset of enzymes belonging to the superfamily of UDP-glycosyltransferases (UGTs) (Liston et al., 2001). These enzymes, which catalyze the glucuronidation of a large number of endobiotics and xenobiotics, are located in the endoplasmic reticulum, mainly in the liver, but also in the kidney, intestine, skin, lung, prostate and brain.

Glucuronidation, which is the most common pathway in phase II drug metabolism, involves the transfer of the glucuronoyl moiety of uridine diphosphate glucuronic
acid (UDPGA) to the substrate, with subsequent release of UDP. While most substrates undergo glucuronide conjugation after phase I reactions, in some cases, i.e. morphine and valproic acid, direct conjugation proceeds without phase I functionalization of the parent compound. In general, glucuronidation leads to formation of water-soluble inactive metabolites, but active and reactive glucuronide metabolites have also been described, as in the case of morphine.

In recent years, at least 33 families within the UGTs superfamily have been identified and classified by a nomenclature similar to that used for the CYP system (Mackenzie et al., 1997). Various UDPGTs have been characterized and assigned to the UGT1 and UGT2 gene families. Among the isoforms of the UGT1 family, UGT1A3 is involved in the O-glucuronidation of valproic acid and UGT1A4 has been found to be the major isoenzyme responsible for the N-glucuronidation of lamotrigine (Dickins and Chen, 2002) and retigabine (Hiller et al., 1999). Among the isoforms of the UGT2 family, the UGT2B7 variant also appears to contribute to the O-glucuronidation of valproic acid (Jin et al., 1993).

In contrast to extensive documentation for CYP-mediated drug interactions, there are fewer data on interactions involving glucuronidation. Any substrate of UGT has the potential to competitively inhibit glucuronidation of other substrates metabolized by the same enzyme. Unlike the CYP system, no specific inhibitors of individual UGT isoforms have been identified. Valproic acid has been reported to inhibit several glucuronidation reactions, while phenobarbital, phenytoin, carbamazepine and, to a lesser extent, oxcarbazepine may act as inducers (Perucca and Richens, 1995; Perucca, 2001). In particular, phenobarbital appears to induce UGT1A1, the major enzyme responsible for the glucuronidation of bilirubin, ethinylestradiol and the opioids buprenorphine, nalorphine and naltrexone (Bock et al., 1999).

**Enzyme induction and enzyme inhibition**

Drug interactions involving CYP isoforms and other drug-metabolizing enzymes may result from one of two processes, enzyme induction or inhibition.

**Enzyme induction**

The activity of drug-metabolizing enzymes in the liver and/or extrahepatic tissues may be increased (‘induced’) by chronic administration of several exogenous agents including drugs, industrial contaminants, dietary or volutary substances, as well as by endogenous compounds (Guengerich, 1997b). Although induction involves predominantly CYP isoenzymes, other enzymes including microsomal EH and UGTs may be affected. Morphologically, enzyme induction may be associated with a proliferation of the smooth endoplasmic reticulum and hepatic hypertrophy. From a biological point of view, induction is an adaptive response that protects the
cells from toxic xenobiotics by increasing the detoxification activity. Therefore, it is
to be expected that induction will result in decreased concentration of an active
compound. However, for those agents that are inactive but are biotransformed to
active metabolites, enzyme induction may paradoxically increase pharmacological
or toxicological activity.

Enzyme induction is the consequence of an increased concentration of the
enzyme protein (Lin and Lu, 1998; Thummel et al., 2000). In most cases, this involves
an enhanced protein synthesis resulting from an increase in gene transcription, usu-
ally mediated by intracellular receptors. However, enzyme induction may also occur
by an inducer-mediated decrease in rate of enzyme degradation, mainly through
protein stabilization. Each inducer has its own specificity in inducing a given range
of drug-metabolizing enzymes, and several mechanisms of induction are often acti-
vated by a single agent, but to a different extent. Five main mechanisms of induction
have been established to date (Fuhr, 2000). The two best known are the polycyclic
aromatic hydrocarbon type and the phenobarbital type of induction.

**Induction mediated by the aryl hydrocarbon receptor**

Polycyclic aromatic hydrocarbons such as benzo(a)pyrene and 3-methylcholanthrene
are environmental contaminants formed by incomplete combustion of organic
matter, i.e. cigarette smoke and charcoal-broiled beef. These agents selectively
induce CYP1A1 and CYP1A2, but they can also stimulate the activity of other
enzymes such as UGTs. The mechanism of this type of induction has been well
characterized and involves a sequence of events: initial binding of the inducer to
the intracellular aryl hydrocarbon (Ah) receptor, dissociation of heat-shock 90
proteins from the receptor, translocation of the receptor–ligand complex into the
nucleus, binding to the Ah receptor nuclear translocator (Arnt), binding of the
Ah–Arnt complex to response elements on the CYP1A genes, resulting in increased
gene transcription (Sogawa and Fujii-Kuriyama, 1997). In addition to polycyclic
aromatic hydrocarbons, certain constituents of cruciferous vegetables, and certain
drugs, such as omeprazole and rifampicin, appear to induce CYP1A enzymes by
the same mechanism (Fuhr, 2000).

**The constitutive androstane receptor and phenobarbital-type induction**

Phenobarbital is recognized as the prototype of a class of agents known to induce
drug metabolism (Perucca and Richens, 1995). Many other compounds, including
phenytoin, primidone, carbamazepine, rifampicin and the oxazaphosphorines
cyclophosphamide and ifosfamide have been shown to stimulate drug-metabolizing
enzymes with an induction pattern which overlaps, at least in part, with that of
barbiturates. Early investigations in liver microsomes from individuals exposed to
phenobarbital and in primary cultures of human hepatocytes have documented
the ability of phenobarbital to induce CYP enzymes, but the specific isoforms induced could not be identified. More recently, with the improvement in culture techniques and the development of isoform-specific reagents, it has been possible to demonstrate that the cluster of enzymes induced by phenobarbital and related agents appears to include several CYPs such as CYP2C subfamily members, CYP3A4, CYP2B6, possibly CYP1A2, but not CYP2D6 (Fuhr, 2000). In addition, microsomal EH and some UGTs appear to be induced by these agents. Thus, the drugs metabolized by enzymes subject to phenobarbital-type induction include a major fraction of all drugs undergoing biotransformation. Endogenous compounds, such as cortisol, testosterone and vitamin D₃, are also susceptible to induction by phenobarbital and related agents (Perucca, 1978).

Recent evidence suggests that the orphan receptor constitutive androstane receptor (CAR) is the molecular target and mediator of phenobarbital-type induction (Sueyoshi et al., 1999). It should be pointed out that the molecular mechanism of phenobarbital-type induction may show partial overlap with that of the pregnane X receptor (PXR), which mediates CYP3A4 induction by rifampicin and glucocorticoids.

**Induction mediated by the PXR**

This type of induction, previously called the rifampicin/glucocorticoid-type induction, has as target CYP3A4 enzymes, mainly in the gut. Induction involves the binding of CYP3A4 inducers, including several steroids, rifampicin and phenobarbital, to the human PXR (Fuhr, 2000).

**Enzyme induction by ethanol**

The ethanol-type induction is probably limited to a single target, CYP2E1. Unlike other types of induction mediated by intracellular ‘receptors’, ethanol-type induction occurs through protein stabilization mediated by the binding of the inducers to the active site of the enzyme (Gonzalez et al., 1991). Ethanol-type inducers stabilize the enzyme by protecting it from degradation, resulting in accumulation of the enzyme. Inducers of CYP2E1 are often substrates of the same enzyme and include ethanol, isoniazid and many organic solvents such as acetone, benzene and carbon tetrachloride.

**Induction caused by peroxisome proliferators**

This type of induction is mediated by binding to two peroxisome proliferator-activated receptors (PPARs), PPARα and PPARγ. PPARα controls the transcription of genes encoding for enzymes mediating the metabolism of lipoproteins and fatty acids, while PPARγ is involved in adipogenesis. Typical peroxisome proliferator inducers are members of the classes of fibrates and glitazones (Fuhr, 2000).
Enzyme induction as a cause of drug interactions

Enzyme induction is a slow regulatory process, which is dose and time dependent (Perucca, 1978, 1987; Perucca et al., 1984). In other words, the extent of induction is generally proportional to the dose of the inducing agent and, since the process usually requires synthesis of new enzyme, it occurs with some delay after the exposure to the inducing agent. In practice, the time required for induction depends on the time to reach the steady state of the inducing agent (approximately five elimination half-lives) and the rate of synthesis of the enzyme(s). Similarly, the time course of de-induction is also gradual and depends on the rate of degradation of the enzyme and the time required to eliminate the inducing drug. Either of these two processes could be the rate-limiting step. As far as classical enzyme-inducing AEDs are concerned, induction by phenobarbital is usually manifest after approximately 1 week, with maximal effect occurring after 2–3 weeks following initiation of therapy. De-induction follows a similar time course (Anderson and Graves, 1994; Anderson, 1998). With phenytoin, maximal induction or de-induction occur approximately 1–2 weeks after initiation or removal of therapy respectively (Anderson and Graves, 1994; Anderson, 1998). Carbamazepine is the only AED which significantly induces its own metabolism (autoinduction) and, as a result of this, its plasma clearance more than doubles during the initial weeks of therapy. The time course of carbamazepine autoinduction should be completed within approximately 3–5 weeks (Anderson and Graves, 1994; Anderson, 1998).

Enzyme induction may have a profound impact on the pharmacokinetics of drugs metabolized by the susceptible enzyme(s) (Perucca, 1978). Elevated enzyme concentrations in the eliminating organ(s) generally result in an increase in the rate of metabolism of the affected drug, leading to a decrease in serum drug concentrations and, possibly, decreased clinical efficacy. If the affected drug has an active metabolite, induction can result in increased metabolite concentrations and possibly enhanced toxicity. There are three different situations where enzyme induction plays a role in therapeutic decision-making: addition of a medication when an inducer is already present, addition of an inducer to an existing therapy, and removal of an inducer from chronic therapy. In the first two cases a higher dose of the affected drug will be needed to achieve or maintain clinical efficacy, while a reduction of the dose of the affected drug may be necessary to prevent toxicity after removal of the inducer. The magnitude and timing of these interactions are critical to allow clinicians to adjust dosages in order to maintain therapeutic effects and prevent toxicity.

Enzyme induction represents a common problem in the management of epilepsy. Based on their enzyme-inducing properties, phenobarbital, phenytoin and carbamazepine have been reported to increase the clearance or reduce the therapeutic efficacy of many different compounds including other AEDs (Perucca, 1982;
As a general rule, these compounds will induce the biotransformation of any drug that is primarily metabolized by CYP3A4, CYP2C9, CYP2C19 and, possibly, CYP1A2 (see Table 5.1). The possibility of induction of CYP1A2 by carbamazepine is supported by evidence that this agent increases the metabolic clearance of CYP1A2 substrates such as olanzapine and R-warfarin, and increases the percentage of labelled caffeine exhaled as carbon dioxide, a marker of CYP1A2 activity in vivo (Parker et al., 1998). Because the induction profiles of phenobarbital, phenytoin and carbamazepine are not fully overlapping, stimulation of the metabolism of all drugs listed in Table 5.1 may not necessarily be observed with each of these AEDs. Moreover, in some cases enzyme induction and inhibition may occur at the same time, complicating the prediction process. In any case, clinically relevant interactions should be expected when enzyme-inducing agents are co-administered with drugs with a low therapeutic index such as warfarin, oral contraceptives or cyclosporin (Anderson, 1998). When active metabolites are formed, enzyme induction may result in potentiation of therapeutic and/or toxic effects. For example, the enhanced hepatotoxicity of valproic acid in children concurrently treated with enzyme inducers could be explained by accelerated formation of reactive oxidation products (Kondo et al., 1990).

In addition to classical enzyme-inducing AEDs, some newer agents, namely felbamate, oxcarbazepine and topiramate, may produce significant enzyme induction, though the spectrum of enzymes induced by these agents appears to be more restricted. In particular, felbamate may induce the activity of CYP3A4 (Glue et al., 1997), as indicated by a decrease in the plasma concentrations of CYP3A4 substrates such as carbamazepine (Fuerst et al., 1988), ethinylestradiol and gestodene (Saano et al., 1995). Unlike carbamazepine, oxcarbazepine is not subject to autoinduction, but it may selectively induce the specific isoforms of the CYP3A group involved in the metabolism of oral contraceptives (Fattore et al., 1999) and dihydropyridine calcium antagonists (Zaccara et al., 1993). In addition, oxcarbazepine may also induce UGTs, as suggested by a significant acceleration of lamotrigine clearance (May et al., 1999). Topiramate is also a weak inducer of CYP3A4, because at dosages above 200 mg/day it may decrease plasma concentrations of ethinylestradiol by approximately 30% with a risk of failure of contraception (Rosenfeld et al., 1997). At lower dosages, topiramate does not appear to affect the metabolism of steroid contraceptives (Doose et al., 2003), reinforcing the important concept that enzyme induction is a dose-dependent phenomenon. Recent evidence indicates that topiramate, at higher dosages, may induce CYP3A4 by activation of PXA (Nalloni et al., 2003)

**Enzyme inhibition**

Enzyme inhibition is the most common mechanism underlying drug interactions. A large number of compounds may inhibit the activity of drug-metabolizing
enzymes, in particular with CYPs. As a consequence of enzyme inhibition, the rate of metabolism of a particular agent is decreased, resulting in increased plasma drug concentrations and potential enhancement of its pharmacological effects.

The mechanisms of enzyme inhibition include reversible inhibition, slowly reversible inhibition and irreversible inhibition (Lin and Lu, 1998; Thummel et al., 2000). In reversible inhibition, the normal function of the enzyme is restored after the inhibitor has been eliminated from the body. In contrast, the loss of enzyme activity caused by irreversible inhibition persists even after the elimination of the inhibitor, and de novo biosynthesis of new enzyme is the only means by which activity can be restored.

**Reversible inhibition**

This type of enzyme inhibition is probably the most common and, kinetically, it can be subdivided further into competitive, non-competitive and uncompetitive inhibition (Lin and Lu, 1998). Competitive inhibition involves a mutually exclusive competition between the substrate and the inhibitor for binding to the catalytic site of the enzyme. Competitive inhibitors can be non-substrates with nevertheless high binding affinity: binding of the inhibitor prevents the substrate from binding to the active site of the enzyme and, therefore, the substrate cannot be metabolized. This inhibition can be reversed by increasing the concentration of the substrate. In the case of non-competitive inhibition, the inhibitor binds to another site of the enzyme and the inhibitor does not affect the binding of the substrate, but formation of the enzyme–inhibitor complex results in loss of enzyme activity. Uncompetitive inhibition occurs when the inhibitor does not bind to the enzyme, but to the enzyme–substrate complex, and again formation of the enzyme–substrate–inhibitor complex results in loss of enzyme activity.

**Slowly reversible inhibition**

Several drugs undergo metabolic activation by CYP enzymes to form inhibitory metabolites. These metabolites can form stable complexes with the prosthetic haem of CYPs, the so-called metabolic intermediate (MI) complexes, so that the CYP isoform is sequestered in a functionally inactive state (Lin and Lu, 1998). While in vitro MI complexation can be reversed, in vivo the MI complex is usually so stable that the CYP involved in the complex is not available for drug metabolism, and the activity can be restored only after synthesis of new enzyme. The effect of this inhibition may, therefore, persist well after the elimination of the interacting drug. Troleandomycin and erythromycin are probably the best-known macrolide antibiotics involved in the formation of MI complexes. These two agents are associated with a clinically significant inhibition of the CYP3A4-mediated metabolism of carbamazepine (Spina et al., 1996). Hydrazine derivatives represent another
class of compounds that may form stable complexes with the haem of CYP enzymes. Among these agents, isoniazid may cause a significant inhibition of phenytoin metabolism (Patsalos et al., 2002), probably through MI complexation with CYP enzymes involved in its biotransformation.

Irreversible inhibition

Some drugs are oxidized by CYPs to reactive intermediates that then cause irreversible inactivation of the enzyme (Lin and Lu, 1998). As metabolic activation is required for enzyme inactivation, these agents are classified as mechanism-based inactivators or suicide inhibitors. This inactivation of CYPs may result from irreversible alteration of the haem or protein, or a combination of both. Classical examples of compounds that alkylate the prosthetic haem group and inactivate the enzyme include olefins, acetylenes and dihydropyridines. Chloramphenicol provides perhaps the best example of a drug causing irreversible (suicide) inactivation of CYP through protein modification.

Enzyme inhibition as a cause of drug interactions

Competitive inhibition is typically a rapid and dose-dependent process (Anderson and Graves, 1994; Anderson, 1998). The initial effect usually occurs within 24 h from the addition of the inhibitor, though the time to reach maximal inhibition will depend on the elimination half-lives of the affected drug and of the inhibiting agent. When the inhibitor is withdrawn, restoration of baseline (pre-interaction) conditions is also dependent on the rates of the elimination of the affected drug and of the inhibitor. With non-competitive and uncompetitive inhibition, the time course of the interaction may be more complex, and a significant role may be played by the turnover (re-synthesis) rate of the enzyme.

Inhibitors of drug metabolism usually interfere with only a limited number of isoenzymes and, therefore, they may be used to discriminate between different isoenzymes (Guengerich, 1997b). Compounds acting as inhibitors of different CYPs are listed in Table 5.1. Some potent inhibitors of a given enzyme are substrates of the same enzyme, but this is generally not the case. For example, quinidine is a potent inhibitor of CYP2D6, but it is metabolized by CYP3A4. Inhibition of non-oxidative phase I and conjugating phase II enzymes has also been documented.

Among AEDs, those acting most commonly as enzyme inhibitors are valproic acid and felbamate (Perucca and Richens, 1995). Valproic acid is considered as a broad-spectrum inhibitor of various enzymes. In particular, studies in human liver microsomes demonstrated that, at clinically relevant concentrations, valproic acid competitively inhibits CYP2C9 activity, inhibits only weakly CYP2C19 and CYP3A4, and it has no appreciable effect on CYP2D6 and CYP2E1 (Wen et al., 2001). This is
consistent with clinical evidence that valproic acid may significantly increase the plasma concentrations of CYP2C9 substrates such as phenytoin and phenobarbital (Scheyer, 2002). Studies in human liver microsomes also indicated that valproic acid inhibits EH, which explains its ability to increase the plasma concentration of carbamazepine-10,11-epoxide in carbamazepine-treated patients (Kerr et al., 1989). Valproic acid also has an important inhibitory effect on UGTs, as indicated by its ability to inhibit in vivo the glucuronide conjugation of lamotrigine, lorazepam and zidovudine, as well as the $N$-glucosidation of phenobarbital (Liston et al., 2001). The specific UGT isoform involved in these metabolic reactions is known only for lamotrigine, whose glucuronidation is metabolized by UGT1A4.

Felbamate is a selective inhibitor of CYP2C19 (Glue et al., 1997), which is consistent with the observation that felbamate reduces the clearance and increases the plasma concentration of phenytoin (Fuerst et al., 1988). Moreover, felbamate has been reported to increase the plasma concentrations of phenobarbital (Gidal and Zupanc, 1994), clobazam, carbamazepine-10,11-epoxide (concomitantly with a reduction in plasma carbamazepine levels) and valproic acid (Patsalos et al., 2002): with the possible exception of the increase in carbamazepine-10,11-epoxide, which may be related to induction of carbamazepine metabolism, these interactions are also ascribed to inhibition of the metabolism of the corresponding compounds, though the precise molecular mechanisms have not been elucidated. In the case of valproic acid, there is evidence that the increase in its plasma levels after addition of felbamate can be ascribed at least in part to inhibition of mitochondrial $\beta$-oxidation (Hooper et al., 1996).

Other AEDs may at times act as enzyme inhibitors. Topiramate has been reported to be a modest inhibitor of the activity of CYP2C19 in vitro, though at concentrations higher than those usually found in therapeutic practice (Sachdeo et al., 2002). Whether this mechanism is responsible for the moderate rise in plasma phenytoin concentration which is seen in a small subset of phenytoin-treated patients given topiramate is unclear. Other inhibitors of CYP2C19 are carbamazepine and oxcarbazepine: in particular, CYP2C19 inhibition explains the ability of oxcarbazepine, especially when used at high dosages, to increase by up to 40% the plasma concentrations of phenytoin (Patsalos et al., 2002). Phenobarbital concentrations may also be increased by oxcarbazepine, though to a lesser extent compared with phenytoin. Interestingly, oxcarbazepine is an inducer of UGT and CYP3A4, as demonstrated by its ability to increase the metabolism of lamotrigine and oral contraceptives respectively (Perucca, 2001): this illustrates the important concept that a compound may act as an inducer or as an inhibitor depending on which isoenzyme is being considered. There are also situations where a drug may induce and inhibit the same isoenzyme simultaneously: for example, at low doses phenobarbital tends to induce the metabolism of phenytoin, probably through
induction of CYP2C9 and/or CYP2C19, whereas at higher doses it may competitively inhibit phenytoin metabolism (Patsalos et al., 2002). The extent of these differential interactions may vary across individuals, which may explain the unpredictable and bi-directional changes in plasma phenytoin concentration after addition or removal of phenobarbital therapy.

Most AEDs undergo extensive biotransformation, and their metabolism is, therefore, vulnerable to inhibition by a large number of competitive substrates and enzyme inhibitors.

**In vitro systems for testing drug metabolism and metabolic drug interactions**

The potential for metabolic drug interactions is an important aspect to be considered during the development of new drugs. In the past, most drug interaction studies were performed relatively late in phase II and III studies, and investigations were focused on compounds chosen for their likelihood of concurrent use. Since susceptibility to involvement in drug interactions is an undesirable property of a drug, information on this should ideally be obtained already, in the preclinical phase. In recent years, different in vitro techniques have been developed and have become widely used as screening tools to predict potential drug interactions before a drug reaches the clinical phases of development. The techniques used for in vitro assessments are described concisely in the sections below. For more comprehensive information, the reader is referred to specialized reviews (Ring and Wrighton, 2000).

**Enzyme-based techniques**

Initially, the simplest approach to the in vitro study of drug metabolism was through use of purified enzymes. One could determine whether a drug is a substrate of a specific isoenzyme, and the ability of the drug to inhibit the same isoenzyme can be evaluated by investigating its effect on the in vitro biotransformation of a probe substrate. However, the complexity of the purification techniques required to isolate these enzymes and the need for detergents, lipids and other enzymes (e.g. cytochrome b₅ and P450 reductase) in the incubation system may limit the possible extrapolation of results obtained with purified enzyme systems to the in vivo situation (Ring and Wrighton, 2000).

Recent advances in molecular biology have allowed isolation of cDNA encoding for drug-metabolizing enzymes. In these systems, the cDNA encoding for a specific enzyme is transfected into a cell host (e.g. *Escherichia coli*, yeast, insect cells) and the expressed enzymes can be isolated and utilized in metabolic studies (Ring and Wrighton, 2000). Although recombinant human enzymes are routinely used, they have the same limitations as purified enzymes when trying to extrapolate results to the in vivo situation.
Microsomes or other subcellular fractions prepared from human livers represent a ready source of enzymes responsible for drug metabolism and, therefore, a primary tool for in vitro interaction studies (Ring and Wrighton, 2000). Human liver samples, frozen and stored at approximately $-80^\circ$C, retain their metabolic potential over a long period of time. These microsomal preparations contain the various human cytochromes in proportion to their quantitative representation in human liver in vivo. In these systems, the contribution of a given isoenzyme to the metabolism of a test drug can be assessed by using different approaches such as the investigation of changes in biotransformation rate after addition of a specific inhibitor of that isoenzyme. Likewise, the potential ability of the test drug to act as an enzyme inhibitor can be investigated by assessing its effect on isoenzyme-specific metabolic pathways of probe substrates added in the system. The data obtained with microsomes from human liver may have a greater relevance to the in vivo situation than those obtained through the use of isolated enzyme systems (Ring and Wrighton, 2000). This is mainly due the similarity of the lipid and enzyme environment to the in vivo situation. It should be noted that microsomal fractions may also be prepared from tissues other than the liver, in order to investigate extrahepatic drug metabolism.

**Cell-based techniques**

The two cell-based systems most commonly utilized to study drug metabolism include cultured hepatocytes and liver slices. The use of an intact cell system is, at least in theory, ideal because of its greater physiologic relevance to the intact organism, as it contains both phase I and II enzymes along with the appropriate cofactors found in vivo. A major advantage of this system, with special reference to primary cultures of human hepatocytes, is the possibility of studying the induction potential of a test compound, an effect which cannot be evaluated in in vitro enzyme systems (Lin and Lu, 1998; Ring and Wrighton, 2000).

Primary cultures of human hepatocytes as a tool to predict enzyme-inducing potential at the preclinical level are advantageous over the use of animal models in vivo because interspecies differences in substrate specificity and regulation of expression preclude extrapolation of animal data to humans. On the other hand, a drawback in the use of primary hepatocytes is the requirement for fresh human tissue.

**Prediction of metabolic drug interactions based on in vitro data**

Two complementary approaches have been developed to predict potential drug interactions in vivo based on in vitro data: (a) identification of the enzymes (CYP isoforms or other drug-metabolizing enzymes) responsible for the biotransformation
of a test drug; (b) determination of the potential of the test drug to inhibit or
induce the activities of the various drug-metabolizing enzymes. The first approach
allows prediction of interactions affecting the metabolism of the test compound
(i.e. interactions affecting the test drug as a substrate), the second allows prediction
of any effect that the test compound may have on the metabolism of other drugs
(i.e. interactions where the test drug may act as an inducer or an inhibitor).

The test drug as a substrate (target for interactions)
Prediction of interactions that may affect the test drug requires (a) knowledge of
the enzyme systems responsible for its biotransformation, and (b) knowledge of
the influence of other drugs on such enzyme systems.

Identification of the enzymes responsible for the metabolism of the test drug
Identification of the isoenzyme(s) responsible for the metabolism of a given drug
is the major prerequisite for rational prediction of metabolic drug interactions. To
this purpose, however, it is also important to determine the relative contribution of
each isoenzyme, and related metabolic pathways, to the overall elimination of that
drug in vivo. Apart from prediction of drug interactions, this information may be
used to anticipate the possible occurrence of genetic polymorphisms (in the case of
involvement of CYP2D6, CYP2C9 or CYP2C19), as well as the likelihood of sub-
stantial extrahepatic contributions to drug metabolism, as most frequently seen
with CYP3A substrates that may be biotransformed in part in the gastrointestinal
mucosa (Dresser et al., 2000).

Information on the CYP isoforms responsible for the oxidative metabolism can
be obtained by using a general in vitro strategy (Lin and Lu, 1998; Ring and
Wrighton, 2000). This may involve assessment of: (a) catalytic activity in human
liver microsomes; (b) correlation of this activity with markers for known CYP iso-
forms; (c) catalytic activity in cDNA-based vector systems; (d) catalytic activity in
purified enzymes; (e) effects of selective inhibitors; and (f) immunoinhibition with
monoclonal or polyclonal antibodies against various CYP isoforms. Each approach
has its advantages and disadvantages, and a combination of approaches is usually
required.

Usually, studies begin with a kinetic analysis of the in vitro formation of
metabolites in human liver microsomes. These analyses allow determination of the
oxidative metabolite(s) of the test drug, and of the range of enzymes that may be
able to form a particular metabolite (Lin and Lu, 1998). The formation of each of
the metabolites is determined over a wide range of substrate concentrations. The
apparent kinetic parameters such as $K_M$ (Michaelis–Menten constant, representing
the concentration of the substrate that results in half-maximal velocity) and $V_{max}$
(maximal velocity of the reaction) for the enzyme(s) responsible for the formation
of a particular metabolite may then be calculated. In this system, a first indication of the isoenzyme(s) involved in the production of the metabolite may subsequently be obtained through studies correlating the formation rate of the metabolite to the activities of various enzyme isoforms in microsomes from different individuals. Isoform-selective catalytic activities for the major CYPs involved in drug metabolism are reported in Table 5.1. Identification of the isoenzyme(s) responsible for the formation of the metabolite may also be obtained by using cDNA expressed enzymes or purified enzymes. Another approach to determine the role of the various drug-metabolizing enzymes is through use of isoenzyme-specific inhibitors. The capacity of a relatively specific chemical inhibitor (Table 5.1) to inhibit the biotransformation of a given drug to its initial metabolite constitutes evidence supporting the participation of the corresponding isoenzyme. A similar approach to confirm the role of specific enzymes makes use of antibodies with relatively specific inhibitory activity against individual isoenzymes.

In order to estimate the contribution of a given CYP isoform to total drug clearance, the information obtained in vitro must be combined with the results from preliminary in vivo quantitative metabolic studies (sometimes carried out with radiolabeled drug) that measure the fraction of dose eliminated by each pathway (including renal excretion).

Predicting interactions affecting the metabolism of the test drug

Once the contribution of different isoenzymes to the metabolism of a given drug has been elucidated, prediction of interactions affecting the clearance of that drug can easily be made. This prediction is based on existing knowledge of the influence that other drugs have on the activity of the same isoenzymes. Moreover, if the influence of a potential interfering agent is not known, this can be easily tested in the in vitro systems described above.

The main isoenzymes responsible for the metabolism of most AEDs have been identified (Riva et al., 1996; Anderson, 1998) and available data are summarized in Table 5.2. Carbamazepine may serve as an example of how this information can be applied to prediction of drug interactions (Levy, 1995). Identification of CYP3A4 as the primary catalytic enzyme for the main clearance pathway of carbamazepine allows the anticipation that any compound known to inhibit CYP3A4 activity at therapeutically meaningful concentrations has the potential to decrease carbamazepine clearance and to increase plasma carbamazepine concentration at steady state. The validity of this prediction is supported by a large bulk of experimental and clinical studies. For example, different compounds known to inhibit CYP3A4 activity such as the calcium-channel blockers diltiazem and verapamil, the macrolide antibiotics troleandomycin and erythromycin, the antidepressants viloxazine and nefazodone, and the antifungals ketoconazole and fluconazole, have been reported
Table 5.2 Elimination pathways for the major AEDs. Fraction of absorbed dose cleared by metabolic and renal elimination refers to average values described for patients on monotherapy. CYP isoforms responsible for metabolic clearance of each drug are shown in brackets (bold characters identify enzymes involved in metabolic pathways responsible for a major proportion of total drug clearance)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fraction cleared by</th>
<th>CYPs</th>
<th>UGTs</th>
<th>Other enzymes</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>75% (CYP3A4, CYP2C8, CYP1A2)</td>
<td>15%</td>
<td>Negligible</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>70% (CYP3A4)</td>
<td>Nil</td>
<td>Negligible</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>15% (CYP3A4, CYP2E1)</td>
<td>10%</td>
<td>25% (hydrolysis)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Nil</td>
<td>&gt;80%</td>
<td>Negligible</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Nil</td>
<td>Nil</td>
<td>30% (hydrolysis)</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>&lt;5%</td>
<td>70%</td>
<td>Nil</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>30% (CYP2C9, CYP2C19, CYP2E1)</td>
<td>Negligible</td>
<td>25% (N-glucosidation)</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90% (CYP2C9, CYP2C19)</td>
<td>Nil</td>
<td>Negligible</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>&gt;95% (CYP3A4)</td>
<td>Nil</td>
<td>Not identified</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>&lt;25%</td>
<td>Nil</td>
<td>Not known</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>10% (CYP2C9, CYP2A6, CYP2B6)</td>
<td>40%</td>
<td>35% (β-oxidation)</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>50% (CYP3A4, CYP2C19, CYP3A5)</td>
<td>Negligible</td>
<td>20% (acetylation)</td>
<td>&lt;30%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Data refer to the active monohydroxycarbazepine derivative (MHD). Oxcarbazepine is transformed to MHD by ketoreduction catalyzed by cytosolic arylketone reductase.

\(^b\)Fractions metabolized through various pathways are dose dependent.
to cause a clinically significant elevation in plasma carbamazepine concentration (Perucca, 1982; Patsalos et al., 2002). Similarly, it is known that CYP3A4 activity is stimulated by enzyme-inducing AEDs such as phenobarbital and phenytoin: this allows prediction of the ability of these compounds to increase carbamazepine clearance and to reduce plasma carbamazepine concentration in patients with epilepsy (Spina et al., 1996).

There can be many other examples of how knowledge of the isoenzymes responsible for the metabolism of an AED can be used to predict interactions affecting the plasma clearance of that drug in vivo. In the case of phenytoin, which is a substrate of CYP2C9 and CYP2C19, clinically documented examples of interactions consistent with inhibition of CYP2C9 are those caused by amiodarone, phenylbutazone, propoxyphene, miconazole and valproic acid, while interactions probably due to inhibition of CYP2C19 are caused by ticlopidine, fluoxetine, omeprazole and felbamate (Raguenau-Majlessi et al., 2002).

When utilizing only in vitro findings to predict in vivo changes in the pharmacokinetics of the affected drug, it is important to remember that the extent of inhibition or induction of a given pathway as assessed on the basis of in vitro data does not necessarily imply that the total clearance of the affected substrate in vivo will be affected to the same extent. In fact, any change in clearance of the affected substrate will also be influenced by other factors, including the degree of inhibition or induction of the affected pathway in vivo (which may not necessarily correspond to the in vitro situation, due to intervention of confounding variables); the contribution of the affected pathway to the overall elimination of the substrate; the pharmacokinetic characteristics of the substrate and its route of administration; any influence that the interfering drug may have on alternative metabolic pathways of the substrate. A more detailed discussion of how these factors impact on the prediction process, including potential pitfalls, is provided in the section 'Crucial factors in predicting in vitro–in vivo correlations'.

**The test drug as a cause of interactions affecting the metabolism of other drugs**

The first step in predicting what effect a test compound may have on the metabolism of other drugs consists in the investigation of the influence of that compound on the activity of the various drug-metabolizing isoenzymes. This information is then interpreted by taking into account existing knowledge on the range of drugs which are substrates of the affected enzymes.

**Assessment of the influence of the test drug on the activity of drug-metabolizing isoenzymes**

In vitro approaches similar to those described in the section 'Identification of the enzymes responsible for the metabolism of the test drug' are applicable to the evaluation of drugs as potential inhibitors of specific enzyme isoforms. Using human
liver microsomes or individual enzymes, a series of drugs and/or their metabolites can be screened relatively quickly to determine quantitatively their potency in inhibiting reactions considered to reflect specifically the activity of individual enzyme isoforms. One approach involves the use of a fixed concentration of the probe substrate incubated with variable concentrations of the potential inhibitor (Greenblatt et al., 1998). Evaluation of the decrease in metabolite formation rate as a function of the inhibitor’s concentration allows calculation of the 50% inhibitory concentration (IC$_{50}$), i.e. the inhibitor’s concentration at which the reaction rate is reduced by 50%. IC$_{50}$ values are independent of the specific biochemical mechanism of inhibition and, therefore, they are suitable for comparing the relative potency of a series of inhibitors. On the other hand, when inhibition is competitive, IC$_{50}$ values depend on substrate concentration: therefore, they cannot be directly applied to in vitro–in vivo scaling models, except when inhibition is established as having a non-competitive mechanism. A second approach to the assessment of inhibitory interactions is based on calculation of the inhibition constant ($K_i$), which reflects inhibitory potency in a reciprocal fashion (Segel, 1975). Determination of $K_i$ is more time and labour consuming, since it requires the study of multiple substrate concentrations and multiple inhibitor concentrations. $K_i$ is model dependent, since it depends upon the specific mechanism of inhibition, which may not be established. However, $K_i$ is independent of substrate concentration and can be used under some defined conditions for the quantitative in vitro–in vivo scaling of drug interactions. Although $K_i$ is less than or equal to IC$_{50}$ as a general rule, $K_i$ will be equal to IC$_{50}$ if inhibition is non-competitive, or if inhibition is competitive and the substrate concentration is far below the reaction $K_M$ (Segel, 1975). Both $K_i$ and IC$_{50}$ provide similar estimates of relative inhibitory potency for a series of inhibitors of a specific reaction.

As discussed in the section ‘Cell-based techniques’, in vitro systems can also be used to estimate enzyme-inducing potential. These experiments are far more complex, time consuming and expensive, as they involve the use of primary cultures of hepatocytes (Li et al., 1997). Evaluation of changes in the activity of specific isoenzymes can be obtained by applying the techniques described in the sections above.

Predicting effects of the test drug on the metabolism of other drugs

The effects of the major AEDs on various drug-metabolizing enzymes are summarized in Table 5.3. Once it has been established that an AED inhibits or induces the activity of a given isoenzyme, then one can predict that the metabolism of substrates of the same isoenzyme will be correspondingly affected. A list of substrates of individual CYP isoenzymes is reported in Table 5.1: for example, if a drug inhibits CYP1A2, then one can predict that the CYP1A2-mediated pathways of substrates such as amitryptiline, fluvoxamine, mirtazepine, clozapine, olanzapine,
haloperidol, theophylline, caffeine and phenacetin will be inhibited. The extent of inhibition will depend on the inhibiting potency and on the concentration (dosage) of the inhibitor, but the concentration of the substrate may also play a role. Similar considerations apply to predictions of drug interactions mediated by enzyme induction.

A good correlation between the ability to inhibit various CYPs in vitro and the in vivo inhibitory interaction profile has been established for a number of AEDs,

### Table 5.3 Effects of AEDs on the most common drug-metabolizing enzyme systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Enzymes involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Inducer</td>
<td>CYP1A2, CYP2B6, CYP2C, CYP3A4 Microsomal EH UGT</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>None (?)</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Inhibitor</td>
<td>CYP2C19 β-oxidation CYP3A4</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Negligible</td>
<td>UGT (weak autoinduction)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Inhibitor</td>
<td>CYP2C19 (weaker induction compared with carbamazepine)</td>
</tr>
<tr>
<td>Phenobarbital/</td>
<td>Inducer</td>
<td>CYP1A2, CYP2B6, CYP2C, CYP3A Microsomal EH UGT</td>
</tr>
<tr>
<td>primidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Inducer</td>
<td>CYP1A2, CYP2B6, CYP2C, CYP3A4 Microsomal EH UGT</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Inhibitor</td>
<td>CYP2C19 (weak inhibition) CYP3A4 (weaker induction compared with carbamazepine)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Inhibitor</td>
<td>CYP2C9 Microsomal EH UGT</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>None (?)</td>
<td></td>
</tr>
</tbody>
</table>
including valproic acid (Scheyer, 2002) and felbamate (Glue et al., 1997). As discussed in the section ‘Predicting interactions affecting the metabolism of the test drug’, it should be noted that the predicted extent of inhibition or induction of a given pathway does not necessarily imply that the total clearance of the affected substrate in vivo will be affected to the same extent. In vivo changes may be influenced by a number of variables such as the action of other metabolites, the accessibility of the inhibitor or inducer to the enzyme, the contribution of the affected pathway to the overall elimination of the affected drug, the pharmacokinetics characteristics of the affected drug and its route of administration, and any influence that the interfering drug may have on alternative metabolic pathways. These factors are discussed concisely in the section below.

**Crucial factors in predicting in vitro–in vivo correlations**

Information on the drug-metabolizing enzyme systems and their substrates, inhibitors and inducers may be of a great value for clinicians to anticipate and eventually avoid potential interactions. Co-administration of two substrates of the same enzyme, or co-administration of a substrate with an inhibitor or an inducer, entails the possibility of a drug interaction. As a consequence, plasma concentrations of the co-administered drugs may be increased or decreased, resulting in clinical toxicity or diminished therapeutic effect. Dosage adjustments may then be required to avoid adverse effects or therapeutic failure. However, not all theoretically possible drug interactions that are predicted from in vitro studies will occur in vivo, and some may not be clinically significant anyway. As suggested by Sproule et al. (1997), different aspects including drug-related, patient-related and epidemiological factors must be taken into account when evaluating the potential occurrence, extent and clinical significance of a metabolic drug interaction.

With respect to prediction of whether an interaction will occur in the clinical situation, it should be pointed out that, although it is relatively easy to assess a drug interaction in vitro, the correct interpretation and extrapolation of in vitro data to the in vivo situation may be complicated by various factors and require a good understanding of pharmacokinetic principles (Bertz and Granneman, 1997; Lin and Lu, 1998; Levy and Trager, 2000). One of the most important factors to be considered is whether in vitro drug interaction studies have utilized clinically relevant concentrations of inhibitor (or inducer) and substrate. While the use of supratherapeutic concentrations may obviously result in a drug interaction in vitro but not in vivo, it may not be easy to determine whether a given range of concentrations tested in vitro is therapeutically relevant. For example, reference to drug concentrations measured at steady state in patients receiving therapeutic dosages may not provide an adequate estimate of the concentration of the interacting (or affected)
drug at the site of metabolism in vivo, due to the confounding effect of binding to proteins, transport systems and presence of other interfering endogenous and exogenous metabolites. A potentially important factor affecting in vitro drug interaction studies is represented by the protein concentration of microsomes. The $K_i$ values of an inhibitor may be overestimated at high microsomal protein concentrations as a result of the depletion of the inhibitor by non-specific binding to microsomal proteins and/or microsomal metabolism. Moreover, the specificity of chemical inhibitor probes is of concern for the interpretation of in vitro studies. No inhibitory probe is completely specific for its corresponding isoform and all ultimately become non-specific at high concentrations. In view of these considerations, no prediction can be expected to be 100% accurate, and both false positive and false negatives need to be anticipated.

While the above limitations should be understood, it is nevertheless true that consideration of a number of factors is essential in maximizing the probability of making accurate predictions about the occurrence, and potential clinical importance, of specific drug interactions. These factors will be briefly discussed in the remaining part of this chapter.

**The therapeutic index of the substrate**

In general, interactions affecting medications with a narrow therapeutic index (e.g. phenytoin, anticoagulants, immunosuppressants or anticancer drugs) are more likely to be clinically relevant than interactions affecting drugs with a broad margin of safety (e.g. gabapentin, penicillin). In fact, given the same degree of inhibition or induction, any change in the plasma levels of the affected substrate is more likely to result in toxic or subtherapeutic values if the substrate has a narrow therapeutic index. Of course, the importance of the interaction will also vary depending on whether at baseline the concentration of the affected agent was near the threshold associated with toxicity or therapeutic failure.

**Extent of metabolism of the substrate through the affected enzyme**

For interactions involving inhibition of drug metabolism, a clinically important change in the plasma concentration of the affected drug can only be expected if the inhibited pathway contributes to a major extent to total drug clearance. For example, inhibition of a pathway which accounts for only 10% of total drug clearance will only increase the concentration of the affected drug by no more than 10%. It should be noted that the relative contribution of a given metabolic pathway to the overall elimination of a drug may vary across individuals, an observation which may explain why some interactions show considerable interindividual variability in their occurrence or extent (Gatti *et al.*, 2001). In some cases, the relative contribution of a given isoenzyme to total drug clearance is concentration dependent.
A good example for this is phenytoin, whose major metabolic pathway, $p$-hydroxylation, is mediated by CYP2C9 and, to a lesser extent, CYP2C19 (Bajpai et al., 1996). At high concentration, the activity of CYP2C9 becomes saturated and the contribution of CYP2C19 to the metabolism of the drug will correspondingly increase. Therefore, a significant impact of CYP2C19 inhibitors on phenytoin disposition will only be expected to occur at higher concentrations, when the CYP2C19-mediated pathway becomes increasingly important for the elimination of the drug.

For interactions involving enzyme induction, the situation is totally different from that described for enzyme inhibition. In fact, there is theoretically no limit to the increase in the efficiency of a given metabolic pathway when the corresponding isoenzyme(s) have been induced. In other words, enzyme induction could transform an initially minor metabolic pathway into a major contributor to the overall elimination of the drug, with a consequent important increase in total drug clearance.

The principles summarized above are well illustrated by the metabolic interactions described for felbamate and topiramate. Since CYP3A4 plays only a minor role in the metabolism of felbamate, inhibitors of this isoform would be expected to have only minimal effects on the overall clearance of this drug and, in line with this prediction, felbamate pharmacokinetics have been found not to be significantly affected by the potent CYP3A4 inhibitor erythromycin (Glue et al., 1997). On the other hand, the total plasma clearance of felbamate is significantly increased and its plasma concentrations are significantly decreased by concomitant treatment with the CYP3A4-inducers phenytoin, phenobarbital and carbamazepine. A similar situation is observed with topiramate, a drug which in healthy subjects is primarily excreted unchanged in urine. Because metabolism is of minor importance in the overall clearance of topiramate, no significant changes in its plasma concentration are expected when an enzyme inhibitor is added for patients receiving topiramate monotherapy. On the other hand, metabolic elimination becomes an important determinant of topiramate clearance in patients treated with enzyme-inducing AEDs, an observation which explains the ability of the latter to decrease plasma topiramate concentration by 40–50% (Perucca and Bialer, 1996). It should be noted that, theoretically, the plasma concentration of felbamate and topiramate could be significantly affected by an enzyme inhibitor only when the latter is added on as a third agent in a patient who is already taking an enzyme inducer. This is because it is only in enzyme-induced patients that the contribution of metabolism to the overall clearance of these drugs becomes clinically significant.

**Role of metabolites**

A factor to be considered is whether metabolites have any enzyme inducing or inhibiting effects independent of those of the parent drug. For example, if a
metabolite has an inhibiting effect on a given isoenzyme that is not shared by the parent drug, in vitro experiments designed to test the enzyme-inhibiting potential of the parent drug may fail to identify a clinically important interaction.

As discussed above, many metabolites are biologically active and this needs to be considered when predicting the clinical consequence of a drug interaction. If the affected drug has a pharmacologically active (or toxic) metabolite, enzyme inhibition may paradoxically result in decreased pharmacological (or toxicological) effect, while the reverse will be true for enzyme induction. It is also important to consider what influence the interaction is expected to have on the subsequent biotransformation of the metabolites.

**Pharmacokinetic characteristics of the drug and route of drug administration**

An example of how pharmacokinetic characteristics can influence the consequences of metabolic drug interactions has already been provided in the section ‘Extent of metabolism of the substrate through the affected enzyme’ when discussing the implications of the concentration-dependent pharmacokinetics of phenytoin.

An even more important aspect to be considered is whether the affected drug shows a low or a high extraction ratio in the organ (usually the liver) responsible for its metabolism. In the case of highly extracted drugs, clearance is mainly determined by the blood flow through the eliminating organ, and changes in enzyme activity will have little or no effect on their pharmacokinetics after parenteral administration. However, if metabolism takes place mainly in the liver or in the gut, enzyme induction or inhibition can have a marked effect on the first-pass extraction of these agents and, hence, on their oral bioavailability. These considerations provide an explanation for the marked reduction in the bioavailability of high clearance drugs such as ethinylestradiol (Perucca, 1982), lidocaine (Perucca and Richens, 1979) and nisoldipine (Michelucci *et al.*, 1998) in patients taking the enzyme-inducers phenobarbital, carbamazepine or phenytoin.

The pharmacokinetics of drugs which show a low metabolic clearance are not influenced by changes in blood flow, and their plasma concentration is largely determined by drug-metabolizing enzyme activity irrespective of the route of intake. Therefore, enzyme induction and inhibition are expected to affect the steady-state plasma concentration of these drugs after both parenteral and oral administration. For a detailed discussion of these principles, the reader is referred to the seminal work of Wilkinson and Shand (1975).

**Complex or biphasic interactions**

Enzyme induction and inhibition are not mutually exclusive and may occur at the same time. The ability of a given compound to act as an inducer and as an inhibitor
at the same time provides an explanation for the inconsistent and apparently contradictory nature of certain drug interactions. As discussed above, for example, phenobarbital may either decrease or increase the plasma concentration of phenytoin depending on whether induction or inhibition of phenytoin metabolism prevails in an individual patient (Perucca, 1982). Even more complex is the interaction between phenytoin and warfarin. When phenytoin is started in a patient stabilized on warfarin therapy, phenytoin may initially competitively inhibit the metabolism of warfarin because both phenytoin and S-warfarin are substrates for CYP2C9 and phenytoin has a $K_M$ (and therefore a $K_i$) within its therapeutic range. After an initial increase, the plasma concentration of S-warfarin will then decline within 1–2 weeks because of CYP2C9 induction (Cropp and Bussey, 1997).

Even more complex situations may be observed when other mechanisms of interaction, e.g. altered gastrointestinal absorption, drug displacement from binding sites, or pharmacodynamic interactions, occur simultaneously with changes in enzyme activity. Other complex situations arise in patients receiving combinations of three or more drugs, and in this case direct and indirect interactions may become difficult to predict. At times, interactions may actually cancel out reciprocally: for example, the clearance of lamotrigine is markedly enhanced by co-administration of enzyme-inducing AEDs (phenobarbital, carbamazepine and phenytoin) and inhibited by valproate. However, patients receiving lamotrigine in a triple therapy regimen that includes valproate and an enzyme inducer show lamotrigine clearance values comparable with those observed in patients on lamotrigine monotherapy (Jawad et al., 1989).

Other sources of variability

There is a large intersubject variability in the extent and clinical relevance of metabolic drug interactions. As discussed above, enzyme induction and inhibition are usually dose dependent, and differences in dosage (or plasma concentration) of the interfering drug are important in determining the occurrence or extent of a drug interaction. Additional sources of variability relate to interindividual differences in the contribution of specific metabolic pathways to overall drug clearance. Age has also been reported to affect response to drug interactions: for example, it has been suggested that the elderly may be less sensitive to enzyme induction (Twum-Barima et al., 1984), even though in a recent study auto- and heteroinduction of carbamazepine metabolism was not found to differ between elderly patients and younger adults (Battino et al., 2003). The role of confounding factors (e.g. the additional influence of enzyme inducers or inhibitors found in the diet or in voluc-tuary substances) also varies considerably across individuals.

In patients receiving drugs metabolized by a polymorphic enzyme, the effects of inhibitors or inducers may vary between phenotypes/genotypes. EMs are generally
more susceptible to enzyme inhibition or induction than PMs. For inhibition, this has been most clearly documented for CYP2D6: interactions caused by potent inhibitors of this isoform, i.e. quinidine, are not observed in PMs, who show a genetically determined lack of functional CYP2D6 in their liver (Steiner et al., 1987). Likewise, PMs for CYP2C19 and CYP2C9, which play a role in the metabolism of phenytoin, are not expected to be vulnerable to the inhibition of phenytoin metabolism caused by selective inhibitors of the corresponding enzymes. More complex effects can be expected when the genotype/phenotype influences susceptibility to drug interactions in an indirect way: for example, the enzyme-inducing effects of 40 mg/day omeprazole (a CYP2C19 substrate) on CYP1A2 activity only occurs in PMs for CYP2C19, because only these subjects achieve plasma omeprazole concentrations which are sufficiently high to cause enzyme induction (Rost et al., 1992).

For any given extent of interaction, clinical consequences also vary widely across individuals. As discussed above, interactions are more likely to be clinically significant when the plasma concentration of the affected drug at baseline is closest to the threshold for toxicity or therapeutic failure. Pharmacodynamic factors affecting response to any drug concentration are also important. Elderly patients in general are more prone to adverse drug interactions, not only because they more frequently receive multiple drug therapy but also because they may show increased pharmacodynamic sensitivity to drugs.

Conclusions

Metabolic drug interactions may have important clinical consequences. In the case of AEDs, these interactions are particularly common, due to the fact that many of these agents are potent inducers (or in some case, inhibitors) of the drug-metabolizing enzymes, and they are usually administered chronically, often in combination therapy. In recent years, an improved understanding of the nature of the main isoenzymes responsible for drug metabolism, coupled with advances in methodology for the in vitro assessment of metabolic reactions and interactions, has resulted in major breakthroughs in our ability to predict the occurrence and the in vivo implications of drug interactions. While the methodology still requires some refinement to improve the predictive power, available knowledge is already applied successfully not only in drug discovery (through design and selection of new agents devoid of undesirable interaction potential) and in drug development (though rational identification of drug interactions to be assessed in the clinical setting), but also in making informed decisions when adding or withdrawing co-medications in routine clinical practice.


Influence of food and drugs on the bioavailability of antiepileptic drugs

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Introduction
Whenever two or more agents are used in combination the potential for interactions can occur. These interactions can occur at the pharmacodynamic and/or pharmacokinetic level. Pharmacokinetic interactions are by far the most frequent and result in the modification of blood or tissue drug concentration as a consequence of alterations in absorption, distribution, metabolism, or elimination of a drug.

Drugs with a narrow therapeutic range or low therapeutic index are more likely to be associated with clinically important interactions. As far as antiepileptic drugs (AEDs) are concerned, they may interact with each other when used in combination therapy, and with other non-epilepsy-related drugs or with over-the-counter medications. Furthermore, food and many excipient components of pharmaceutical formulations may also interact with AEDs. This chapter deals with interactions which occur before (pharmaceutical interactions) and during (pharmacokinetic interactions) absorption.

General principles
Since many AEDs are sparingly soluble in aqueous solutions, they are sensitive to any effects that alter solubility, dissolution, or gastrointestinal motility. The delivery of drugs into the circulation may be altered by physicochemical interactions that occur prior to absorption. For example, drugs may interact in an intravenous solution to produce an insoluble precipitate or may be damaged by light (Figueiredo et al., 1993). Moreover, in the gut, drugs may chelate with metal ions or adsorb to resins. Thus the absorption of a particular drug is profoundly influenced by a great number of factors, which can be classified as follows:

(a) chemical characteristics and formulation,
(b) food and fluid intake,
Absorption, regardless of the site, is dependent upon drug solubility. Drugs administered in an aqueous solution are more rapidly absorbed than those administered in an oily solution, a suspension, or in a solid form because they mix more readily with the aqueous phase at the absorptive site. For those drugs administered as a solid form, the rate of dissolution may be the limiting factor in their absorption.

Large fluid intake results in faster emptying of the stomach due to the distension of the stomach wall (Deutsch et al., 1991). Thus, a drug that is ingested with large volume of fluid will travel faster into the small intestine, ensuring a better and more complete absorption.

Whilst the effect of large fluid volume on the absorption of a drug is predictable, the effect of food is unpredictable. As a general rule, after the ingestion of solid food, the emptying time of the stomach is decreased and intestinal motility and splanchnic blood flow are increased. However, an increase in the extent of drug dissolution in the stomach, as a result of meal prolongation of gastric residence time, does not appear to contribute substantially to fed-state increases in drug plasma concentrations that are observed when a lipid meal is co-administered (Miles et al., 1997). One hypothesis is that the solid meal may enhance the pancreatic secretion thus providing a greater fluid volume for drug dissolution in the small intestine (Miles et al., 1997).

Several drugs can also interfere with the physiologic conditions and function of the gastrointestinal tract and therefore alter the absorption of other drugs. These interactions might be the consequence of altered pH, decreased or increased motility, toxic effects on mucosa and changes in splanchnic blood flow. Therefore, antacids could raise the pH of gastric juice; metoclopramide and other gastrokinetic drugs (cisapride and domperidone) accelerate stomach emptying; propantheline retards stomach emptying; laxative agents decrease the intestinal transit time; cytostatic agents and antibiotics can damage the intestinal mucosa or the normal bacterial flora. Although all of these changes may result in a modified rate and/or extent of absorption, it is not possible to predict whether or not the interaction will be of clinical significance.

Another mechanism of interaction is via the cytochrome P450 (CYP) isoenzymes that are present in the gut and which contribute to the first-pass metabolism of some drugs. For instance, the isoenzyme CYP3A4 is abundant in the gut and can be stimulated by carbamazepine, phenytoin, phenobarbital and primidone thus reducing the plasma concentrations of drugs that are metabolized by CYP3A4. In contrast, CYP3A4 can be inhibited by acetazolamide, macrolide antibiotics, isoniazid, metronidazole, certain antidepressants, verapamil, diltiazem, cimetidine, danazol and
propoxyphene (Spina et al., 1996), increasing plasma concentrations of drugs that are metabolized by CYP3A4.

Disease states also influence absorption of drugs: in diseases accompanied by decreased motility of the stomach the absorption of drugs is generally delayed or reduced, while in diseases with faster gastric emptying absorption is enhanced. Subjects with an ileojejunal bypass are likely to require increased oral dosages (e.g. phenytoin) to achieve an optimal plasma concentration (Kennedy and Wade, 1979). When blood flow is reduced, as can occur in cardiac failure or shock, or after drugs, the rate of absorption is generally diminished, although the extent is unpredictable. In contrast, increased blood flow may serve to augment absorption.

On the other hand, if optimizing drug therapy aims at achieving and maintaining therapeutic and safe drug concentrations, the sustained release formulations can be useful. The sustained release formulations are designed to be absorbed by an efficient gastrointestinal system that is not limited to certain sites along the gastrointestinal tract. Nevertheless, in the gastrointestinal tract some interactions can occur, namely with drugs which modify intestinal motility. Thus it is possible for all the drug dose, which is encapsulated in the sustained release formulation, to be released at once through some accidental chemical or physiological mechanism. In this setting, the patient could be in danger of a drug overdose (Bialer, 1992). If the drug has a long half-life the probability of interactions during absorption is lower, as was verified for topiramate.

Regarding the formulation and administration of AEDs by the rectal route, there are only a few studies. Generally, drug administration by the rectal route is not acceptable to patients, particularly since absorption can be interrupted by defaecation (de Boer et al., 1982).

Intramuscular drug absorption can be slow, erratic and incomplete, and this has been particularly demonstrated for phenytoin (Tuttle, 1977). Factors which play a role in the bioavailability of these medications include the water solubility of the drug, dispersion of the injected solution and blood flow at the muscle site.

Finally, chronovariability in absorption–elimination parameters (such as peak concentration and peak time) has been observed for many AEDs. Sometimes these changes had been attributed to interactions with food or drugs. The fasting-induced increase in hepatic glucuronidation during the night and the relative inactivity of the gut during this period may explain variations in circulation plasma drug concentrations (Chaudhary et al., 1993). Loiseau et al. (1982) found diurnal variations in steady-state plasma concentrations of valproic acid, when administered by the oral route. Similar findings were observed by Yoshiyama et al. (1989) who reported that $C_{\text{max}}$ tended to be higher and $T_{\text{max}}$ shorter in the morning than in the evening. Such circadian variations of pharmacokinetic parameters have also been shown for carbamazepine (Bruguerolle et al., 1981) but not for phenytoin (Petker and Morton, 1993).
Interactions with the established AEDs

Phenytoin

Phenytoin is the most studied of the AEDs, principally because it has been in use the longest. Much of the knowledge about this drug may be applied to other AEDs. Phenytoin, a weak acid with a pKa of 8.3, is practically insoluble in water. The salt is readily soluble in water but in the acidic medium of the stomach it precipitates after dissolving (Levy, 1976). In relation to the parenteral formulation of phenytoin, despite the fact that this phenytoin salt is water soluble, it precipitates in a large-volume, glucose-containing fluid.

The factors influencing the absorption rate are the particle size, nature of the filler, and whether the free acid or the sodium salt of phenytoin is the active ingredient. Thus, the rate of absorption varies considerably among dosage forms. Numerous studies (Cacek, 1986) have shown that phenytoin products from different manufacturers vary in absorption rate and differ in the time to reach maximum concentration, even if the area under the curve (AUC) is adequate. Many generic preparations are more rapidly absorbed and may produce an intolerable fluctuation in the plasma phenytoin concentration. In fact, differences in absorption significant enough to be associated with clinical toxicity have occurred with changes in the excipient (Bochner et al., 1972; Carter et al., 1981) – for instance, when calcium sulfate dihydrate was replaced by lactose, since the calcium compound interferes with phenytoin absorption. Therefore, changes in dosage form or manufacturer should be avoided once a patient’s dosage requirements have been established, as a relatively small decrease or increase in bioavailability can greatly alter the steady-state plasma concentration during chronic administration.

Phenytoin suspensions of the acid have limited clinical utility for two reasons. First, unless well dispersed, precipitation of the drug in the bottle gives rise to doses lower-than-expected initially and higher-than-expected as the container is emptied. Second, the usual methods for measurements of liquids, especially with teaspoons, are inexact. When the phenytoin suspension is put into a unit-dose package, it is important to state on the label whether or not rinsing of the container is needed to ensure proper delivery of the intended dose.

The time to reach the maximum phenytoin plasma concentration after a single oral dose increases with the dose – the greater the dose, the longer the time to reach the peak (Tozer and Winter, 1990). The greatly increased peak time with dose is probably a consequence of two mechanisms. One is the relatively low solubility, slow dissolution and continued absorption of the drug; the other is the capacity-limited metabolism that is associated with phenytoin.

Burstein et al. (2000) reported that the absorption of phenytoin from polyethylene glycol rectal suppositories in healthy subjects is highly variable and unpredictable. Thus, this formulation is not recommended.
Food effect on phenytoin absorption

Food has been found to have variable but modest, usually enhancing, effects on phenytoin absorption (Cacek, 1986). The mechanisms include increased phenytoin dissolution in the stomach, saturation of the first-pass mechanisms, and increased splanchnic blood flow (Melander et al., 1979). High-fat meals appear to increase phenytoin bioavailability (Sekikawa et al., 1980), probably due to a combination of stimulation of bile flow and accelerated dissolution of phenytoin particles or by the delay of the gastric emptying time caused by the fat intake (Hamaguchi et al., 1993).

A protein-rich diet had the same effect on phenytoin acid but not on the sodium salt (Kennedy and Wade, 1982). Food may also enhance the delivery of phenytoin from prodrug formulations (e.g. 3-pentanonyloxymethyl-5,5-diphenylhydantoin and 3-octanoyloxymethyl-5,5-diphenylhydantoin; Stella et al., 1999).

Grapefruit juice, which inhibits the intestinal CYP3A4, does not affect the oral bioavailability of phenytoin (Kumar et al., 1999). A possible explanation for this may relate to the fact that only a small amount (dose) of grapefruit juice was ingested by the subjects investigated in the study and also because phenytoin is not a substrate of CYP3A4.

The absorption of phenytoin is significantly impaired when given concurrently to epileptic patients receiving continuous nasogastric feeds (nutritional formulae). Substantial reduction in steady-state phenytoin plasma concentration have been reported in neurosurgery patients and in normal subjects (Bauer, 1982; Prichard et al., 1987). The most likely mechanism is a reduced bioavailability due to rapid gastro-intestinal transit. In addition, it has been demonstrated that the presence of caseinate salts and calcium chloride may decrease phenytoin absorption (Smith et al., 1988). Binding of phenytoin to the nasogastric tube apparatus has been largely excluded, since the tube is flushed after dosing (Cacek et al., 1986). Decreased plasma phenytoin concentration associated with enteral feeding formulations may increase the risk of seizures (Au Yeung and Ensom, 2000).

Phenytoin and gastrointestinal diseases

The bioavailability of phenytoin may be reduced by gastrointestinal diseases, particularly those associated with increased intestinal motility. Thus, in cases of severe diarrhea, malabsorption syndromes, or gastric resection, decreased bioavailability should be considered (Tozer and Winter, 1990).

Drugs which may affect the gastrointestinal absorption of phenytoin

Activated charcoal

The absorption of phenytoin was almost completely prevented when given just before the oral ingestion of activated charcoal (Nation et al., 1990). When a single
dose of activated charcoal was administered 1 h after a dose of phenytoin, there was still an estimated 80% reduction in absorption (Welling, 1984).

**Antacids and inhibitors of gastric hydrochloric acid secretion**

Studies regarding the effect of antacids on the disposition of phenytoin have produced conflicting results. Overall, it appears that the influence of antacids is variable, both between antacid preparations and between subjects (Kutt, 1984). Moreover, both the timing of antacid dosing and the volume of antacid used may also contribute to this variability (D’Arcy and McElnay, 1987). The magnesium-containing antacids primarily increase gastric pH that enhances the solubility of weak acids and reduces the absorption rate from the stomach as it increases the ionization of the drug (Kutt, 1989). Aluminium-containing antacids, in addition, prolong gastric emptying time which under these circumstances further slows the rate of absorption (Marano et al., 1985). Chelation or adsorption of phenytoin into the calcium-containing preparations has been suspected (Kutt, 1989; Nation et al., 1990). On the whole, antacids containing aluminium hydroxide, magnesium hydroxide, and calcium carbonate decreased the bioavailability of phenytoin. It is generally recommended that, if antacids are to be used in patients receiving phenytoin, the administration of the two agents should be separated by a few hours.

Omeprazole does not affect the single-dose kinetics of phenytoin in healthy volunteers (Bachmann et al., 1994). However, Prichard et al. (1987) have reported that the extent and rate of oral absorption of phenytoin is increased during omeprazole therapy. The mechanism of this is unknown but may relate to changes in gastric pH. Multiple doses (for 7 days) of pantoprazole were without effect on the rate or the extent of single-dose phenytoin absorption (Middle et al., 1995). The hydrogen receptor antagonist cimetidine may increase the bioavailability of orally administered phenytoin (Hetzel et al., 1981) through inhibition of CYP isoenzymes, although additional factors relating to absorption may also be involved.

**Sucralfate**

Concurrent administration of sucralfate significantly reduced the AUC of phenytoin (Hall et al., 1986). Further studies are required to assess the effect of long-term sucralfate administration on phenytoin plasma concentrations.

**Theophylline**

It was suggested by Hendeles et al. (1979) that theophylline decreased the absorption of phenytoin when the two agents were administered at the same time.

**Antineoplastic therapy**

Some antineoplastics (e.g. cisplatinum, vinblastine, and bleomycin) impair the gastrointestinal absorption of phenytoin (Sylvester et al., 1984).
Other drugs
Erythromycin, clarithromycin, and roxithromycin may increase the bioavailability of phenytoin (al-Humayyd, 1997). This effect may be due to an increased gastrointestinal motility induced by these macrolide antibiotics and subsequent augmented phenytoin absorption.

Co-administration of ciprofloxacin and phenytoin revealed a significant decrease in steady-state maximum and minimum concentrations and in the area under the plasma time concentration curve (Islam et al., 1999). This finding warrants close monitoring of levels when these two agents are given simultaneously.

An approximately 30% reduction in dietary fat absorption induced by orlistat administered at doses of 120 mg three times daily did not significantly alter the pharmacokinetics of a single 300 mg oral dose of phenytoin in healthy volunteers (Melia et al., 1996).

Interactions during phenytoin parenteral administration
Although phenytoin sodium could be given both intravenously and intramuscularly, both of these routes of administration have limitations.

The major disadvantage of the intravenous route is the requirement for slow administration of the propylene glycol/alcohol diluent which is adjusted to pH 12 with sodium hydroxide (Tozer and Winter, 1990). This vehicle is required to maintain phenytoin in solution at a concentration of 50 mg of the sodium salt per milliliter. Due to the inconvenience of administering the drug slowly, there is often a desire to give phenytoin with other intravenous fluids. If phenytoin admixtures are to be used, only normal saline or lactated Ringer’s solution should be used, since admixtures with other solutions could result in phenytoin precipitation (Tozer and Winter, 1990).

The intramuscular route of administration should be avoided because phenytoin precipitates at the site of injection. Consequently, absorption from the injection site tends to be rather erratic and slow, often continuing for 5 days or more (Tozer and Winter, 1990).

Phenytoin actions affecting the pharmacokinetics and/or pharmacodynamics of other drugs
It seems that phenytoin does not alter the absorption of other drugs. However, epileptic patients receiving phenytoin have been reported to exhibit a significantly smaller diuretic response to furosemide (Williamson, 1986). Furthermore, the time to peak diuretic response was considerably delayed in these patients. This was attributed to delayed oral absorption of furosemide, perhaps the result of a phenytoin-induced decrease in the spontaneous activity of gastrointestinal smooth muscle (Williamson, 1986). However, other factors may be involved, such as the reduction of the sensitivity of the renal tubule to the diuretic action of furosemide.
(Ahmad, 1974). In contrast with the observations with furosemide, Keller et al. (1981) have reported that pre-treatment with phenytoin did not alter the disposition of orally administered hydrochlorothiazide. There is some evidence that phenytoin treatment may decrease the gastrointestinal absorption of thyroxin and folic acid (Nation et al., 1990). Phenytoin can act as folate antagonist and precipitate folic acid deficiency (Matsui and Rozovski, 1982). Finally, Rowland and Gupta (1987) suggested that the treatment with phenytoin leads to decreased gastrointestinal absorption of cyclosporine.

**Carbamazepine**

The gastrointestinal absorption of carbamazepine formulations is slow, erratic and unpredictable (Morselli, 1989). The mechanisms that are associated with these characteristics may be:

(a) low water solubility (<200 mg/ml) and other physicochemical properties of the molecule (a neutral drug which cannot be converted to a soluble salt), leading to a very slow dissolution rate in gastrointestinal fluid,

(b) anticholinergic properties of the drug which may become more evident during prolonged treatment and which modify its gastrointestinal transit time (Morselli, 1989).

It has been suggested that the rate and extent of its absorption may be dose-dependent.

Carbamazepine usually peaks 3–8 h after oral dosing, but the addition of propylene glycol, polysorbate, or ethanol can accelerate the absorptive process and reduce the time to peak to 1.5–4 h and increase its bioavailability (Leppik and Wolff, 1993). There is evidence that the dissolution rate of tablets can be affected by moisture (Wang et al., 1993). Furthermore, absorption of the suspension is more rapid than that of tablets, resulting in peak concentrations at 1–3 h (Morselli, 1989). Therefore, liquid oral carbamazepine dosage formulations are typically associated with a doubling in their oral bioavailability compared with tablet formulations (Brewster et al., 1997). However, the relative bioavailability of carbamazepine suspension with enteral or nasogastric feeding administration is slightly diminished and generally slower than during fasting (Bass et al., 1989). Changes in gastric pH induced by ranitidine in healthy adults did not affect the bioavailability of carbamazepine (Dalton et al., 1985).

Carbamazepine induces the CYP3A4 catalyzed sulfoxidation of omeprazole, apparently without major clinical implication, and it has no or less effect on hydroxylation via the CYP2C19 (Bertilsson et al., 1997). CYP3A4 isoenzyme exists in the gut and liver. Carbamazepine half-life and 24 h post dose concentration increased significantly during erythromycin administration (Miles and Tennison,
Aminophylline reduced the bioavailability of carbamazepine which may be of clinical significance (Kulkarni et al., 1995); 400 mg pentoxifylline administered at 22:00 h reduced the rate but not the extent of carbamazepine absorption (Poondru et al., 2001). Interestingly, these effects were not observed when pentoxifylline was administered at 10:00 h.

Valproic acid

Valproic acid is a branched-chain fatty acid which is rapidly and completely absorbed once it is released from its pharmaceutical formulation. In spite of differences in populations and pharmaceutical formulations, the absolute bioavailability of valproate is consistently found to be close to unity. This observation indicates that valproate is not subject to a first-pass effect which is consistent with its low metabolic clearance.

Meals can have a profound effect on the time to peak concentration for the enteric-coated tablets; however, the long peak times represent delayed, rather than prolonged, absorption. Ramadan, with its changes in eating and rest/activity rhythms, significantly influences the pharmacokinetics of valproic acid. A significant decrease in the bioavailability of valproic acid was found at the end of the 3rd week of Ramadan, compared to the control period (Aadil et al., 2000).

Carbapenem antibiotics induce a decrease in plasma concentration of valproic acid in epileptic patients (Torii et al., 2002). By using Caco-2 cell monolayers, the influence of carbapenems was tested on the transepithelial transport of valproic acid (Torii et al., 2002); it was found that carbapenems may inhibit the absorption of valproic acid at the basolateral membrane of intestinal epithelial cells. The same authors had verified that imipenem inhibits the intestinal absorption of valproic acid but not through an inhibition of a carrier-mediated transport of valproic acid (Torii et al., 2001).

Repeat charcoal administered several hours after sodium valproate ingestion appears not to impair the absorption of valproic acid or indeed its pharmacokinetics (al-Shareef et al., 1997). Aminophylline also seems not to alter the pharmacokinetic parameters of valproic acid (Kulkarni et al., 1995).

Phenobarbital

Phenobarbital has a pKa of 7.2 and is more water soluble than phenytoin or carbamazepine. Early work on the rate and extent of absorption of phenobarbital indicated the potential for dissolution-rate-limited absorption after oral administration (Rust and Dodson, 1989). More recent studies have found that phenobarbital (acid and tablets) is absorbed rapidly and completely. The absolute bioavailability of phenobarbital has been found to be close to unity.
The bioavailability of phenobarbital appears to be greater in protein malnourished subjects (Syed et al., 1986). Activated charcoal reduces phenobarbital absorption, a characteristic that is exploited clinically in the early treatment of phenobarbital overdose (Neuvonen and Elonen, 1980; Welling, 1984). However, colestipol hydrochloride, a hypocholesterolemic bile acid-binding anion-exchange polymer, does not change phenobarbital absorption (Phillips et al., 1976).

It has been suggested that the absorption of griseofulvin may be reduced by phenobarbital (Riegelman et al., 1970), perhaps as a result of diminished dissolution. Phenobarbital may cause a modest reduction of cimetidine absorption (Somogyi and Gugler, 1982), mainly due to induction of its gastrointestinal metabolism (Somogyi et al., 1981). Patients receiving phenobarbital have been reported to exhibit a significantly smaller diuretic response to furosemide and this may be the consequence of reduced absorption (Williamson, 1986).

**Ethosuximide**

Ethosuximide is relatively water soluble and is rapidly absorbed from tablets. The time required to reach peak plasma concentration is less than 3 h (Chang, 1989). Due to its very low clearance, no first-pass effect is expected. Ethosuximide has not been associated with any interactions at the gastrointestinal site of absorption.

**Interactions with other AEDs**

Over the past few years, eight new AEDs (felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate, zonisamide, vigabatrin, and levetiracetam) have reached the market and are licensed for clinical use. Due to the risks associated with the use of an unproved new drug as monotherapy, current guidelines for AED trials require that the test drug be evaluated as add-on therapy. Thus, drug interactions are important considerations. Very dramatic pharmacokinetic interactions were observed with some new AEDs that were evaluated during the 1980s. For example, nafimidone is a potent inhibitor of both carbamazepine and phenytoin (Leppik et al., 1993); the inhibition is of such magnitude that clinical toxicity is observed, and this limited the development of the drug. Another example is that of MK-801 (Leppik et al., 1993). These examples underscore the need for evaluating pharmacokinetic interactions in the early stage of new AED development. However, in general, AED interactions with food are not studied during preclinical studies (phases I–III) and therefore information in this regard is sparse.

**Vigabatrin**

Vigabatrin is a synthetic gamma aminobutyric acid (GABA) derivative which was designed to increase brain GABA concentrations by inhibiting GABA transaminase,
the enzyme responsible for the breakdown of GABA. Vigabatrin is a racemic mixture but only the S(+) enantiomer is pharmacologically active. However, the R enantiomer does not interfere with the disposition of the S enantiomer, nor does it undergo chemical inversion in vivo (Haegle and Schechter, 1986; Richens, 1989; Rey et al., 1992).

The bioavailability of vigabatrin is considered to be at least 60–80% (Haegle and Schechter, 1986). The AUC for fasted and fed volunteers is not significantly different, indicating that food does not affect the extent of absorption (Frisk-Holmberg et al., 1989). Overall the interaction potential of vigabatrin is minimal.

**Tiagabine**

This AED, a nipecotic acid derivative, increases brain GABA concentrations through inhibition of GABA re-uptake (Natsch et al., 1997). After oral ingestion tiagabine is rapidly absorbed with peak plasma concentrations occurring within 1 h. Its bioavailability is 90% (Jansen et al., 1995). Whilst the rate of tiagabine ingestion is slowed by food co-ingestion ($T_{\text{max}}$ increases from 0.9 to 2.6 h), the extent of absorption remains the same (Mengel et al., 1991). To date there are no data on the effects of drugs on the absorption of tiagabine.

**Felbamate**

Felbamate is a lipophilic dicarbamate which is only very slightly soluble in water. After oral ingestion felbamate is rapidly absorbed with a bioavailability of over 90% (Shumaker et al., 1990). Food co-ingestion has no significant effect on either the rate or extent of absorption of felbamate (Graves et al., 1989; Leppik et al., 1993). To date there are no data on the effects of drugs on the absorption of felbamate.

**Gabapentin**

Gabapentin is a GABA-related amino acid with properties of an amino acid, but unlike GABA it readily penetrates the blood–brain barrier. Gabapentin is a substrate of intestinal large neutral amino acid carriers (Gidal et al., 1998b). A consequence of this type of transport is the dose-dependent oral absorption of gabapentin, with saturation at high doses (McLean, 1994). Thus, the bioavailability of gabapentin which is reported to be only 35% at a steady dosage of 1500 mg t.i.d., may be improved by ingesting the drug more frequently (e.g. from t.i.d. to q.i.d.; Gidal et al., 1998a).

High-protein meals do not seem to interfere with the absorption of gabapentin in spite of the fact that amino acids could interfere with the carrier system (Benetello et al., 1997). In contrast, a trend was noted for a modest increase in both $C_{\text{max}}$ and AUC values when gabapentin was ingested with a fat-free chocolate pudding.
(Gidal \textit{et al.}, 1998b), which led these authors to state that dietary macronutrient composition (i.e. protein) may favourably influence gabapentin absorption. However, this conclusion is not in accordance with the transport of gabapentin though an amino acid carrier. Overall, it can be concluded that the bioavailability of gabapentin is not significantly affected by food.

An interaction between gabapentin and antacids containing aluminium and magnesium hydroxide has been reported (Turnheim, 2004). The gastrointestinal absorption of gabapentin appears to be reduced and typically gabapentin plasma concentrations are approximately 15\% lower; this interaction is not considered to be of clinical significance. To date there are no other data on the effects of drugs on the absorption of gabapentin.

**Lamotrigine**

Lamotrigine is a phenyltriazine derivative which was initially developed as an antifolate compound. Following oral ingestion, lamotrigine is rapidly well absorbed with peak plasma concentrations occurring at 1–3 h post ingestion (Cohen \textit{et al.}, 1987; Yuen, 1991; Leppik \textit{et al.}, 1993). The absolute bioavailability of lamotrigine after a 75-mg oral dose is 98 ± 5\% (Yuen, 1991). Whereas food co-ingestion slightly delays the occurrence of the peak plasma lamotrigine concentration, it does not affect the extent of absorption (Goa \textit{et al.}, 1993). To date there are no data on the effects of drugs on the absorption of lamotrigine.

**Topiramate**

Topiramate is a sulfamate-substituted monosaccharide which is structurally distinct from other AEDs. It is rapidly absorbed, with peak plasma concentrations occurring within 2 h to 4 h after oral ingestion. The bioavailability of topiramate is estimated to be 81–95\% (Easterling \textit{et al.}, 1988). Co-administration with food moderately slows absorption (11–13\% decreased mean maximum absorption) whereas the extent of absorption is unaffected (Doose \textit{et al.}, 1996). Thus topiramate can be ingested without due regard to meal times. To date there are no data on the effects of drugs on the absorption of topiramate.

**Oxcarbazepine**

Oxcarbazepine, a keto compound chemically related to carbamazepine, has a similar therapeutic profile to that of carbamazepine but is associated with an improved tolerability profile (Jensen and Dam, 1990). Following oral ingestion, oxcarbazepine is rapidly absorbed with peak plasma concentrations of its pharmacologically active metabolite (a monohydroxylated derivative), occurring 4–6 h later. Its bioavailability is 89\% (Feldmann \textit{et al.}, 1978). After a fat- and protein-rich breakfast there was a moderate increase in the monohydroxylated derivative AUC (16\%) and $C_{\text{max}}$ (23\%)
values but with no changes in $T_{\text{max}}$ and terminal half-life values (Degen et al., 1994). These changes should be of little therapeutic consequence. To date there are no data on the effects of drugs on the absorption of oxcarbazepine.

**Zonisamide**

Zonisamide is a benzisoxazole compound which is structurally different to other AEDs. Absorption is rapid after oral ingestion with peak plasma concentrations occurring after 2.4–3.6 h. The bioavailability of zonisamide is estimated to be 65%. The bioavailability of zonisamide is unaffected by food co-ingestion although there is a delay in peak plasma concentration values to 4–6 h. To date there are no data on the effects of drugs on the absorption of zonisamide.

**Levetiracetam**

Levetiracetam is the $S$ enantiomer of the ethyl analog of piracetam and as such is structurally unrelated to other AEDs. The absorption of levetiracetam after oral ingestion is rapid with peak plasma concentrations occurring approximately 1 h later. Its bioavailability is considered to be essentially 100% (Patsalos, 2002). Although food co-ingestion slows the rate of absorption of levetiracetam, the extent is unaffected (Patsalos, 2003). To date there are no data on the effects of drugs on the absorption of levetiracetam.

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Interactions between antiepileptic drugs

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Summary
Old and new antiepileptic drugs (AEDs) are associated with a wide range of pharmacokinetic drug–drug interactions. The classic AEDs exert important inducing and inhibiting effects on old and new AEDs.

Phenobarbital (PB) concentrations are significantly increased by valproic acid (VPA) and to a variable degree also by phenytoin (PHT). PHT levels may be decreased or increased by PB, depending on the PB concentration. The protein binding of PHT is decreased by VPA. Enzyme-inducing AEDs decrease primidone concentrations, but increase the levels of its metabolite PB. Carbamazepine (CBZ) concentrations are decreased by PB and PHT, whereas its metabolite CBZ-10,11-epoxide (CBZ-E) may be increased by VPA. Concentrations of VPA are considerably decreased by enzyme-inducing AEDs such as PB, PHT or CBZ. Sulthiame, a rarely used AED, increases PHT levels. Methsuximide (MSM), another rarely used AED, inhibits the metabolism of PB and PHT, but induces the metabolism of lamotrigine (LTG) and oxcarbazepine (OXC).

New AEDs exert relatively few inhibiting or inducing effects on the classic AEDs and hardly any on the new AEDs. However, felbamate (FBM) increases concentrations of PHT, PB, VPA and of CBZ-E, but reduces concentrations of CBZ. OXC (and some other new AEDs) may also increase PHT, whereas vigabatrin reduces the serum levels of PHT by approximately 20%. OXC has less pronounced enzyme-inducing effects than CBZ; however, topiramate (TPM) and LTG may be lowered by OXC.

On the other hand, enzyme-inducing AEDs reduce serum concentrations of FBM, LTG, tiagabine (TGB), TPM, zonisamide (ZWS) and to a minor extent of 10-hydroxy-carbazepine, the clinically relevant metabolite of OXC. VPA markedly increases LTG and FBM. In comparison to other AEDs the potential for clinically relevant interactions associated with gabapentin and levetiracetam is low.

Introduction
Antiepileptic therapy has been associated with a wide range of drug–drug interactions. Classical pharmacokinetic interactions are enzyme induction, enzyme
inhibition and displacement from protein binding. From the pharmacological point of view monotherapy with AEDs is often considered as the treatment regime of choice for epileptic patients in order to avoid undesirable consequences of drug interactions such as side effects by increased AED concentrations or inefficacy of the therapy due to decreased serum levels. But for clinical reasons, in practice, many patients have to be treated with AED combinations. Furthermore, newly introduced AEDs are licensed usually as comedication.

Correspondingly, the knowledge of pharmacokinetic interactions is most important. Countless papers have been published about interactions of AEDs. However, many of these interactions are hardly clinically relevant in so far as they concern only weak influences or they have no practical consequences. This overview will deal especially with the clinically important interactions of AEDs. Of course, the extent and the significance of an interaction can vary individually, as it often depends not only on the relative dosages of the interacting drugs, but also on previous drug exposure and on pharmacogenetic factors.

Benzodiazepines are not regarded in this review. The effects of these drugs are minimal as they usually occur only in relatively low concentrations in the serum compared to AED concentrations. Possibly enzyme-inducing drugs may reduce their serum concentrations, but there are hardly any investigations on this topic.

Interactions between classic AEDs (phenobarbital, phenytoin, primidone, carbamazepine, valproic acid, ethosuximide, methsuximide) and other AEDs

Phenobarbital

Phenobarbital (PB) is about one-third metabolized to a p-hydroxylated derivative. It is partially (50–60%) bound to serum proteins.

Effect of phenobarbital on other drugs

PB is the prototype among inducers of the hepatic mixed-function oxidase system. Numerous studies have been performed showing that PB decreases concentrations of other concomitantly given AEDs. Particularly impressive is the effect of PB on CBZ and VPA. A typical investigation, which documents the influence of PB on CBZ metabolism, is a detailed study with data of 609 epileptic patients (Rambeck et al., 1987). PB decreases CBZ levels by about 34% when compared to levels of patients on CBZ alone. The inducing effect was thereby comparable with that of PHT and primidone (PRM).

PB shows not only inducing effects, but also inhibiting effects on some enzyme systems. In some cases, such as for the influence of PB on PHT, results are controversial as two apparently contradictory mechanisms, competitive metabolic inhibition
and enzyme induction may play a role (Inoue and Chambers, 1985). There are studies which show that PB tends to lower PHT levels when the two drugs are used simultaneously (Abarbanel et al., 1978) and others which demonstrate a significant increase of PHT in the presence of PB, but returning to prevalues some weeks later (Müller et al., 1977). Another study with stable isotope tracer techniques concluded that PB does not alter PHT steady-state concentration or kinetics (Browne et al., 1988a). A statistical investigation of a large collective with 1992 epileptic patients indicated that low levels of PB induce PHT metabolism and thereby decrease PHT concentrations, but higher PB levels inhibit PHT metabolism in a competitive manner and thereby increase PHT concentrations (May et al., 1982).

PB increases the clearance of VPA. For example, in a representative study with 259 epileptic patients, VPA levels were about 24% lower when VPA was given concomitantly with PB than when it was given alone (May and Rambeck, 1985). The inducing effect in this case was smaller than that of CBZ and PHT, where reductions of 34% and 50% respectively were found.

PB shows its inducing effect also in the presence of some new AEDs. PB reduces LTG levels considerably. A typical study with data of 302 epileptic patients documented that LTG levels are decreased by PB by 48% (May et al., 1996a). The inducing effect was somewhat stronger than that of CBZ (43%) but smaller than that of PHT (68%). TGB levels are reduced by PB (see section on TGB), and TPM metabolism is increased (see section on TPM); furthermore, PB induces the metabolism of ZNS (see section on ZNS). There is also a study (Tartara et al., 1993) which indicates that the biotransformation of OXC and its metabolite 10-hydroxy-carbazepine (or monohydroxy-derivative, MHD) may be accelerated by concomitant treatment with PB, but the magnitude of this effect is unlikely to be of great clinical significance. PB does not seem to influence FBM levels (Kelley et al., 1997) or gabapentin (GBP) levels (Hooper et al., 1991).

Effect of other drugs on phenobarbital

The metabolism of PB itself is inhibited by some other AEDs when given in combination. VPA increases PB concentrations and often thereby causes side effects such as sedation and drowsiness. In a study with 186 epileptic patients, PB levels were about 40% higher when VPA was given additionally. This effect was independent whether PB was directly given or occurred as a metabolite of PRM (Rambeck et al., 1979). Wilder et al. (1978) documented a comparable influence for 25 epileptic adults. Various studies showed a reduced hydroxylation of PB (Bruni et al., 1980) and a prolongation of the half-life of PB by VPA by about 50% (Patel et al., 1980; Kapetanovic et al., 1981).

As PHT and PB are metabolized by the same phenyl hydroxylating enzyme system, PHT may inhibit PB metabolism in a competitive manner. PB concentrations are
then increased (Windorfer and Sauer, 1977). Correspondingly, Duncan et al. (1991) found a decrease in PB concentrations when the concomitant PHT medication was stopped. A study with 121 patients (Eadie et al., 1976) failed to find any significant elevations of plasma levels attributable to PHT. But there is also a study (Encinas et al., 1992) which concludes that PHT may interact with PB as an inducer or an inhibitor of metabolism depending on the length of treatment with the combination of the two drugs.

An important interaction is the competitive inhibition of PB metabolism by methsuximide or its clinically relevant metabolite N-desmethyl-MSM, whereby PB concentrations are increased by about 40% (Rambeck, 1979).

FBM increases PB levels by a reduction of its p-hydroxylation (Reidenberg et al., 1995a; Glue et al., 1997). Furthermore, OCBZ may increase PB but to a minor extent (Barcs et al., 2000). The other new AEDs do not show clinically relevant influences on PB; these facts are discussed in the respective sections.

Phenytoin

PHT is nearly completely metabolized to p-hydroxy-PHT and glucuronidated derivatives. It is bound to serum proteins to about 92%. Due to its saturable non-linear Michaelis–Menten kinetics, even moderate influences of other drugs on its metabolism may lead to considerable increases of PHT serum concentration.

Effect of phenytoin on other drugs

PHT has enzyme-inducing properties and decreases drug concentrations of concomitant AEDs.

CBZ metabolism is increased by PHT to a considerable extent. The above-mentioned study with 609 epileptic patients indicated a reduction of CBZ levels by 40% (Rambeck et al., 1987). As already mentioned the interaction between PHT and PB is controversial as different effects may play a role. Some studies found an increase of PB concentrations by about 30% (Windorfer and Sauer, 1977; Duncan et al., 1991), others found no influence of PHT on PB levels (Eadie et al., 1976). PHT induces the metabolism of PRM to its important metabolite PB. The ratio between PRM and its metabolite PB which is usually about 1:1 in monotherapy is then changed to about 1:4 (Fincham et al., 1973).

Addition of PHT to a VPA therapy leads to a considerable decrease in VPA levels. An analysis of data from 259 epileptic patients on polytherapy with AEDs indicated that PHT was a strong inducer (reduction 50%) of VPA levels (May and Rambeck, 1985).

LTG levels are also reduced by PHT. This was shown in the already mentioned study with 302 epileptic patients on LTG where LTG levels were reduced by 68%
when patients were on PHT comedication (May et al., 1996a). PHT exerts its inducing effect also on some other new AEDs such as TGB (see section on TGB), TPM (see section on TPM) and ZNS (see section on ZNS).

The influence of PHT on FBM is not quite clear. In a study by Kelley et al. (1997) PHT increased the clearance of FBM by about 40%, whereas Troupin et al. (1997) found no appreciable changes in FBM clearance for comedication with PHT.

Effect of other drugs on phenytoin

The metabolism of PHT itself may be increased or decreased by comedicated drugs; in some cases even by the same substance, depending on the serum concentration of the interacting drug. These effects have been discussed exemplarily for the influence of PB on PHT in the section ‘Effect of PB on other drugs’.

An investigation by Browne et al. (1988b) of six otherwise healthy men found that CBZ increases PHT serum concentrations. Concomitant therapy with MSM often leads to a remarkable increase in PHT concentrations (mean 78%) and thereby disturbing side effects may occur (Rambeck, 1979). Sulthiame also inhibits PHT metabolism and increases PHT levels (Hansen et al., 1968). Although today sulthiame is only rarely used, this interaction is noteworthy as it may induce severe side effects. Furthermore, this was one of the first important drug interactions observed in the treatment of epilepsy.

The interaction of PHT with VPA is somewhat complex as it primarily concerns protein binding. VPA displaces PHT from serum proteins and increases the free fraction of this drug from normally 8% in the absence of VPA to 20%, depending on the VPA concentration (May et al., 1991). But, as the total concentration of PHT decreases, the actually important free concentration of PHT often remains unchanged. Lai and Huang (1993) concluded that there are at least two mechanisms involved in this interaction. Whereas VPA displacing PHT from plasma protein decreased the total drug concentration of PHT, the enzyme inhibition by VPA increased both the total and unbound concentration of PHT. A detailed analysis of data from 237 patients on PHT with and without VPA comedication indicated a significant decrease in total PHT concentration by VPA (Rambeck et al., 1979). The interaction between PHT and VPA may even be time dependent as the plasma concentration of VPA fluctuates during the day, resulting in variable displacement of PHT from its protein binding (Riva et al., 1985; May and Rambeck, 1990).

The new AEDs show no or only small effects on PHT metabolism. LTG does not influence the disposition of PHT (Grasela et al., 1999) and no significant effect by ZNS on the serum concentration or protein binding of PHT was found (Tasaki et al., 1995). As expected, the addition of levetiracetam (LEV) did not bring about clinically relevant changes in PHT pharmacokinetic parameters (Browne et al., 2000).
Total PHT plasma concentrations increased with coadministered FBM (Fuerst et al., 1988), accordingly the PHT dosage should be reduced by about 20% (Sachdeo et al., 1999). OXC also seems to inhibit the metabolism of PHT (Barcs et al., 2000). Some studies showed that vigabatrin (VGB) decreases serum PHT concentrations, but the mechanism is unknown (Gatti et al., 1993).

**Primidone**

PRM is metabolized to PB and phenyl-ethyl-malonamide (PEMA). The ratio of PRM to PB and PEMA depends not only on auto-induction but also on induction by other AED.

**Effect of primidone on other drugs**

As PRM is metabolized to a great extent to PB, it shows the same influences on other drugs as PB itself. This means that it decreases levels of VPA, CBZ, LTG and many other drugs.

**Effect of other drugs on primidone**

When discussing influences of other AEDs on PRM metabolism two effects have to be considered. Primarily, the degradation of PRM to PB is induced by drugs such as PHT or CBZ and furthermore other comedicated AEDs may increase the resulting metabolite PB (Porro et al., 1982).

In the first days of a PRM monotherapy, only PRM is found in the serum. Then the auto-induction of its own metabolism leads to increasing PB concentrations. After some weeks, in steady-state conditions, PB/PRM ratios of about 1:1 are reached. In the presence of other inducing AEDs such as PHT or CBZ the PB/PRM ratio is further increased to 5:1. This has been documented in various studies (Fincham et al., 1973; Schmidt, 1975).

But, it must also be considered that the same drugs that increase PB levels also increase levels of PB occurring as a metabolite of PRM. This has been shown for PHT (Lambie and Johnson, 1981), MSM (Rambeck, 1979) and VPA (Rambeck et al., 1979). A further increase of the PB/PRM ratio to 10:1 may be the consequence. In such cases, it is questionable how far or whether the anticonvulsant effect of a PRM therapy is still exerted by PRM itself or more or less by PB.

**Carbamazepine**

CBZ is largely metabolized to CBZ-E and then to CBZ-10, 11-diol. CBZ-E seems to contribute to the side effects of a CBZ therapy whilst the diol is physiologically inactive. CBZ and CBZ-E are bound by about 40% to serum proteins.
Effect of carbamazepine on other drugs

CBZ has enzyme-inducing properties and correspondingly decreases concentrations of other concomitantly given AEDs.

The influence of CBZ on PHT is not quite clear. Lai et al. (1992) showed in a study with volunteers that CBZ may decrease PHT levels possibly by decreased bioavailability of PHT when CBZ was co-administered. As mentioned above CBZ may induce the metabolism of PRM.

VPA is considerably reduced by CBZ. In a study with 259 patients on VPA, CBZ reduced VPA levels by about 34%. Its inducing effect was larger than that of PB but smaller than that of PHT (May and Rambeck, 1985). Comparable results were found in a study of Reunanen et al. (1980) with epileptic patients and in a study of Bowdle et al. (1979) with healthy volunteers.

CBZ reduces LTG levels (Bartoli et al., 1997; Battino et al., 1997). In a study of 302 patients on LTG, patients on CBZ comedication had LTG levels that were about 50% lower than that of patients on LTG monotherapy. The inducing effect was comparable with that of PB but less than that of PHT (May et al., 1996a). Furthermore, CBZ reduces FBM levels (Kelley et al., 1997; Troupin et al., 1997), TGB levels (Brodie, 1995; So et al., 1995; Snel et al., 1997), TPM levels (Sachdeo et al., 1996) and ZNS concentrations (Ojemann et al., 1986). GBP concentrations are not influenced (Radulovic et al., 1994).

Effect of other drugs on carbamazepine

Besides the inducing effect of CBZ it has to be borne in mind that CBZ itself is subject to enzyme induction. Various studies have documented that simultaneously given AEDs reduce CBZ concentrations.

An investigation by Michele et al. (1985) with 58 patients showed that PB reduces CBZ levels to a considerable extent. Christiansen and Dam (1973) showed in 123 epileptic patients that PB and PHT reduce CBZ concentrations. In a study with 609 epileptic patients on CBZ therapy (Rambeck et al., 1987), the mean serum concentration of CBZ was reduced when given in combination with PHT by 42%, with PB by 34% and with VPA by 17%.

Besides the inducing effect on CBZ metabolism some drugs inhibit the degradation of CBZ-E. In the above-mentioned study (Rambeck et al., 1987) the mean concentration of CBZ-E was increased by VPA (+45%), PRM (+19%) and a combination of the latter (+67%) compared to CBZ monotherapy. These effects are reflected by the ratios between CBZ and its CBZ-E. In CBZ monotherapy a ratio of about 7:1 is found in adults (Rambeck et al., 1987). In the presence of inducing AEDs the ratio is lowered to 3:1, and in the presence of inducing AEDs in combination with VPA it is 2:1. VPA appears to inhibit the conversion of CBZ-E to the trans-diol derivative and furthermore the glucuronidation of this CBZ-10,11-diol
(Bernus et al., 1997). In the special case of adding CBZ to a basic VPA therapy, the inhibiting effect of VPA on the metabolism of CBZ-E is particularly impressive, especially in children. CBZ-E concentrations of up to 13 µg/ml have been observed, accompanied by side effects such as vomiting and tiredness, although the CBZ levels were in the usually accepted effective range (Rambeck et al., 1990). After a few days the CBZ-E concentration decreases, but CBZ/CBZ-E ratios of 3:1 remain.

FBM appears to induce CBZ metabolism and decrease CBZ levels (Liu and Delgado, 1997), whereby CBZ-E levels are increased (Wagner et al., 1993). In a study by Jedrzejczak et al. (2000), VGB increased CBZ concentrations. There was no significant change in the serum concentrations of CBZ when LTG was added to a CBZ therapy (Eriksson and Boreus, 1997; Gidal et al., 1997b; Besag et al., 1998). Data regarding the influence of LTG on CBZ-E are conflicting. TPM (Sachdeo et al., 1996) and GBP (Radulovic et al., 1994) also do not influence CBZ levels.

Valproate

VPA is metabolized to a series of saturated and unsaturated carbonic acids and glucuronidated derivatives. It is largely bound to serum proteins.

Effect of valproate on other drugs

As already discussed, VPA shows an inhibiting effect on the CBZ metabolite CBZ-E. When VPA is given in combination with CBZ, CBZ-E is increased (Sälke-Treumann et al., 1988; Rambeck et al., 1990; Bernus et al., 1997).

VPA increases PB levels by about 40% (Rambeck et al., 1979). Regarding PHT, there seem to be two mechanisms involved in the interaction of VPA with PHT. Whereas VPA displacing PHT from the plasma protein decreased the total drug concentration of PHT, the enzyme inhibition by VPA increased both the total and unbound concentration of PHT (Lai and Huang, 1993).

VPA increases levels of LTG in an impressive manner (Yuen et al., 1992; Anderson et al., 1996; May et al., 1996a; Battino et al., 1997; Kanner and Frey, 2000). In our study with 302 epileptic patients the LTG levels of patients on a combination of LTG with VPA were increased by a factor of 3.6 in comparison to patients on LTG monotherapy (May et al., 1996a). This could benefit the patient with epilepsy not only by attaining higher plasma LTG concentrations with ‘standard’ dosages of LTG, but also possibly by achieving better seizure control through providing a less variable peak-to-trough fluctuation in LTG concentrations as a result of extending the half-life of LTG (Morris et al., 2000).

VPA decreased the clearance of FBM by about 21% (Kelley et al., 1997). Although VPA seems to decrease the protein binding of TGB, the relevance of this effect is unclear. VPA does not influence the metabolism of other new AEDs.
Effect of other drugs on valproate

Inducing AEDs such as PB (May and Rambeck, 1985), PHT (May and Rambeck, 1985) or CBZ (May and Rambeck, 1985; Yukawa et al., 1997) decrease VPA levels considerably. In accordance with our own observations (Mataringa et al., 2002) Besag et al. (2001) reported that MSM also significantly decreases VPA levels. Besides the inducing effects of other AEDs on VPA, it has to be considered that the kinetics of VPA is non-linear, resulting in a lower than proportional increase of the serum concentration when increasing the dose. These two facts are the reason why in polytherapy even with high dosages of up to 6 g VPA per day, morning concentrations higher than 100 μg/ml are rarely exceeded.

Ethosuximide (ESM) seems to reduce VPA levels by an unknown mechanism (Sälke-Kellermann et al., 1997).

VPA levels rose by 12.7% when FBM was added (Wagner et al., 1994; Hooper et al., 1996; Siegel et al., 1999). In a study with human volunteers, the addition of LTG was associated with a small but significant decrease in steady-state VPA plasma concentration (Anderson et al., 1996). Mataringa et al. (2002) observed also a slight decreasing effect of LTG on VPA (−7%) in a retrospective study. However, in clinical studies such an effect was not documented (Jawad et al., 1987; Eriksson et al., 1996). The effect of TPM on VPA kinetics seems to be negligible (Rosenfeld et al., 1997). GBP (Radulovic et al., 1994) or VGB (Armijo et al., 1992) do not influence the kinetics of VPA.

Ethosuximide

ESM is a simple aliphatic compound which is metabolized to hydroxylated compounds. It is not bound to proteins. Besides a weak decreasing effect on VPA, ESM does not influence other drugs.

The metabolism of ESM itself may be induced to some degree by PB and PHT, but this is hardly of clinical relevance (Sälke-Kellermann et al., 1997).

Methsuximide

MSM is rapidly metabolized to the therapeutically active derivative N-desmethyl-MSM and then to hydroxylated and glucuronidated derivatives.

Effect of methsuximide on other drugs

MSM inhibits the metabolism of PHT and PB. In a study with 94 epileptic patients MSM increased concentrations of PB by 38%, of PB as metabolite of PRM by 40% and of PHT by 78%, in many cases with ensuing side effects (Rambeck, 1979).

But MSM also has enzyme-inducing effects and lowers LTG (May et al., 1999; Besag et al., 2000), VPA (Besag et al., 2001) and TPM levels (May et al., 2002).
Effect of other drugs on methsuximide

PB and PHT can increase concentrations of N-desmethyl-MSM, the metabolite of MSM, in a competitive manner as these substances are metabolized by the same hydroxylating liver enzymes (Rambeck, 1979).

Interactions between new AEDs and other AEDs

In the last decade, a series of new AEDs have become available for the treatment of epileptic patients. One of the basic reasons to develop new AEDs was the aim of finding agents which are not or only to a small degree interactive with other drugs; but this aim has only partially been reached.

Felbamate

FBM is partly bound to plasma proteins (24–35%) and eliminated by renal excretion, hydroxylation and conjugation.

Effect of felbamate on other drugs

Early studies (Wilensky et al., 1985; Fuerst et al., 1988) with only a few patients showed that adding FBM resulted in an increase in PHT concentrations and a small decrease in CBZ concentrations. These effects were also found in a clinical trial with FBM by Graves et al. (1989) where 32 patients received concomitant PHT and CBZ treatment. All patients required a PHT dose reduction of 10–30% during FBM treatment to maintain stable PHT concentrations. CBZ serum concentrations decreased (mean 1.3 μg/ml) in nearly all patients. Theodore et al. (1991) also found a significant reduction (24%) of CBZ concentrations in a clinical study with FBM. Albani et al. (1991) reported on a controlled trial where FBM was added to a stable CBZ monotherapy of 22 patients. CBZ total concentrations were lower during FBM treatment (mean reduction 25%). Wagner et al. (1993) evaluated the effect of FBM on CBZ and its major metabolites during a trial in 26 patients. Mean CBZ concentrations decreased from 7.5 μg/ml during placebo treatment to 6.1 μg/ml during FBM treatment. Mean CBZ-E concentrations increased from 1.8 to 2.4 μg/ml. The effects of FBM on the kinetics of PB and its hydroxylated metabolite were assessed in a study with 24 healthy volunteers by Reidenberg et al. (1995a). FBM increased the area under the curve (AUC) of PB by 22% and the maximum concentration ($C_{max}$) by 24%.

Wagner et al. (1994) showed that VPA doses may require reduction when FBM is added to a regimen of VPA. Co-administration of FBM increased the mean AUC, $C_{max}$ and average steady-state concentrations (from 67 to 103 μg/ml) of VPA in 10 epileptic patients who received FBM in addition to a stable VPA dosage. This effect
has also been documented by Hooper et al. (1996) in a study of 18 healthy volunteers.

FBM has only a small increasing effect (Colucci et al., 1996) or no effect on LTG (Gidal et al., 1997a). Reidenberg et al. (1995b) found no clinically relevant interactions between FBM and VGB in a study of 18 healthy volunteers. The influence of FBM on the multiple dose kinetics of monohydroxy and dihydroxy metabolites of OCBZ was assessed in healthy volunteers (Hulsman et al., 1995). FBM had no effect on MHD kinetics.

Effect of other drugs on felbamate

PHT and CBZ induce the metabolism of FBM resulting in lower than expected steady-state concentrations. Wagner et al. (1991) performed a controlled discontinuation study of PHT and CBZ in five patients with FBM. As PHT dosages were reduced, FBM clearance decreased by 21% and as the CBZ dosages were reduced, FBM clearance decreased by an additional 16.5%.

In a study by Kelley et al. (1997), PB had no influence on FBM, and VPA reduced the clearance of FBM by about 21%.

Reidenberg et al. (1995b) did not find any clinically relevant influence of VGB on FBM. Furthermore, LTG has no influence on FBM (Troupin et al., 1997). However, a study indicated that the half-life of FBM is increased by GBP via an unknown mechanism (Hussein et al., 1996).

Gabapentin

GBP shows dose-dependent absorption kinetics. It is not bound to plasma proteins and it is eliminated unchanged in the urine.

Effect of gabapentin on other drugs

The US Gabapentin Study Group (1994) found no influence of GBP on CBZ, PHT and VPA concentrations in a study with GBP as add-on therapy.

When administered over a period of 3 days, GBP had no statistically significant effect on PB concentrations in 12 healthy volunteers (Hooper et al., 1991). Clinical studies have also documented a lack of interaction between GBP and PB (Crawford et al., 1987; Goa and Sorkin, 1993). Radulovic et al. (1994) investigated the effect of GBP co-administration for more than 3 days on steady-state CBZ concentrations (12 epileptic patients) and for more than 5 days on VPA concentrations (14 epileptic patients). Mean CBZ and CBZ-E and mean VPA concentrations before, during and after GBP administration were not significantly different.

Crawford et al. (1987) performed a dose-ranging study with 300, 600 and 900 mg/day GBP as add-on therapy. No significant drug interactions were seen,
although there was a trend towards elevation of serum PHT concentration in patients taking 900 mg/day of GBP.

There is also a case report about a considerable PHT increase after the addition of low doses of GBP (300 and 600 mg/day) to PHT with CBZ and clobazam as comedication (Tyndel, 1994). The authors conclude that the unusual step of adding GBP to three AEDs may have allowed this unusual interaction. But, it seems rather problematic to draw such a conclusion from a single clinical observation with few serum level determinations since, for example, irregular drug intake prior to addition of GBP may also result in an increase of serum concentrations.

As mentioned above, GBP might elevate FBM levels.

Effect of other drugs on gabapentin

The above-mentioned investigation by Hooper et al. (1991) found no statistically significant influences of PB on GBP kinetics. There are no special studies about PHT, but according to our own experience PHT does not significantly influence GBP concentrations. In the study by Radulovic et al. (1994), GBP pharmacokinetic parameters during CBZ or VPA co-administration were similar to data reported in healthy subjects. The authors conclude that no pharmacokinetic interaction exists between CBZ or VPA and GBP.

Lamotrigine

LTG is about 55% bound to plasma proteins and is extensively metabolized by glucuronidation.

Effect of lamotrigine on other drugs

Concentrations of concomitant VPA, PHT or CBZ were unaltered by 1 week of LTG administration in 22 patients examined by Jawad et al. (1987). Loiseau et al. (1990) reported on a controlled add-on trial of LTG in 23 patients. Concentrations of PHT, CBZ and PB remained unchanged. Sander et al. (1990) also performed a controlled add-on trial of LTG in 21 epileptic patients. Serum concentrations of CBZ, PHT, VPA and PB were unaffected by LTG treatment. Jawad et al. (1989) assessed the antiepileptic effects of LTG in a crossover trial in 24 adult patients. No statistically significant changes in concentrations of PHT, CBZ, PRM or PB were found between the two treatment periods. Schapel et al. (1993) performed a controlled trial of LTG as add-on therapy in 41 patients. Concomitant AEDs (CBZ, PHT and VPA) concentrations were virtually unchanged. Moreover, no clinically important changes in plasma concentrations of CBZ, VPA, ESM and PB were observed in epileptic children during LTG therapy (Eriksson et al., 1996).

In contrast, an interaction between LTG and CBZ metabolism resulting in an increase of CBZ-E of 45% was reported by Warner et al. (1992). These observations
are at variance with those of Wolf (1992). He added LTG to a subtoxic, just tolerated dose of CBZ in nine patients. Cerebellar toxicity developed in eight of them. In the total group, a small (about 10%) but significant increase of CBZ-E was found, whereas no consistent change could be detected in CBZ. The increase in the CBZ-E, however, was too small and too inconsistent to explain the toxicity in all cases. These results indicate that the interaction of CBZ and LTG may be primarily pharmacodynamic rather than pharmacokinetic. Pisani et al. (1994) found no effect of LTG on CBZ-E. They compared the pharmacokinetics of a single dose of 100 mg CBZ-E in 10 patients on chronic LTG monotherapy and in 10 drug-free healthy control subjects. CBZ-E kinetic parameters were similar in subjects on LTG and in controls.

Effect of other drugs on lamotrigine

Binnie et al. (1986) reported on short-term effects of a single dose of LTG in 16 persons with epilepsy. Comedication with CBZ and/or PHT reduced the elimination half-life to a mean of 15 h and comedication with VPA prolonged the half-life to a mean of 59 h. In a study by Jawad et al. (1987), patients receiving LTG together with enzyme-inducing AEDs showed as LTG plasma elimination half-life of 14 ± 7 h (mean ± SD). Those receiving LTG plus an inducing AED plus VPA exhibited a mean LTG half-life of 30 ± 10 h.

Yuen et al. (1992) studied six healthy volunteers who received LTG as a single dose alone or together with VPA. Concomitant administration of VPA reduced LTG total clearance by approximately 21% and increased the elimination half-life and AUC. Renal elimination of LTG was not impaired.

May et al. (1996a) studied the influence of comedication on LTG concentrations in 588 blood samples of 302 epileptic patients. The LTG serum concentration in relation to LTG dose per body weight (level-to-dose ratio, LDR, μg/ml per mg/kg) was calculated and compared for different drug combinations. The results showed that comedication had a highly significant influence on the LTG serum concentrations. The mean LDR for LTG was as follows: 0.32 (LTG + PHT) < 0.52 (LTG + PB) ≈ 0.57 (LTG + CBZ) < 0.98 (LTG monotherapy) ≈ 0.99 (LTG + VPA + PHT) < 1.67 (LTG + VPA + CBZ) ≈ 1.80 (LTG + VPA + PB) < 3.57 (LTG + VPA). The considerable influence of various AED and their combinations on LTG concentrations is shown in Figure 7.1. It is interesting that a comparable study by Battino et al. (1997) with 482 LTG determinations form 106 epileptic patients found nearly the same values. The LDR of LTG for patients on VPA was 3.2, for patients on enzyme-inducing drugs 0.6 and on VPA in combination with enzyme-inducing drugs 1.9. These data furthermore were confirmed in a prospective study with epileptic children (Bartoli et al., 1997).

As already mentioned, several studies (May et al., 1999; Besag et al., 2000) found that MSM lowers LTG levels by about 50–70%.
The decreasing effect of OXC on LTG levels (29%) is less than that of CBZ but statistically significant (May et al., 1999). FBM and TPM (Berry et al., 1998; Doose et al., 2003) have no important influence on LTG.

**Oxcarbazepine**

OXC is the 10-keto analogue of CBZ. OXC is a prodrug for MHD, and is rapidly converted to this substance. MHD is approximately 40% bound to serum proteins and is excreted mainly by direct conjugation to glucuronic acid.

**Effect of oxcarbazepine on other drugs**

McKee et al. (1994) investigated the interaction between OXC and other AEDs in three groups of 12 epileptic patients taking CBZ, VPA or PHT as monotherapy. No differences in the median AUC at steady-state of CBZ and its metabolite CBZ-E, as well as VPA and PHT, were observed during additional treatment with OXC at steady-state compared with the AUC calculated for the placebo phase, suggesting an absence of metabolic interference with these AEDs. In contrast, Barcs et al. (2000) found in an OXC dose-ranging trial a slight decrease in CBZ levels of 13%,

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Figure 7.1 Influence of PHT, PB, CBZ, MSM, GBP, OCBZ, VPA and of their combinations on serum concentrations of LTG. LTG monotherapy is taken as 100% (n.s.: not significantly; bars ±95% confidence intervals); data of 302 patients (May et al., 1996a)
an increase in PB levels of 15% and an increase of PHT levels of 40% in patients with high MHD concentrations, compared to placebo. The in vitro study by Lakehal et al. (2002) indicated that MHD inhibited CYP2C19-mediated PHT metabolism at therapeutic concentrations. Thus, administration of OXC with CYP2C19 substrates with narrow therapeutic ranges should be done cautiously.

Battino et al. (1992) investigated changes of unbound and total VPA concentrations after replacement of CBZ with OXC in four epileptic patients. In confirmation of the above results, total and free VPA concentrations rose when the medication was switched from CBZ to OXC. Houtkooper et al. (1987) also observed a statistically significant increase of concomitant VPA and PHT concentrations in a crossover trial with 48 patients when CBZ was replaced by OXC. The increase in the serum concentrations during OXC therapy can be explained by a decrease in the prior enzyme induction caused by CBZ (Houtkooper et al., 1987).

The inducing properties of OXC on the metabolism of LTG and TPM are less pronounced than that of CBZ but the inducing effect is statistically significant (May et al., 1999, 2002). A mean decrease in LTG levels of about 30% compared to LTG monotherapy was found. A comparable effect was also found on TPM metabolism, patients on OXC comedication had about 30% lower TPM levels than patients on TPM monotherapy (May et al., 2002).

**Effect of other drugs on oxcarbazepine**

Kumps and Wurth (1990) analyzed the concentrations of MHD and of the inactive metabolite CBZ-diol in 15 epileptic patients, six of them receiving PB and/or PHT as comedication. The results indicate that MHD concentrations are unaffected by the comedication, but oxidation of MHD to its inactive metabolite may be induced. However, this seems to be of little clinical significance. In the above-mentioned study of McKee et al. (1994), patients taking CBZ or PHT had lower MHD concentrations compared with control patients without CBZ or PHT, the difference being small and statistically significant only for the CBZ-treated group. VPA had no effect at all in this study. In contrast, the OXC dose-ranging study of Barcs et al. (2000) found that patients receiving concomitant treatment with PHT and PB had statistically lower MHD levels than patients not receiving these AEDs.

The absence of an effect of VPA was confirmed by Tartara et al. (1993). The kinetics of OXC and MHD after a single oral OXC dose were comparable in healthy control subjects and in epileptic patients treated with VPA. However, in patients on PB the AUC values of both OXC and MHD were lower and the MHD half-life marginally shorter than in controls. But the magnitude of this effect was judged to be only of minor clinical significance. In combination with VPA the free fraction of MHD (64%) was slightly, but significantly, higher than in monotherapy (52%) with OXC (May et al., 1996b).
The study of Hulsman et al. (1995) documented the absence of an influence of FBM on MHD and its metabolite. Further observations indicate that LTG and GBP have no influence on MHD (Sallas, 1999; Viola et al., 2000).

Vigabatrin

VGB does not bind to plasma proteins, does not appear to undergo metabolic transformation and is excreted extensively in urine in its unchanged form.

Effect of vigabatrin on other drugs

In an early double-blind study (Grant and Heel, 1991) of VGB in epileptic patients, serum concentrations of PHT were about 20% lower during VGB treatment than during placebo, but concentrations of other concomitant AEDs did not change. In a study with 89 epileptic patients, Browne et al. (1989) also found a statistically significant decrease of 20% in PHT concentrations when VGB was added. Furthermore, minor decreases in PB (7%) and PRM (11%) were observed. Dalla Bernardina et al. (1995) performed a study in 46 epileptic children. Serum concentrations of associated AEDs (CBZ, PB and VPA) showed no significant changes, except for PHT which decreased from $19.3 \pm 8.0$ to $11.9 \pm 5.2 \mu g/ml$ on VGB treatment. The effect of VGB on PHT has been further studied by Rimmer and Richens (1989). When VBG was added to the PHT therapy of eight epileptic patients, mean plasma PHT concentrations fell significantly by 23% during the 5th week. No change was found in plasma protein binding of PHT, the urinary ratio of PHT to its metabolite p-hydroxy-PHT, and the antipyrine clearance before and at the end of the treatment period. It is not clear why the fall in PHT levels may show a delay of a few weeks. This slight, but unequivocal, effect was confirmed in 21 epileptic patients by Gatti et al. (1993). By switching from oral to intravenous PHT for 5 days before and after combined treatment with VGB and by measuring p-hydroxy-PHT, it could be demonstrated that the oral availability of PHT is unaffected by VGB. So the mechanism of the VGB-induced decrease in serum PHT is still unclear. A dose–response study of VGB in 20 children aged 2 months to 18 years also showed a modest decrease in PHT plasma levels (Herranz et al., 1991), but no changes in CBZ and VPA levels.

Armijo et al. (1992) investigated the effects of adding VGB to the antiepileptic regimens of 16 children. In the eight patients receiving VPA, no significant changes of VPA concentrations were observed.

Furthermore, several controlled trials have shown that VGB has no significant effect on serum concentrations of CBZ and VPA (Gram et al., 1985), CBZ, PB, PHT and VPA (Loiseau et al., 1986) or CBZ and PB (Cocito et al., 1989).

On the other hand, Jedrzejczak et al. (2000) found in a study with 66 epileptic patients a small increasing influence (of about 10%) of VGB on CBZ. Some patients
responded with adverse, toxic symptoms. Also Sanchez-Alcaraz et al. (2002) reported higher CBZ concentrations during comedication with VGB compared to CBZ monotherapy in 15 patients.

As already mentioned, the study of Reidenberg et al. (1995b) found no clinically relevant influence of VGB on FBM in healthy volunteers.

Effect of other drugs on vigabatrin

In the study of Armijo et al. (1992) no differences were found in VGB concentrations between patients with and without VPA. In a retrospective study (Armijo et al., 1997), patients with and without enzyme-inducing AEDs (PHT, PB and CBZ) had comparable VGB levels. One study (Sanchez-Alcaraz et al., 1996) reported on a small decreasing influence of CBZ.

An investigation by Reidenberg et al. (1995b) concluded that FBM does not influence the inactive $R(-)$-VGB enantiomer, but produced a 13% increase in AUC and an 8% increase in urinary excretion of the active $S(+)\text{ enantiomer.}$

Topiramate

TPM is only 15% plasma protein bound and it is mainly excreted unchanged in the urine (80%), but significant metabolism occurs when TPM is administered in conjunction with enzyme-inducing AEDs.

Effect of topiramate on other drugs

TPM has no significant or only little effect on the serum concentrations of CBZ or its metabolite CBZ-E (Sachdeo et al., 1996) or on PB, PRM and LTG, except for an occasional moderate increase in plasma PHT levels (Walker and Patsalos, 1995), and a small mean decrease of VPA levels, but this is hardly clinically relevant (Rosenfeld et al., 1997).

LTG does not influence TPM levels to a clinically relevant extent (Berry et al., 1998; Doose et al., 2003).

Effect of other drugs on topiramate

The elimination half-life of TPM of approximately 20–30 h may be shortened considerably in the presence of concomitant treatment with enzyme inducers such as PB, PHT or CBZ and lead to a decrease in TPM levels (Sachdeo et al., 1996; Glauser et al., 1999; Rosenfeld et al., 1999; May et al., 2002). Furthermore, MSM and to a lesser degree OXC reduces TPM levels (May et al., 2002). VPA (Rosenfeld et al., 1999), LTG and GBP (Contin et al., 2002; May et al., 2002; Doose et al., 2003) have no significant influence on TPM.
Tiagabine
TGB is 96% protein bound. It is metabolized in the liver and only small portions are excreted unchanged.

Effect of tiagabine on other drugs
TGB does not influence serum concentrations of other AEDs, as was shown in studies for CBZ and PHT (Gustavson et al., 1998a), VPA (Gustavson et al., 1998b) and for CBZ, PHT, VPA, VGB (Richens et al., 1995). This lack of interactions is understandable because of its low concentration, in the nanogram range.

Effect of other drugs on tiagabine
Enzyme inducers such as CBZ, PB and PHT reduce the elimination half-life of TGB considerably (So et al., 1995; Snel et al., 1997).

Levetiracetam
LEV is a new AED with a nearly ideal pharmacokinetic profile. It shows a high bioavailability, linear and time-invariant kinetics, minimal protein binding and a low metabolism to an inactive metabolite.

In some clinical trials, the addition of LEV increased PHT levels to variable degrees in a few patients (Sharief et al., 1996; Patsalos, 2000), but this effect could not be confirmed by trials with deuterium-labeled PHT (Browne et al., 2000). Besides this unexplained effect no clinically relevant interactions are known. Perucca et al. (2000) found no interactions between other AED and LEV. However, more recent studies indicate that enzyme-inducing AEDs (May et al., 2003; Perucca et al., 2003) and OCBZ (May et al., 2003) slightly decrease LEV concentrations.

Zonisamide
ZNS is rapidly and completely absorbed. It is approximately 50% bound to proteins and has a relatively long half-life of about 63–69 h. It is partly metabolized with non-linear kinetics.

Effect of zonisamide on other drugs
Conflicting results have been found regarding the influence of ZNS on comedicated AEDs. Sackellares et al. (1985) showed a consistent rise in concentrations of the comedication, particularly of CBZ, when ZNS was administered to 10 adult patients in a pilot study. In contrast, in a study by Minami et al. (1994) the average LDR of CBZ was lower in patients with ZNS than in patients without ZNS. Other studies could not demonstrate a relevant influence of ZNS on concentrations or protein binding of concomitant AEDs such as CBZ, PHT, PB, PRM or VPA (Schmidt et al., 1993) and PHT or VPA (Tasaki et al., 1995).
### Table 7.1 Pharmacokinetic interactions of AEDs

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=: no relevant or statistically significant interaction. ↑ and ↓: increase and decrease, respectively, of serum concentrations mostly without clinical relevance. ↑↑ and ↓↓: clinically relevant increase and decrease, respectively, of serum concentrations. Different symbols (e.g. =/↑): indication of inconsistent or contradictory observations. Arrows in parentheses: indication of interactions based on case reports or on a small number of patients. Empty cells: no data available.

*CBZ decreases, ratio CBZ-E/CBZ increases.

*Dependent on concentration of PB.

VPA decreases PHT total concentration; however, as VPA simultaneously increases the free fraction of PHT, these effects cancel each other to a great extent.

VPA probably increases the free fraction of TGB.

*Data regarding the clinically relevant 10-hydroxy-carbazepine (MHD).

VPA slightly increases the free fraction of 10-hydroxy-carbazepine (MHD).

VPA slightly increases the free fraction of ZNS.

For clarity, bromide, sulthiame and benzodiazepines are not listed. Clinically relevant interactions of bromide with other AEDs are unlikely and were not reported. Sulthiame can increase concentrations of PHT markedly; other clinically relevant interactions with sulthiame are unknown. For benzodiazepines, relatively few interactions with other AEDs are reported.
Effect of other drugs on zonisamide

The study of Shinoda et al. (1996) indicated that enzyme-inducing AEDs (PB, PHT and CBZ) reduce the ZNS LDR. Ojemann et al. (1996) investigated the influence of CBZ and PHT on kinetics of a single dose of ZNS in epileptic patients. Plasma half-life of ZNS was significantly higher in patients on CBZ (36.4 h) than in those on PHT therapy (27.1 h), but both values were shorter than half-life values (50–68 h) usually found after administration of single oral doses on ZNS in healthy volunteers.

VPA has no clinically relevant influence on ZNS levels (Shinoda et al., 1996).

Therapeutic implications

The experience of several decades with the classic AEDs has shown that interactions may have severe clinical consequences. However, in the case of the pharmacokinetic interactions of the new AEDs their clinical importance is less clear. This is because the relevance of serum concentrations and of therapeutic drug monitoring for avoidance of side effects or for reduction of seizures has not yet been definitively established for most of the new AEDs. For FBM, LTG, OXC, TPM and GBP, a relation between serum concentrations and antiepileptic effect probably exists, but further studies are necessary to clarify this important topic. This seems also to be true for the correlation between serum concentrations and side effects of FBM, LTG and OXC. In contrast, in the case of VGB the antiepileptic effect and side effects seem to be unrelated to the serum concentration of the drug.

Reports on AED interactions usually focus on the increase or decrease of serum concentrations. But, it should be borne in mind that interactions moreover influence the whole pharmacokinetic properties of an AED. For example, changes of the half-life time also affect daily fluctuations of serum levels and furthermore the time to reach steady-state concentrations or the speed of elimination after withdrawal of a drug.

The pharmacokinetic interactions (summarized in Table 7.1) of the old and new AEDs have been investigated by many studies. Most interactions correspond to the pharmacokinetic properties of the compounds, but it should be borne in mind that rare interactions may also play an important role in the individual.

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Interactions between antiepileptic drugs


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Interaction between antiepileptic and non-antiepileptic drugs

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Introduction

Clinically important drug interactions occur essentially at two levels – at the pharmacokinetic level and at the pharmacodynamic level (Patsalos et al., 2002; Patsalos and Perucca, 2003a). By far the most important interactions are pharmacokinetic in nature and this is partly due to the fact that they are particularly prevalent in relation to antiepileptic drug (AED) use and also because they are more readily detected and quantitated. Whilst pharmacodynamic interactions are also of clinical significance they are less well documented and indeed difficult to quantitate. Pharmacokinetic interactions are associated with a change in blood concentration as a consequence of alterations in absorption, protein binding, distribution, metabolism or elimination of a drug.

Since AEDs are frequently used for years, decades or even throughout a patient’s life, it is inevitable that drugs for the treatment of concurrent diseases will be co-prescribed. In this setting the potential for interactions is high and there are many such interactions that have been described (Patsalos and Perucca, 2003b). By far the most important and clinically significant interactions occur either as the consequence of hepatic enzyme inhibition or hepatic enzyme induction of cytochrome P450 (CYP) isoenzymes. Enzyme induction results in reduction in blood concentrations and possibly a loss of an adequate therapeutic response whilst enzyme inhibition results in an elevation in blood concentrations and possibly toxicity.

The characterization of the isoenzymes involved in the metabolism of individual drugs during the past decade has greatly enhanced our ability to predict whether or not a metabolic interaction will occur and this is covered in more detail in Chapter 5. In clinical practice it is best to avoid prescribing drugs that have a high propensity to interact. However, it is sometimes necessary to co-prescribe such drugs. In this setting, it is advisable to undertake therapeutic monitoring and
to measure plasma drug concentrations, particularly after an interacting drug is introduced or withdrawn but also when a dosage change has occurred. Occasionally, it may be necessary to measure the free (pharmacologically active) concentration in plasma so as to aid a dose change and dose optimization. This would apply to drug interactions that involve the displacement of a drug that is highly protein bound (>90%) from its plasma protein-binding site combined with an inhibition of its metabolism (e.g. phenytoin (PHT) and phenylbutazone).

In this chapter, clinically significant interactions between AEDs and non-AEDs are described. Interactions between AEDs and oral contraceptives, and between AEDs and psychoactive drugs are not described here as they are discussed in detail in Chapters 16 and 19, respectively. The interactions are presented in alphabetical order and are divided into those affected by a particular AED and those that affect the AED. However, in some instances we discuss interactions within a drug class. With regard to the new AEDs, because of the scarcity of available information, all interactions are highlighted regardless of whether or not a significant interaction was identified. In contrast, non-interaction drug combinations with the established AEDs are not reported.

It should be remembered that for interactions that are associated with an increase in clearance, a reduction in plasma concentrations and a reduction in area under the concentration versus time curve (AUC) values would probably require that a dose increase be undertaken so as to maintain an adequate therapeutic response. Conversely, interactions that are associated with a decrease in clearance, an increase in plasma concentrations and an increase in AUC values would probably require that a dose reduction be undertaken so as to prevent drug toxicity. In both settings it is appropriate that patients are closely monitored and that plasma concentrations are measured.

**Carbamazepine**

Carbamazepine is extensively metabolized to carbamazepine-10,11-epoxide and then to carbamazepine-10,11-diol by CYPP450 enzymes. The formation of the epoxide is mediated primarily via CYP3A4, with some contribution by CYP2C8, whilst the metabolism of the epoxide is via the enzyme epoxide hydrolase. Plasma protein binding is 70%.

**Interactions affecting carbamazepine**

**Antibiotics**

As the macrolide antibiotics are metabolized by CYP3A4 they have the propensity to interact with carbamazepine. The interactions can be classified into three
groups according to their risk of interaction with AEDs (Periti et al., 1992). The first group comprises clarithromycin, erythromycin and troleandomycin and these drugs have a high propensity to inhibit the metabolism of carbamazepine (Babany et al., 1988). Typically, plasma carbamazepine concentrations increase by up to four-fold (Mesdjian et al., 1980; Majkowski, 1995).

The second group compromises flurithromycin, josamycin, midecamycin, miocamycin and roxithromycin. These antibiotics are less potent CYP3A4 inhibitors and are usually associated with only a modest increase in plasma carbamazepine concentrations (Albin et al., 1982; Vincon et al., 1987; Barzaghi et al., 1988; Couet et al., 1990; Levy, 1995). For example, the addition of clarithromycin (500 mg/day) to carbamazepine, can result in an increase in plasma carbamazepine concentration of 30–50%, and a concurrent decrease of carbamazepine-epoxide concentrations (Albani et al., 1993; O’Connor and Fris, 1994; Yasui et al., 1997). In one study roxithromycin was not associated with any interaction (Saint-Salvi et al., 1987).

Azitromycin, dirithromycin, rokitamycin and spiramycin comprise the third group of macrolide antibiotics and these do not have any effect on CYP3A4 and therefore do not interact with carbamazepine (Periti et al., 1992; Principi and Esposito, 1999).

**Antiviral agents**

The antiviral agents delavirdine, indinavir and ritonavir are potent CYP3A4 inhibitors. Thus, their co-administration with carbamazepine can result in carbamazepine toxicity. Indeed, there are reports of ritonavir causing a two- to three-fold increase in plasma carbamazepine concentration (Burman and Orr, 2000; Garcia et al., 2000; Kato et al., 2000; von Moltke et al., 2000; Mateu-de Antonio et al., 2001). Carbamazepine toxicity was similarly observed in a patient taking ritonavir and efavirenz in combination (Burman and Orr, 2000).

**Cimetidine**

During combination therapy with cimetidine, carbamazepine intoxication has been reported. However, the interaction does not occur consistently and is probably of little clinical significance since the effect on carbamazepine is small (17% increase in plasma concentrations) and possibly transient (Dalton et al., 1986; Spina et al., 1996).

**Cisplatin**

It has been reported that a young woman with epilepsy had seizures during antineoplastic therapy and that the seizures were the consequence of a reduced plasma carbamazepine concentration (Neef and de Voogd-van der Straaten, 1988). The mechanism of this interaction may be induction of metabolism or an increased volume of distribution.
Danazol

Co-administration of danazol with carbamazepine results in a clinically significant increase (50–100%) in plasma carbamazepine concentrations. Moreover, danazol inhibits carbamazepine-epoxide elimination via an action on epoxide hydrolase and this too can contribute to the associated carbamazepine toxicity (Krämer et al., 1986; Zielinski et al., 1987; Hayden and Buchanan, 1991; Spina et al., 1996).

Diltiazem

Plasma carbamazepine concentration can increase by up to 50% during combination therapy with diltiazem (Brodie and MacPhee, 1986; Eimer and Carter, 1987; Bahls et al., 1991; Maoz et al., 1992). Diltiazem is metabolized to two metabolites (N-desmethyl-diltiazem and N,N-didesmethyl-diltiazem) and both are potent inhibitors of CYP3A4-mediated testosterone-6-β-hydroxylation (11 and 200 times, respectively), compared to that of diltiazem. This would suggest that the major contribution to this interaction is the consequence of the two metabolites.

Fluconazole

Many imidazole antifungals are potent inhibitors of CYP isoenzymes and these drugs commonly interact with carbamazepine. Fluconazole is a strong inhibitor of carbamazepine metabolism and a mean 120% increase in plasma carbamazepine concentration has been reported (Nair and Morris, 1999). During combination therapy carbamazepine intoxication can occur.

Isoniazid

Isoniazid can inhibit the metabolism of carbamazepine, via an action on CYP3A4, resulting in elevated plasma concentrations and associated toxicity (Valsalan and Cooper, 1982). The clearance of carbamazepine can be decreased by up to 45% (Block, 1982; Wright et al., 1982; Spina et al., 1996).

Ketoconazole

Like fluconazole, ketoconazole is also a strong inhibitor of carbamazepine metabolism. The administration of ketoconazole to patients taking carbamazepine has been found to result in a significant (mean 29%) increase in plasma carbamazepine concentrations and possibly in carbamazepine intoxication (Spina et al., 1997).

Metronidazole

The metabolism of carbamazepine can be inhibited by metronidazole. This results in an increase in plasma carbamazepine concentration and possible adverse events (Patterson, 1994).
Nicotinamide
Nicotinamide has been reported to increase plasma carbamazepine concentrations (Bourgeois et al., 1982).

Propoxyphene
Propoxyphene appears to reduce the activity of CYP3A4 and consequently inhibits the metabolism of carbamazepine (Abernethy et al., 1985). Thus during combination therapy, plasma carbamazepine concentrations can increase by 45–77% (Dam and Christensen, 1977; Hansen et al., 1980). In addition, plasma carbamazepine-epoxide concentrations are significantly reduced (Bergendal et al., 1997).

Quinine
In healthy volunteers, single doses of the antimalarial agent quinine have been reported to increase plasma carbamazepine concentrations (Amabeoku et al., 1993).

Ticlopidine
Ticlopidine increased plasma carbamazepine concentrations which resulted in symptoms of neurological intoxication in a patient with epilepsy undergoing coronary stenting (Brown and Cooper, 1997).

Verapamil
Verapamil is extensively metabolized in the liver to several metabolites by numerous CYP isoenzymes: CYPCA4, CYP2C8 and CYP1A2 (Kroemer et al., 1993; Spina et al., 1996; Tracy et al., 1999). Verapamil inhibits CYP3A4 and it has been reported that plasma carbamazepine concentrations can increase by a mean of 46% resulting in neurotoxicity (MacPhee et al., 1986). Interestingly, an increase in free carbamazepine concentrations can also occur (mean rise of 33% in five of six patients) (MacPhee et al., 1986).

Interactions affected by carbamazepine
Carbamazepine is a potent hepatic enzyme inducer and, as well as inducing its own metabolism via an action on CYP3A4, it also induces the metabolism of many other drugs that are CYP3A4 substrates. There is also evidence to suggest that it induces CYP2C9, CYP2C19 and CYP1A2.

Antihypertensive drugs
Carbamazepine enhances the metabolic clearance of the β-adrenoceptor blocking agents propranolol, metropranol and alprenolol, and the dihydropyridine calcium antagonists nimodipine, nifedipine, felodipine and nisoldipine as well as verapamil (Tartara et al., 1991; Flockart and Tanus-Santos, 2002). In relation to
nimodipine, nifedipine, felodipine and nisoldipine, the magnitude of the interaction is so substantial (e.g. with nimodipine, plasma concentrations can decline seven-fold) that the usefulness of these agents in patients co-medicated with carbamazepine, and indeed other enzyme inducing AEDs, is questionable (Tartara et al., 1991).

Cyclosporin

Cyclosporin is metabolized by CYP3A4 and consequently during combination therapy with carbamazepine the metabolism of cyclosporin A is enhanced (Alvarez et al., 1991). Typically, plasma cyclosporin concentrations can be expected to decline by 65% (Cooney et al., 1995).

Dicoumarol

Carbamazepine reduces the anticoagulant effect of dicoumarol by enhancing its metabolism, possibly via an action on CYP2C9 (Freedman and Olatidoye, 1994). Overall, whenever there is a change in carbamazepine therapy (and indeed that of any other enzyme inducing AED; see sections later) it is advisable to monitor internationalized normalized ratio (INR) because all anticoagulants are associated with a narrow therapeutic ratio (Cropp and Bussey, 1997).

Doxycycline

The half-life of the antibiotic doxycycline is reduced two-fold when co-administered with carbamazepine (Penttila et al., 1974).

Fentanyl

The anaesthetic fentanyl is primarily metabolized by CYP3A4 and its metabolism is enhanced by carbamazepine. Consequently, induction of anaesthesia requires substantially higher doses of fentanyl in patients taking carbamazepine (Tempelhoff et al., 1990; Feierman and Lasker, 1996).

Indinavir

In one case report, the addition of carbamazepine (200 mg/day) to indinavir treatment (800 mg t.i.d.) resulted in a reduction in plasma indinavir concentration by up to 16 times (Bonay et al., 1993). This interaction has recently been reported in another case report (Hugen et al., 2000).

Itraconazole

Co-administration of carbamazepine with itraconazole results in a clinically significant reduction in plasma itraconazole concentrations (Bonay et al., 1993).
Methotrexate

The clearance of methotrexate is significantly enhanced by carbamazepine, resulting in a clinically significant reduction in the therapeutic efficacy of methotrexate (Relling et al., 2000).

Phenprocoumon

Carbamazepine induces the metabolism of phenprocoumon and consequently reduces its anticoagulant effect (Schlienger et al., 2000). Overall, whenever there is a change in carbamazepine therapy (and indeed that of any other enzyme inducing AED; see sections later) it is advisable to monitor INR because all anticoagulants are associated with a narrow therapeutic ratio (Cropp and Bussey, 1997).

Rocuronium

Carbamazepine, through its induction of CYP3A4, CYP2C19 and CYP1A2, enhances the metabolism of rocuronium, and some other neuromuscular blocking agents, and therefore reduces their efficacy (Soriano et al., 2000).

Steroids

Carbamazepine enhances the metabolic clearance of a variety of steroids including prednisolone, methylprednisolone and dexamethasone (Spina et al., 1996).

Teniposide

Carbamazepine enhances the clearance of teniposide and consequently reduces the efficacy of teniposide (Relling et al., 2000).

Vincristine

During co-medication with carbamazepine, vincristine clearance was increased by 63% when compared to a control group (Villikka et al., 1999). As vincristine is metabolized in part by CYP3A4, induction of this isoenzyme by carbamazepine is the most likely explanation of this interaction.

Warfarin

The metabolism of warfarin is significantly enhanced by carbamazepine and this is associated with an increase in prothrombin time and a reduced anticoagulant effect (Schlienger et al., 2000). The interaction is mediated via an action on CYP2C9, although some induction of CYP3A4 may also occur (Rettie et al., 1992; Kunze et al., 1996). Overall, whenever there is a change in carbamazepine therapy (and indeed that of any other enzyme inducing AED; see sections later) it is advisable to monitor INR because all anticoagulants are associated with a narrow therapeutic ratio (Cropp and Bussey, 1997).
Ethosuximide

Ethosuximide is eliminated primarily by metabolism with 30–60% of an administered dose recovered in urine. Metabolism is primarily mediated by CYP3A and to a lesser extent by CYP2E and CYP2B/C. Approximately 20% of an administered dose is excreted unchanged in urine. Ethosuximide is not bound to plasma proteins.

Interactions affecting ethosuximide

Isoniazid

Isoniazid may increase plasma ethosuximide concentrations resulting in clinical signs of intoxication (Van Wieringen and Vrijlandt, 1983).

Rifampicin

In adult healthy volunteers, rifampicin has been observed to decrease plasma ethosuximide concentrations by induction of its metabolism (Bachmann and Jauregui, 1993).

Interactions affected by ethosuximide

There are no clinical data to suggest ethosuximide induces or inhibits the metabolism of other non-AEDs.

Felbamate

Approximately 50% of an administered dose is metabolized to form two hydroxylated metabolites. Felbamate is a substrate of CYP3A4 and CYP2E1. Approximately 40–50% of an absorbed dose is excreted unchanged in urine. Plasma protein binding is 23%.

As a new AED, knowledge of the interaction profile of felbamate with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting felbamate

Erythromycin, a potent CYP3A4 inhibitor is without effect on the metabolism of felbamate and indeed plasma felbamate concentrations are not significantly affected during combination therapy (Glue et al., 1997).

Interactions affected by felbamate

To date there are no clinical data to suggest that felbamate induces or inhibits the metabolism of other non-AEDs. However, interactions may conceivably occur with drugs that are substrates for the same isoenzymes as occur with felbamate.
**Gabapentin**

Gabapentin is not metabolized and is exclusively eliminated as unchanged gabapentin in urine. It is not protein bound. Consequently, gabapentin should have little propensity to interact with other drugs and indeed this is the case.

As a new AED, knowledge of the interaction profile of gabapentin with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

**Interactions affecting gabapentin**

**Antacids**

Antacids containing aluminium and magnesium hydroxide reduce the absorption of gabapentin by approximately 15% (Busch *et al.*, 1992). This interaction is of little clinical significance.

**Cimetidine**

Cimetidine appears to decrease plasma gabapentin concentrations by approximately 15%. The mechanism appears to be renal in nature and is considered not to be of clinical significance.

**Interactions affected by gabapentin**

To date there are no clinical data to suggest that gabapentin affects the metabolism of other non-AEDs.

**Lamotrigine**

Lamotrigine undergoes extensive metabolism via glucuronidation and the primary metabolite is N-2 glucuronide (71% of dose). Glucuronidation is a major conjugation reaction that is catalyzed by a number of different isoforms of uridine 5’ diphosphate (UDP)-glucuronosyl transferase (UGT). The N-2 glucuronidation of lamotrigine is catalyzed by UGT1A4. Plasma protein binding is 50%.

As a new AED, knowledge of the interaction profile of lamotrigine with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

**Interactions affecting lamotrigine**

**Acetaminophen (paracetamol)**

Since acetaminophen is excreted by glucuronidation, as is indeed lamotrigine, it was anticipated that an interaction between the two drugs would occur. In a healthy volunteer study acetaminophen enhanced the clearance of lamotrigine (15%) and decreased AUC (20%) and half-life values (15%) (Depot *et al.*, 1990).
Bupropion

In healthy volunteers, bupropion was observed not to interact with lamotrigine (Odishaw and Chen, 2000).

Cimetidine

In healthy volunteers, cimetidine was observed not to interact with lamotrigine (Ebert et al., 2000).

Rifampicin

Rifampicin is a potent inducer of CYPP450 and of the UGT enzyme system. In adult healthy volunteers, rifampicin enhanced the clearance of lamotrigine and the amount of lamotrigine excreted as a glucuronide was increased by 36% when compared to placebo (Ebert et al., 2000). The corresponding half-life and AUC values for lamotrigine were significantly reduced (60% and 56%, respectively) compared to placebo.

Interactions affected by lamotrigine

To date there are no clinical data to suggest that lamotrigine affects the metabolism of other non-AEDs.

Levetiracetam

Levetiracetam undergoes minimal metabolism with approximately 30% being metabolized non-hepatically in blood to an inactive metabolite. Furthermore, the elimination of levetiracetam is predominantly renal with approximately 70% of a levetiracetam dose excreted unchanged in urine. It is not protein bound, consequently levetiracetam should have little propensity to interact with other drugs and indeed this is the case.

As a new AED, knowledge of the interaction profile of levetiracetam with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting levetiracetam

Digoxin

No clinically relevant effect of digoxin on the pharmacokinetics of levetiracetam was observed in a study of 11 healthy adult volunteers (Levy et al., 2000).

Probenecid

The pharmacokinetics of levetiracetam were unaffected by co-administration of probenecid (Patsalos, 2000). However, the plasma concentration of the primary
pharmacologically inactive metabolite of levetiracetam (ucb LO 57) was increased 2.5-fold. The clinical significance of the latter effect is unknown.

Warfarin

The co-administration of warfarin with levetiracetam did not result in any significant change in the pharmacokinetics of levetiracetam (Ragueneau-Majlessi et al., 2001).

Interactions affected by levetiracetam

Digoxin

Plasma digoxin concentrations are not significantly affected by levetiracetam (Levy et al., 2000).

Warfarin

Levetiracetam does not alter the anticoagulant effect or the pharmacokinetics of warfarin (Ragueneau-Majlessi et al., 2001).

Oxcarbazepine

Although oxcarbazepine is clinically related to carbamazepine, its pharmacokinetic and interaction profiles are substantially different. Oxcarbazepine undergoes rapid and extensive metabolism to its pharmacologically active metabolite, 10-hydroxycarbazepine, which is subsequently eliminated by glucuronidation or undergoes hydroxylation to form a dihydrodiol metabolite. Only the latter reaction depends on CYP isoenzymes (Patsalos and Duncan, 1993; Baruzzi et al., 1994; Tecoma, 1999). Oxcarbazepine can induce CYP3A4 and CYP3A5 activities and inhibit CYP2C19. Plasma protein binding is 40%.

As a new AED, knowledge of the interaction profile of oxcarbazepine with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting oxcarbazepine

Cimetidine

Co-administration of cimetidine and oxcarbazepine in healthy volunteers was not associated with any significant change in the pharmacokinetics of oxcarbazepine (Keränen et al., 1992b).

Dextropropoxyphene

In a study of eight patients taking oxcarbazepine, dextropropoxyphene administration was without effect on steady-state plasma 10-hydroxycarbazepine concentrations (Mogensen et al., 1992).
Erythromycin

Co-administration of erythromycin and oxcarbazepine to eight healthy volunteers over a 1-week period did not result in any major change in oxcarbazepine or 10-hydroxycarbazepine pharmacokinetic parameters (Keränen et al., 1992a).

Verapamil

The potential interaction between verapamil and oxcarbazepine was investigated in 10 healthy volunteers (Krämer et al., 1991). A 20% decrease in 10-hydroxycarbazepine AUC values was observed and the investigators concluded that this interaction may be of clinical relevance in some patients.

Interactions affected by oxcarbazepine

Felodipine

The potential interaction of oxcarbazepine and felodipine, a calcium antagonist, was studied in eight healthy volunteers (Zaccara et al., 1993). It was observed that the bioavailability of felodipine was reduced by 28% but the clinical relevance of this observation is as yet not clear.

Warfarin

The influence of oxcarbazepine on the anticoagulant effect of warfarin was studied in 10 adult healthy volunteers (Krämer et al., 1992). Oxcarbazepine was without any significant effect as measured by prothrombin time.

Phenobarbital

Phenobarbital is extensively metabolized to two major metabolites, $p$-hydroxyphenobarbital, and 9-$D$-glucopyranosylphenobarbital. CYP2C9 plays a major role in the metabolism of phenobarbital with minor metabolism by CYP2C19 and CYP2E1. Phenobarbital is a potent enzyme inducer. Plasma protein binding is 50%.

Interactions affecting phenobarbital

Activated charcoal

Co-administration of activated charcoal with phenobarbital results in reduction of phenobarbital absorption (Neuvonen and Elonen, 1980). This interaction is used clinically to treat those patients that have overdosed with phenobarbital. After phenobarbital intravenous administration, repeated administration of charcoal over 2–4 days results in an increased phenobarbital clearance (60–270%) whilst half-life values are decreased 2.5–8-fold (Berg et al., 1982, 1987; Frenia et al., 1996).
This effect is considered to be the consequence, in part, of impaired phenobarbital enterohepatic recirculation (Wakabayashi et al., 1994).

**Chloramphenicol**

Co-administration of chloramphenicol and phenobarbital results in a significant decrease (40%) in phenobarbital clearance (Koup et al., 1978).

**Ethanol**

During chronic use, alcohol enhances the metabolism of phenobarbital (Sands et al., 1993). In contrast, the acute effect of alcohol is to inhibit the metabolism of phenobarbital (Forney and Hughes, 1964).

**Interactions affected by phenobarbital**

**Cefotaxime**

High dose phenobarbital administration to children along with β-lactam antibiotics results in toxic exanthematous skin reactions in about 50% of cases (Harder et al., 1990). This potentiating of antibiotic-related allergic features is particularly prevalent in children receiving phenobarbital and cefotaxime in combination. This interaction may be pharmacodynamic in nature.

**Cimetidine**

Phenobarbital enhances the metabolism and clearance (15%) of cimetidine (Somogyi et al., 1981).

**Cyclosporin**

Phenobarbital can significantly enhance the metabolism of cyclosporin in a dose-dependent manner (Carstensen et al., 1986; Nishioka et al., 1990). Withdrawal of phenobarbital from a paediatric renal transplant patient resulted in a 70% reduction in cyclosporin clearance (Burckart et al., 1984).

**Dexamethasone**

The administration of dexamethasone intravenously to asthmatic patients receiving phenobarbital was associated with significantly shorter dexamethasone half-life values (45%) and increased clearance (87%), when compared to values before phenobarbital administration (Brooks et al., 1972).

**Felodipine**

The clearance of felodipine can be significantly enhanced (~9-fold) by phenobarbital co-administration (Capewell et al., 1988).
Fentanyl
Phenobarbital enhances the metabolism of fentanyl and decreases its plasma concentration (Tempelhoff et al., 1990).

Folic acid
As phenobarbital is a potent hepatic enzyme inducer, it enhances the metabolism of folic acid and, typically, folate concentrations can be reduced by 24% during long-term treatment (Reynolds, 1974). Consequently, folic acid supplementation is mandatory if one is to avoid adverse foetal outcome (e.g. neural tube defects) that is associated with low plasma folate concentrations (Kishi et al., 1997).

Ifosfamide
A reversible toxic encephalopathy was reported in a girl with epilepsy who was taking phenobarbital. The symptoms presented after a single dose of ifosfamide/mesna and the authors concluded that it was the consequence of an interaction with phenobarbital (Ghosn et al., 1988).

Itraconazole
Phenobarbital decreases plasma itraconazole concentrations (Bonay et al., 1993).

Metronidazole
Phenobarbital enhances the metabolism of metronidazole resulting in significant decreases in metronidazole half-life (23%) and AUC (30%) values (Eradiri et al., 1988). This drug interaction is associated with clinical failure of metronidazole treatment in women with vaginal trichomoniasis and gardiasis (Mead et al., 1982; Gupte, 1983).

Methylprednisolone
The co-administration of methylprednisolone with phenobarbital results in pharmacokinetic changes to methylprednisolone, which are similar in magnitude to that described for dexamethasone (Stjernholm and Katz, 1975; Wassner et al., 1976).

Nifedipine
The clearance of nifedipine can be significantly (270%) enhanced by phenobarbital co-administration (Schellens et al., 1989).

Nimodipine
The clearance of nimodipine can be significantly enhanced (nine-fold) by phenobarbital co-administration (Tartara et al., 1991). Thus clinically relevant reduced nimodipine efficacy can be observed.
Prednisolone
Phenobarbital enhances the metabolism of prednisolone resulting in significantly shorter (32%) prednisolone half-life values and increased (44%) clearance values. Co-administration of prednisolone with phenobarbital in patients with rheumatoid arthritis has resulted in shorter (25%) half-life values and marked worsening of clinical symptoms (Brooks, S., et al., 1972; Brooks, P., et al., 1976).

Teniposide
Phenobarbital co-administered with teniposide results in a two- to three-fold increase in clearance of teniposide (Baker et al., 1992). The resultant reduced efficacy of teniposide (Relling et al., 1994) is the consequence of induction of CYP3A4 and possibly CYP3A5 (Relling et al., 2000).

Theophylline
Phenobarbital enhances (34%) the clearance of theophylline in older children and adults (Landay et al., 1978; Saccar et al., 1985; Yazdani et al., 1987). However, in premature neonates this interaction does not occur (Kandrotas et al., 1990).

Tirilazad
Phenobarbital significantly decreases plasma concentrations of tirilazad by 50–69% (Fleishaker et al., 1996).

Tolbutamide
Phenobarbital increases the free fraction of tolbutamide by displacing it from plasma protein-binding sites (Fernandez et al., 1985). The clinical significance of this interaction is not established.

Verapamil
The clearance of orally ingested verapamil can be enhanced five-fold during combination therapy with phenobarbital. When verapamil was administered intravenously, the clearance of verapamil was enhanced two-fold (Rutledge et al., 1988).

Warfarin
Co-administration of warfarin and phenobarbital results in a significant increase (≈50%) in warfarin clearance and a decrease in its half-life (≈40%) (Orme and Breckenridge, 1976). These changes are accompanied by a 25% reduction in prothrombin time which may persist for 3–4 weeks after phenobarbital discontinuation (Udall, 1975; Cropp and Bussey, 1997). This prolonged effect requires that patients are closely monitored.
Phenytoin

PHT is eliminated almost entirely by metabolic transformation. Metabolism is via the isoenzymes CYP2C9 and CYP2C19. PHT is an enzyme inducer (CYP2A, CYP2C and CYP3A) and has a high propensity to interact with other drugs. Plasma protein binding is 92%.

Interactions affecting phenytoin

Activated charcoal

Co-administration of activated charcoal with PHT results in reduction of PHT absorption (Welling, 1984). This interaction is used clinically to treat those patients that have overdosed with PHT.

Acyclovir

Co-administration of PHT and acyclovir may result in a reduction in PHT plasma concentrations (Permeggiani et al., 1995).

Amiodarone

Amiodarone is potent inhibitor of CYP2C9. In healthy subjects, amiodarone has been observed to increase the half-life of PHT several fold (Nolan et al., 1989), whilst in patients, plasma PHT concentrations have been increased two- to three-fold (McGovern et al., 1984), resulting in possible PHT intoxication.

Antacids

The gastrointestinal absorption of PHT may be reduced by co-ingestion with antacids such as aluminium or magnesium hydroxides and calcium bicarbonate. This interaction is avoided if the ingestion of PHT and the antacid is separated by a few hours. Sucralfate, a complex of aluminium hydroxide and sulphated sucrose, which has minimal antacid properties but acts by protecting the mucosa from acid–pepsin attack, can similarly impede the absorption of PHT.

Antineoplastic agents

It has been reported that antineoplastic agents such as adriamycin, bleomycin, cisplatin or vinblastine can decrease plasma PHT concentrations (Bollini et al., 1983; Sylvester et al., 1984; Neef and de Voogd-van der Straaten, 1988). It has been reported that a young woman with epilepsy had seizures during antineoplastic therapy and that the seizures were the consequence of a reduced (37%) plasma PHT concentration (Neef and de Voogd-van der Straaten, 1988). The mechanism of this interaction may be induction of metabolism or an increased volume of
distribution. In contrast, tamoxifen has been associated with increased plasma PHT concentrations and signs of PHT toxicity (Rabinowicz et al., 1995).

**Bishydroxycoumarin**
Plasma bishydroxycoumarin concentrations can increase in some patients co-administered with PHT (Skovsted et al., 1974).

**Calcium channel blockers**
Whilst verapamil and nifedipine have little or no effect on plasma PHT concentrations, diltiazem may cause an elevation and cause PHT intoxication in some patients (Bahls et al., 1991).

**Chloramphenicol**
Whilst chloramphenicol may cause only modest elevations of plasma PHT concentrations in some patients, it may produce marked elevations in others (Koup, 1978; Nation et al., 1990).

**Cimetidine**
Cimetidine inhibits the metabolism of PHT thereby increasing plasma PHT concentrations and this may result in clinical intoxication (Salem et al., 1983; Phillips and Hansky, 1984; Levine et al., 1985).

**Disulfiram**
Disulfiram inhibits the metabolism of PHT and increases its plasma concentration. This can result in signs of PHT intoxication in the majority of patients (Olesen, 1967; Levy, 1995). In healthy volunteers, disulfiram was shown to reduce PHT clearance by 30% (Svendsen et al., 1976).

**Ethanol**
Chronic use of alcohol decreases plasma PHT concentrations, probably as a consequence of enzyme induction (Sandor et al., 1981), whereas occasional moderate or heavy alcohol consumption can result in an increase in PHT plasma concentration and this can result in PHT toxicity (Kutt, 1984).

**Fluconazole**
Fluconazole inhibits both CYP2C9 and CYP2C19 activities and consequently would be expected to inhibit the metabolism of PHT. Indeed there are several case reports, both of healthy volunteers and patients, that describe significant increases in plasma PHT concentrations and toxicity during combination therapy with
fluconazole (Howit and Oziemski, 1989; Mitchell and Holland, 1989; Blum et al., 1990; Lazar and Wilner, 1990; Cadle et al., 1994; Levy, 1995).

Isoniazid

PHT metabolism is inhibited by isoniazid. In patients taking isoniazid and PHT, significant PHT accumulation with consequent intoxication has been reported in 10–15% of patients (de Wolff et al., 1983; Witmer and Ritschel, 1984). This interaction would be particularly prevalent in patients that exhibit slow acetylation. In the Groote Schuur Hospital, South Africa, where 74% of patients with epilepsy are taking PHT, it has been observed that ~12% of patients have plasma PHT concentrations in the toxic range because they are taking antituberculous medication of which the primary drug is isoniazid (Walubo and Aboo, 1995).

Miconazole

As miconazole is an inhibitor of CYP2C9, it inhibits the metabolism of PHT resulting in elevated plasma PHT concentrations and symptoms of PHT toxicity (Rolan et al., 1983; Levy, 1995).

Omeprazole

In healthy subjects, the co-administration of omeprazole with PHT has been shown to result in a significant increase in PHT plasma concentrations (Gugler and Jensen, 1985; Prichard et al., 1987).

Phenylbutazone

When PHT and phenylbutazone are co-administered, the half-life of PHT is significantly increased and this may be accompanied by clinical intoxication (Levy, 1995). The mechanism of this interaction involves the displacement of PHT from plasma albumin binding sites and a concurrent inhibition of PHT metabolism (Skovsted et al., 1974). Thus, the interaction can present as an increase in the free pharmacologically active concentration of PHT in the absence of a change in the total PHT concentration. Dosage adjustment may be needed and should be based on the measurement of free PHT concentrations.

Propoxyphene

Propoxyphene inhibits the metabolism of PHT via an action on CYP2C9 (Levy, 1995). The consequent increase in plasma PHT concentrations can result in intoxication (Dam et al., 1980; Kutt, 1984).

Rifampin

Rifampin may significantly increase the clearance of PHT by as much as two-fold and consequently decrease plasma PHT concentrations (Kay et al., 1985). It should
be noted that rifampin minimizes the inhibitory effect of isoniazid on PHT, even in patients that are slow acetylators.

Salicylates

Although salicylates can displace PHT from its plasma protein-binding site so that the unbound fraction of PHT is increased from 10% to 16%, the concurrent increase in PHT clearance makes this interaction of little clinical significance for the majority of patients (Fraser et al., 1980).

Sulfonamides

Numerous bacteriostatic sulfonamides (sufadiazine, sulfamethiazole, sulfamethoxazole and sulfaphenazole) are inhibitors of PHT metabolism and can decrease its clearance and prolong its half-life (Molhom Hansen et al., 1979). Sulfaphenazole is particularly potent in this regard.

Ticlopidine

Ticlopidine is a potent CYP2C19 inhibitor. Consequently, when co-administered with PHT the clearance of PHT is decreased and PHT intoxication can occur (Privitera and Welty, 1996; Klaassen, 1998; Denahue et al., 1999).

Tolbutamide

Tolbutamide displaces PHT from its plasma protein-binding sites and this can result in lower plasma PHT concentrations (Wesseling and Molsthurkow, 1975). However, as free PHT concentrations are unaffected, this interaction is not of clinical significance.

Interactions affected by phenytoin

Acetaminophen (paracetamol)

PHT enhances the metabolism of acetaminophen and reduces its plasma concentration (Nation et al., 1990).

Chloramphenicol

During combination therapy with PHT and chloramphenicol, plasma chloramphenicol concentrations have been observed to decline significantly (Krasinski et al., 1982).

Cyclophosphamide

It has been reported that PHT increases the clearance of both the R- and S-isomers of cyclophosphamide by 100% and 150%, respectively (Williams, M., et al., 1999).
Cyclosporin

PHT significantly enhances the metabolism of cyclosporin and reduces its maximal plasma concentration as well as AUC and half-life values, resulting in a reduction of the clinical efficacy of cyclosporin (Freeman et al., 1984).

Dexamethasone

The metabolism of dexamethasone is substantially enhanced by PHT, probably via enzyme induction. In one study the elimination half-life of dexamethasone was reduced from 3.5 to 1.8 h (Chalk et al., 1984). In another patient study, plasma dexamethasone concentrations were reduced by 50% (Wong et al., 1985).

Dicoumarol

PHT can decrease blood dicoumarol concentrations, probably via induction of metabolism (Hansen, J., et al., 1971). Overall, whenever there is a change in PHT therapy (and indeed that of any other enzyme-inducing AED) it is advisable to monitor INR because all anticoagulants are associated with a narrow therapeutic ratio (Cropp and Bussey, 1997).

Digitoxin

In some patients, PHT is associated with a modest reduction in plasma digitoxin concentrations (Solomon et al., 1971).

Digoxin

In healthy volunteers, PHT increased digoxin clearance by 27% and this was associated with a significant decrease in its half-life (Rameis, 1985).

Disopyramide

Although PHT enhances the metabolism of disopyramide and therefore reduces plasma disopyramide concentrations, the fact that plasma concentration of its pharmacologically active metabolite is also increased, may not necessarily result in a loss of effectiveness (Aitio et al., 1981).

Doxycycline

PHT enhances the metabolism of doxycycline and decreases its plasma concentration (Neuvonen et al., 1975).

Fluconazole

Plasma fluconazole concentrations are substantially reduced during co-medication with PHT probably via induction of fluconazole metabolism (Tucker et al., 1992).
Folic acid

As PHT is a potent hepatic enzyme inducer, it enhances the metabolism of folic acid (Lewis et al., 1995). Consequently, folic acid supplementation is mandatory if one is to avoid adverse fetal outcomes (e.g., neural tube defects) that are associated with low plasma folate concentrations (Kishi et al., 1997).

Furosemide

The diuretic effect of furosemide is reduced when PHT is co-administered. The interaction is primarily due to a reduction in furosemide absorption from the alimentary tract but a pharmacodynamic interaction in the kidneys may also occur (Ahmad, 1974).

Itraconazole

In healthy volunteers, PHT has been observed to decrease itraconazole AUC values by 93% and half-life values by 83% (Tucker et al., 1992; Ducharme et al., 1995).

Ketoconazole

Plasma ketoconazole concentrations are substantially reduced during co-medication with PHT probably via induction of ketoconazole metabolism (Tucker et al., 1992).

Methadone

Plasma methadone concentrations were decreased by ~50% during co-medication with PHT (Tong et al., 1981). In this setting patients may experience symptoms of methadone withdrawal.

Meperidine (pethidine)

During combination therapy with PHT and meperidine, the half-life of meperidine was reduced by ~30% and the AUC of its primary metabolite was increased (Pond and Kretschzmar, 1981).

Methotrexate

PHT increases the clearance of methotrexate. This interaction has been reported to compromise the efficacy of methotrexate in the treatment of lymphoblastic leukemia in children (Relling et al., 2000).

Mexiletine

In healthy volunteers, PHT increased the metabolism of mexiletine and reduced the AUC of mexiletine by 55% (Begg et al., 1982).
Misonidazole
PHT enhances the metabolism of misonidazole and reduces its half-life. Therefore, lower plasma misonidazole concentrations are achieved which may serve to reduce the toxicity of misonidazole whilst not reducing its effectiveness as a therapeutic adjunct in radiation therapy (Williams, K., et al., 1983).

Nisoldipine
In patients with epilepsy, PHT has been observed to significantly enhance the metabolism of nisoldipine with a mean reduction in nisoldipine AUC values of ~90% (Nation et al., 1990; Michelucci et al., 1996).

Praziquantel
PHT induces the metabolism of praziquantel, a drug used to treat neurocysticercosis. The interaction results in a two- to three-fold reduction in plasma praziquantel concentrations (Bittencourt et al., 1992).

Prednisolone
PHT enhances the clearance of prednisolone and consequently reduces the effectiveness of this corticosteroid (Nation et al., 1990).

Quinidine
PHT decreases the half-life of quinidine by 50% (Nation et al., 1990).

Rocuronium
In patients taking PHT chronically, muscle relaxation after rocuronium administration was only achieved at higher doses of rocuronium and also it was necessary to administer rocuronium more frequently (Soriano et al., 2000). This effect is considered to be the consequence of enzyme induction.

Teniposide
PHT induces the metabolism and enhances the clearance of teniposide and this interaction is of clinical significance (Baker et al., 1992; Relling et al., 2000).

Theophylline
In healthy volunteers, PHT administration (300–400 mg/day) was associated with an enhanced clearance and a 40% reduction in theophylline half-life values after intravenously administered theophylline (Jonkman and Upton, 1984; Sklar and Wagner, 1985).
Tirilazad

In healthy volunteers PHT enhanced the clearance of tirilazad by ~92% (Fleishaker et al., 1998). The mechanism of this interaction is probably enzyme induction.

Vecuronium

In patients taking PHT chronically, muscle relaxation after vecuronium administration was only achieved at higher doses of vecuronium and it was necessary to administer vecuronium more frequently (Platt and Thackery, 1993). This effect is considered to be the consequence of enzyme induction.

Warfarin

The effect of PHT on warfarin is variable. Overall, the observed interaction involves a reduction in warfarin blood concentrations, via hepatic induction of warfarin metabolism. However, an increase in anticoagulant effect has been reported in some patients (Nappi, 1979). Overall, whenever there is a change in PHT therapy (and indeed that of any other enzyme-inducing AED) it is advisable to monitor INR because all anticoagulants are associated with a narrow therapeutic ratio (Cropp and Bussey, 1997).

Primidone

Primidone is metabolized to two pharmacologically active metabolites, namely phenylethylmalonamide and phenobarbital. Phenobarbital, the primary metabolite, subsequently undergoes oxidation to form p-hydroxyphenobarbital. Primidone, via its metabolite phenobarbital, is an enzyme inducer. Plasma protein binding of primidone is 15%. The interactions of primidone are primarily those involving phenobarbital.

Interactions affecting primidone

Acetazolamide

Acetazolamide may impair the absorption of primidone (Syverson et al., 1977). Similar effects can be expected with other drugs that alter gastric pH (antacids) or motility.

Isoniazid

Isoniazid decreases the conversion of primidone to phenobarbital resulting in increased plasma primidone concentrations. The interaction is considered to be a consequence of CYP inhibition (Sutton and Kupferberg, 1975).
Nicotinamide decrease the conversion of primidone to phenobarbital resulting in increased plasma primidone concentrations. The interaction is considered to be a consequence of CYP inhibition (Bourgeois et al., 1982).

**Interactions affected by primidone**

**Folic acid**

The absorption of folic acid appears to be hindered by primidone (Reynolds et al., 1972).

**Tiagabine**

Tiagabine is extensively metabolized by CYP3A and is also extensively protein bound (98%).

As a new AED, knowledge of the interaction profile of tiagabine with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

**Interactions affecting tiagabine**

**Cimetidine**

A multiple-dose crossover study of the effect of cimetidine on the pharmacokinetics of tiagabine showed a small (~5%) increase in tiagabine plasma concentrations (Mengel et al., 1995). This is not considered to be of clinical significance.

**Erythromycin**

The effect of erythromycin on the pharmacokinetics of tiagabine in 13 healthy volunteers was investigated and it was observed that erythromycin was without effect (Thompson et al., 1997).

**Other drugs**

The effects of numerous other drugs on the pharmacokinetics of tiagabine have been investigated. Triazolam (Richens et al., 1998), ethanol (Kastberg et al., 1998), theophylline (Mengel et al., 1995), digoxin (Snel et al., 1998) or warfarin (Mengel et al., 1995) showed no effect.

In vitro studies have shown that tiagabine is displaced from its protein-binding sites by the analgesics naproxen and salicylate (Brodie, 1995; Gustavson and Mengel 1995; Patsalos et al., 2002). The clinical significance of these interactions is not known.
Interactions affected by tiagabine

**Digoxin**

Tiagabine was without effect on the pharmacokinetics of digoxin in a series of 13 healthy volunteers (Snel et al., 1998).

**Ethanol**

Tiagabine was without effect on the pharmacokinetics of ethanol in a series of 20 healthy volunteers (Mengel et al., 1995; Kastberg et al., 1998).

**Theophylline**

Tiagabine was without effect on the pharmacokinetics of theophylline in healthy volunteers (Mengel et al., 1995).

**Triazolam**

Tiagabine was without effect on the pharmacokinetics of triazolam in healthy volunteers (Mengel et al., 1995).

**Warfarin**

The pharmacokinetics of warfarin are unaffected by warfarin (Mengel et al., 1995). Tiagabine does not appear to displace other highly protein-bound drugs, such as amitriptyline, tolbutamide and warfarin, from their plasma protein-binding sites (Brodie, 1995).

Topiramate

In the absence of hepatic enzyme inducers, only 40% of topiramate is metabolized, whilst in the presence of inducers this value is doubled. Although the specific CYP isoenzymes responsible for the metabolism of topiramate have not been identified, it is evident that isoenzymes induced by carbamazepine (CYP3A4) and PHT (CYP2C9 and CYP2C19) play a major role. Elimination occurs both via hepatic metabolism and renal excretion. Plasma protein binding is 10%.

As a new AED, knowledge of the interaction profile of topiramate with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting topiramate

There have been no clinical studies to investigate the effect of non-AEDs on the pharmacokinetics of topiramate.
Interactions affected by topiramate

Digoxin
In a study of 12 healthy volunteers the pharmacokinetics of a single oral dose of digoxin were compared during monotherapy and in combination with topiramate (Liao and Palmer, 1993). Digoxin plasma concentrations were reduced by 16% and clearance was increased by 13% during topiramate administration when compared with administration of digoxin alone.

Valproic acid
The metabolism of valproic acid is both extensive and complex in that it involves multiple metabolic pathways, including β- and ω-oxidation, CYP2A6, CYP2C9, CYP2C19 and CYP2B6 isoenzymes and glucuronidation by UGT. To date, in excess of 25 metabolites of valproic acid have been identified. Valproic acid is 92% protein bound.

Interactions affecting valproic acid

Cholestyramine
There is a report suggesting that cholestyramine may decrease valproic acid plasma concentrations during combination therapy (Malloy et al., 1996).

Cimetidine
Cimetidine inhibits the metabolism of valproic acid and increases its plasma concentrations (Webster et al., 1984).

Cisplatin
It has been reported that a young woman with epilepsy presented with seizures during antineoplastic therapy and that the seizures were the consequence of a reduced valproic acid plasma concentration (Neef and de Voogd-van der Straaten, 1988). The mechanism of this interaction may be induction of metabolism or an increased volume of distribution.

Doxorubicin
Doxorubicin (adryamicin) can decrease plasma valproic acid concentrations (Neef and de Voogd–van der Straaten, 1988).

Ibuprofen
In vitro data show that ibuprofen can significantly displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid
Isoniazid

Isoniazid may increase valproic acid plasma concentrations resulting in clinically significant intoxication (Jonville et al., 1991).

Ketoconazole

In vitro data show that ketoconazole can significantly displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid (Dasgupta and Luke, 1997). The clinical significance of this interaction is not known.

Mefenamic acid

In vitro data show that mefenamic acid can significantly displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid (Dasgupta and Volk, 1996). The clinical significance of this interaction is not known.

Methotrexate

Methotrexate significantly decreases (75%) plasma valproic acid concentrations (Schroder and Ostergaard, 1999).

Naproxen

In vitro data show that naproxen can significantly displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid (Dasgupta and Volk, 1996). The clinical significance of this interaction is not known.

Rifampicin

Rifampicin enhances the metabolism of valproic acid and its clearance can increase by 40%.

Salicylic acid

Salicylic acid displaces valproic acid from its protein-binding sites on albumin and consequently higher unbound concentrations occur (Fleitman et al., 1980; Abbott et al., 1986). In addition, salicylic acid inhibits the metabolism of valproic acid (Schobben et al., 1978; Goulden et al., 1987). The combination of these two effects can result in elevated valproic acid plasma concentrations and consequent toxicity.
Tolbutamide
Tolbutamide can displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid (Fernandez et al., 1985). The clinical significance of this interaction is not known.

Tolmetin
In vitro data show that tolmetin can significantly displace valproic acid from its plasma protein-binding sites and increase the free concentration of valproic acid (Dasgupta and Volk, 1996). The clinical significance of this interaction is not known.

Interactions affected by valproic acid

Warfarin
Valproic acid can displace warfarin from its plasma protein-binding sites but this is not considered to be of clinical significance (Panjehshahin et al., 1991).

Zidovudine
The clearance of zidovudine is significantly reduced by valproic acid resulting in elevated plasma (Lertora et al., 1993) and cerebrospinal fluid concentrations (Akula et al., 1997). The probable mechanism of this effect is by inhibition of zidovudine glucuronidation (Lertora et al., 1993).

Vigabatrin
Vigabatrin is not metabolized and is exclusively eliminated as unchanged vigabatrin in urine. It is not protein bound. Consequently vigabatrin should have little propensity to interact with other drugs and indeed this is the case.

As a new AED, knowledge of the interaction profile of vigabatrin with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting vigabatrin
To date there have been no reports of non-AEDs affecting the pharmacokinetics of vigabatrin.

Interactions affected by vigabatrin
To date there have been no reports of vigabatrin affecting the pharmacokinetics of non-AEDs.
Zonisamide

Zonisamide undergoes extensive metabolism, via CYP3A4, and approximately 30% of zonisamide is excreted in urine as unchanged zonisamide. Plasma protein binding is 50%.

As a new AED, knowledge of the interaction profile of zonisamide with non-AEDs is rather limited. Only interactions with specific drugs have been investigated.

Interactions affecting zonisamide

Sulfonamides

In vitro studies show that sulfonamides can readily displace zonisamide from its binding to erythrocytes (Matsumoto et al., 1989) but not from albumin (Matsumoto et al., 1983). The clinical significance of this interaction is not known.

Other drugs

In vitro studies have shown that the metabolism of zonisamide is inhibited in descending order of potency by ketoconazole, cyclosporin, dihydroergotamine, itraconazole, miconazole, triazolam and fluconazole (Sugihara et al., 1996). The clinical significance of these interactions is not known.

Interactions affected by zonisamide

To date there are no reports of zonisamide affecting the pharmacokinetics of non-AEDs.

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177 Interaction between antiepileptic and non-antiepileptic drugs


Part III

Pharmacodynamic interactions
Pharmacodynamic principles and mechanisms of drug interactions

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Distinction between pharmacodynamic and pharmacokinetic drug interactions

The term pharmacokinetics refers to mostly quantitative assessments of what happens to a drug in the body following its administration by any route. The processes that are assessed include absorption into the blood, serum protein binding, distribution into various tissues or compartments, biotransformation, and elimination from the body. The drug can be eliminated unchanged through the kidneys or in the form of a conjugate or metabolite following conjugation or enzymatic biotransformation in the liver. Metabolites can be eliminated through the kidneys or through the bile. Pharmacokinetics rely on measurements of drug concentrations in various body fluids or tissues (in practice mostly in the blood, urine, or saliva) and assessments of changes in these concentrations over time. The clinical relevance of pharmacokinetics is based on the fact that optimal treatment with a drug requires achieving and maintaining certain levels in the target organs, and corresponding levels in the blood.

The term pharmacodynamics refers to qualitative and quantitative assessments of all possible effects of a drug in various organs of the body. These effects may include:

1. one or more desirable therapeutic effects (e.g. seizure reduction, prevention of migraine headaches or a positive psychotropic effect);
2. one or more undesirable/harmful adverse effects (e.g. sedation or an allergic reaction);
3. side effects that may be either desirable or undesirable (e.g. weight loss);
4. side effects that are neither desirable nor undesirable (e.g. elevation of gamma-glutamyl transpeptidase (gamma-GT), lowering of bilirubin levels).

Some desirable and undesirable pharmacodynamic drug effects can be assessed quantitatively (e.g. seizure reduction, excessive weight gain, and hyponatremia), some can be assessed semi-quantitatively (e.g. decreased seizure severity, sedation
or gum hypertrophy), and some can virtually not be assessed quantitatively (mostly idiosyncratic reactions). Obviously, pharmacodynamics are more complex and more difficult to assess than pharmacokinetics. Also, since many pharmacodynamic effects of drugs are related to concentrations, pharmacodynamic observations may be influenced by pharmacokinetics. However, pharmacodynamics have no influence on pharmacokinetics, with the exception of hepatic enzyme induction and inhibition.

Based on the above concepts, there is a fundamental difference between pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions consist of alterations in the concentration of a drug that are caused by the presence of another drug in the body. This may include competition for absorption, displacement from protein-binding sites, enzymatic induction, enzymatic inhibition, or competition for renal excretion. Pharmacokinetic interactions are relatively easy to assess quantitatively. They are mostly undesirable but, when they are known, they can be anticipated and corrected. Any pair of drugs may or may not have pharmacokinetic interactions.

Pharmacodynamic interactions consist of the quantitative or qualitative alterations of any effect of a drug on any organ when these alterations are caused by the presence of another drug in the body. Pharmacodynamic interactions are much more difficult to assess quantitatively. They can be desirable (enhancement of a therapeutic effect or reduction of an adverse effect) or undesirable (enhancement of an adverse effect or reduction of a therapeutic effect). However, even when they are known and predicted, pharmacodynamic interactions cannot be influenced, corrected, or avoided. By altering drug concentrations, pharmacokinetic interactions may cause apparent pharmacodynamic interactions in the absence of a true pharmacodynamic interaction. However, pharmacodynamic interactions will never cause an apparent pharmacokinetic interaction.

**Types of pharmacodynamic interaction**

In order for two drugs to have a pharmacodynamic interaction, they have to share at least one common pharmacodynamic property or, more specifically, they have to share an identifiable clinical effect. Just as pharmacokinetic interactions may result in a drug concentration that is greater or smaller than expected, a pharmacodynamic interaction may result in a measurable response that is greater or smaller than expected. In general, it is assumed that each drug alone could elicit that response to some extent. However, it is conceivable that a specific effect of a drug could be enhanced or inhibited by another drug that does not have that particular effect by itself, even in the absence of a pharmacokinetic interaction. Nevertheless, for most pairs of drugs that do not share a common effect, the
pharmacodynamic interaction will be absent or indifferent. For instance, in the absence of a pharmacokinetic interaction, an antiepileptic drug (AED) is unlikely at any dose to alter the antimicrobial effect of an antibiotic, and an antibiotic is unlikely to alter the seizure protection provided by an AED. Of course, if that antibiotic is known to lower the seizure threshold by itself, it could diminish the seizure protection provided by the AED and this would represent a pharmacodynamic interaction.

The various types of pharmacodynamic interaction are listed in Table 9.1. If the combined effect C of drug A and B administered together corresponds to the expected sum of the effects of drug A alone and drug B alone, the interaction is said to be additive. If the combined effect is greater than the expected sum, the interaction is said to be supra-additive. A supra-additive effect is also called potentiation and the terms can be considered to be synonymous. The term synergism is used by some synonymously with a supra-additive effect, but it has been argued that synergism means literally that drugs just work together. Therefore, the term synergism should be used preferably for any type of pharmacodynamic interaction that is not indifferent. When the combined effect of two drugs is greater than that of each drug alone at the same concentration, but less than the expected sum of the two actions, the pharmacodynamic interaction is said to be infra-additive. As there is no other reason why a drug should be less effective in combination than when it is given alone, this type of pharmacodynamic interaction is also called antagonistic. This implies that at least one of the two drugs somehow decreases the effectiveness of the other. Antagonism may exist between two drugs with a common pharmacological effect and, of course, between two drugs with an opposite pharmacological effect (for instance elevation and lowering of the seizure threshold).

These definitions raise one obvious question: what is the expected sum of the effects of two drugs that are administered together and how is it determined? The difficulty of quantifying individual and combined drug actions is the main reason why pharmacodynamic interactions are much more difficult to assess than the pharmacokinetic interactions. For most AEDs the relationship between dose and level is linear, such as the relationship between single dose and peak level, or

<table>
<thead>
<tr>
<th>Table 9.1 Basic pharmacodynamic interactions</th>
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<tbody>
<tr>
<td><strong>Additive</strong></td>
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<tr>
<td>$C = A + B$</td>
</tr>
<tr>
<td><strong>Supra-additive</strong></td>
</tr>
<tr>
<td>$C &gt; A + B$</td>
</tr>
<tr>
<td><strong>Infra-additive</strong></td>
</tr>
<tr>
<td>$C &lt; A + B$</td>
</tr>
<tr>
<td><strong>Indifferent</strong></td>
</tr>
<tr>
<td>$C = A$ and/or $B$</td>
</tr>
</tbody>
</table>

A, effect of drug A alone; B, effect of drug B alone;
C, combined effect of drugs A and B administered together;
A + B, expected sum of individual effects of drugs A and B.
between maintenance dose and steady-state level (the main exception to this rule is phenytoin). If the administered dose is doubled, this will result in a level that is twice as high. In contrast, the magnitude of the response to a drug as a function of its dose or of its concentration usually follows a sigmoid curve (see Figure 9.1). Therefore, at twice the dose or level of drug A, the magnitude of the response is not twice as high. It may be less or it may be greater. Similarly, the magnitude of the response to combined doses of two drugs that produce the same effect individually will not be twice the magnitude of the individual effect. These issues will be addressed in detail in the next chapter devoted to the methods for assessing pharmacodynamic interactions.

**Clinical significance of pharmacodynamic interactions**

Whenever a patient takes two or more medications simultaneously, there is the potential for some type of pharmacodynamic interaction. If, in the absence of a pharmacokinetic interaction, any clinical response to one of the drugs is enhanced or reduced by another drug, a pharmacodynamic interaction can be assumed. For the desirable primary effect of either drug, and for the desirable and undesirable secondary effect of either drug, the interaction can be additive, supra-additive or infra-additive. The clinical spectrum of possible pharmacodynamic interactions is summarized in Table 9.2:

1. The common primary therapeutic effect of two drugs can be enhanced when they are administered together. An obvious example would be further seizure reduction when a second AED is added to the first.
2. A common adverse effect of two drugs can be enhanced when they are administered together. An example would be increased sedation when a second potentially sedative AED is added to the first.
The common primary therapeutic effect can be reduced, or less than additive, when two drugs are administered together. An example would be a lack of further seizure reduction, or even an increase in seizure frequency, when two AEDs are administered together, compared with each one administered alone.

A common adverse effect of two drugs can be reduced, or less than additive, when they are administered together. For example, there may be no increase in sedation when a second potentially sedative AED is added to the first.

The therapeutic effect of a drug could be enhanced by a drug that does not by itself possess this property. For instance, the seizure protection by an AED could be enhanced by adding another drug for which no antiepileptic efficacy has been demonstrated.

Inversely, an adverse effect of a drug could be enhanced by the addition of a second drug that does not by itself cause this adverse effect. For instance, the incidence of liver failure could be higher when a drug is combined with other drugs that do not cause liver failure.

The therapeutic effect of a drug can be reduced after the addition of a second drug that does not share this therapeutic effect or that has an opposite effect. For example, the seizure frequency can increase when an AED is combined with a drug that potentially can lower the seizure threshold, such as certain psychoactive drugs.

Finally, an adverse effect of a drug can be reduced by the addition of a drug that does not share this side effect, or that has an opposite effect. For example, the sedative effect of an AED could be reduced after the addition of a psychostimulant.

Whenever two or more drugs are taken simultaneously by a patient, more than one pharmacodynamic interaction may occur, and any combination of the interactions listed in Table 9.3 is possible. Whether or not a drug combination is therapeutically more desirable than the individual drugs taken alone will ultimately not depend on a single pharmacodynamic interaction between the drugs, but on the ultimate clinical result of all the pharmacodynamic interactions that exist between the drugs.

### Table 9.2 Clinical spectrum of pharmacodynamic interactions

<table>
<thead>
<tr>
<th>1</th>
<th>Enhancement of common (primary) therapeutic effect</th>
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<tr>
<td>2</td>
<td>Enhancement of common adverse effect</td>
</tr>
<tr>
<td>3</td>
<td>Reduction of or less than additive common therapeutic effect</td>
</tr>
<tr>
<td>4</td>
<td>Reduction of or less than additive common adverse effect</td>
</tr>
<tr>
<td>5</td>
<td>Enhancement of a therapeutic effect that is not shared by the drugs</td>
</tr>
<tr>
<td>6</td>
<td>Enhancement of an adverse effect that is not shared by the drugs</td>
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<tr>
<td>7</td>
<td>Reduction of a therapeutic effect that is not shared by the drugs</td>
</tr>
<tr>
<td>8</td>
<td>Reduction of an adverse effect that is not shared by the drugs</td>
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</table>
Desirable and undesirable pharmacodynamic interactions

Potential advantages of drug combinations
Better effectiveness (higher-therapeutic index)
Milder or absent (subthreshold) side effects
Broader spectrum of seizure control

Potential disadvantages of drug combinations
Potentiation of side effects (lower-therapeutic index) or more, different side effects
Idiosyncratic toxicity
Seizure exacerbation

Desirable interactions

Potential clinical advantages and disadvantages of drug combinations over single drug therapy are listed in Table 9.3. Although enhancement of the primary therapeutic efficacy seems to be the obvious pharmacodynamic interaction that will render a particular drug combination desirable, other considerations will have to be included in order to take into account clinical realities. For instance, in the treatment of epilepsy, further seizure reduction could be achieved by increasing the dose of an AED in monotherapy. However, even if the efficacy of the drug continues to increase as its dose is increased, there will come a point when the patient will no longer tolerate a further dosage increase because of dose-related adverse effects. The maximal tolerated dose is an easily defined clinical therapeutic endpoint. The clinical value of a drug will be determined not only by its efficacy, but also by its tolerability. This relationship between efficacy and tolerability can be expressed as the therapeutic index (for instance the ratio between toxic dose and therapeutic dose). It can also be expressed as clinical effectiveness, which reflects both efficacy and tolerability (Deckers et al., 2000). If a drug is more efficacious at a high dose but not tolerated, it will not be more effective at a higher dose. These considerations that apply to increases in the dosage of a single drug also apply to the addition of a second drug. In order for a combination of two drugs to be more desirable than either drug taken alone, the combination has to be more effective than either drug alone. In other words, either the combination provides better seizure protection at the maximal tolerated dose, or it is better tolerated at the same level of seizure protection than either drug alone. In both cases, the combination can be said to be more effective or to have a better therapeutic index. Whether or not this is the case for a certain combination of two drugs will depend on the ultimate result of all possible pharmacodynamic interactions that occur between the two drugs. Specifically, this may be the case if the common therapeutic effect (for
instance seizure protection) is supra-additive and the dose-related adverse effects are additive or infra-additive, or if the therapeutic effect is additive and the dose-related adverse effects are infra-additive. If, however, the therapeutic effect and the adverse effects are both supra-additive, or both additive, the combination is unlikely to be clinically more effective than either drug taken alone.

A drug combination could be superior to either drug used alone by causing milder side effects or no side effects, even if the actual seizure protection is not better. The reason is that all AEDs share an antiepileptic effect, whereas they do not share all of their adverse effects. In addition, many side effects are dose related and may occur only once a certain dosage threshold is attained. When two AEDs are combined, a certain degree of seizure protection could be achieved at a dose of both drugs that is below their individual threshold for this specific side effect. That same degree of seizure protection with either drug alone might require a dose that is above their threshold dose. This represents a concept that is opposite to the widespread concept of high-dose monotherapy, namely low-dose polytherapy. For example, a patient may become seizure free on valproate, but only at a dose that causes thrombocytopenia and tremor. In the same patient, topiramate alone may then fully control the seizures, but only at a dose that causes undesired weight loss or word finding difficulties. It is conceivable that this patient’s seizures might be controlled on valproate and topiramate in combination at lower doses that cause none of these side effects. This concept of low-dose polytherapy is supported by the literature analysis of Deckers et al. (1997). These authors concluded that it is the total drug load of a patient that determines the number of adverse effects, and not just the number of AEDs that the patient is taking (see section ‘Undesirable interactions’).

An obvious potential advantage of combining AEDs is a broadening of the spectrum of activity. This applies only to patients who have more than one seizure type and in whom no single drug is fully effective against all seizure types and also well tolerated. For example, in patients with juvenile myoclonic epilepsy, the generalized tonic–clonic seizures might come under full control with either valproate, lamotrigine or topiramate, but the myoclonic seizures may persist. Inversely, clonazepam has been shown to be more effective against the myoclonic seizures than against the generalized tonic–clonic seizures in patients with juvenile myoclonic epilepsy (Obeid and Panayiotopoulos, 1989). In some patients, only a combination of clonazepam with one of the above three drugs may provide full control of the generalized tonic–clonic and the myoclonic seizures.

**Undesirable interactions**

There can be little doubt that one of the main disadvantages of antiepileptic combination therapy is an increase in the intensity or the number of side effects. In general, decreasing the number of AEDs will be associated with a decrease in side effects. This decrease in side effects involves a reduction in their severity, in their
number, or both. Several studies have suggested that a reduction in the number of AEDs reduces the overall occurrence of side effects, in particular the sedative effects and the dose-related neurological side effects in general (Fischbacher, 1982; Bennett et al., 1983; Schmidt, 1983; Theodore and Porter, 1983; Albright and Bruni, 1985; Pellock and Hunt, 1996). Interestingly, there was little or no increase in seizure frequency among the patients enrolled in these studies, and a reduction in seizures was actually not uncommon. When patients undergoing a temporal lobe resection were randomized to ongoing polytherapy or reduction to carbamazepine monotherapy, the seizure recurrence rate was the same for both groups, but side effects were more common in the polytherapy group (30%) than in the monotherapy group (10%). Also, controlled monotherapy trials with some of the newer AEDs have shown lower incidence of side effects than for the same drug in add-on trials.

Deckers et al. (1997) studied the relationship between AED polytherapy and adverse effects by analyzing published data from a literature review. They introduced a concept that they called total AED load. This concept is based on the ratio PDD/DDD, or prescribed daily dose (PDD) divided by the usual or defined daily dose (DDD). The total antiepileptic load in a patient is then calculated as the sum of the PDD/DDD ratios for all AEDs taken by the patient. For instance, if a patient takes 1.5 times the usual dose of two different AEDs, that patient’s total drug load is three, whereas a patient taking the usual dose of one drug has a total drug load of one. This type of analysis takes into account not only the number of drugs taken by a patient, but also the total relative dosage of these drugs. In 15 selected articles, the authors found a relationship between total drug load and number of adverse effects, but they found no relationship between just the number of AEDs prescribed and these adverse effects. This finding was later confirmed in a randomized study (Deckers et al., 2001). In this study, 130 adult patients with untreated generalized tonic–clonic and/or partial seizures were randomized to equal drug loads of monotherapy with carbamazepine, 400 mg/day, or combination therapy with carbamazepine 200 mg/day and valproate 300 mg/day. The study was designed to detect differences in neurotoxicity, and no such difference was found between the two groups. There was also no difference in efficacy, but this was not the primary outcome variable.

In addition to the dose-related central nervous system side effects of AEDs, there is no doubt that eliminating drugs from the regimen will eliminate the various individual and specific side effects of those drugs that are discontinued, such as excessive weight gain or tremor from valproate, behavioural problems from levetiracetam, or cognitive impairment from topiramate.

Exacerbation of side effects by combination therapy is not limited to central nervous system toxicity of AEDs. For instance, ammonia levels following a first dose of valproate were significantly higher than baseline in patients treated with
phenobarbital, phenytoin, or both, whereas ammonia levels did not differ from baseline in patients receiving no other medication (Zaccara et al., 1985). Also, the rates of fatality from valproate hepatotoxicity have been found to be substantially higher in polytherapy than in monotherapy for all age groups (Bryant and Dreifuss, 1996). In patients less than 3 years old, the rate was 1 in 618 on polytherapy, whereas there was no death in this age group among 4533 patients on monotherapy. For all ages, the rate of death was 6–7 times higher on polytherapy than on monotherapy.

At times, combining two AEDs may increase the likelihood of an idiosyncratic toxic reaction. For instance, treatment with valproate can be associated with an acute encephalopathy characterized by a change in mental status that can evolve to stupor or coma, as well as by seizure exacerbation (Sackellares et al., 1979; Marescaux et al., 1982). It has been shown that this encephalopathic reaction to valproate is more likely to occur in the presence of another AED, and it is invariably reversible after valproate is discontinued. This reaction can also subside after another AED is removed from the drug regimen, although that drug itself may never have been associated with such an encephalopathic reaction (Sackellares et al., 1979; Marescaux et al., 1982).

Antiepileptic combination therapy can at times cause seizure exacerbation. As mentioned above, a reduction in the number of AEDs has been at times found to be associated with a decrease rather than an increase in seizure frequency. Besides a spontaneous fluctuation, there are possible explanations for this observation:

(a) **Seizure aggravation by AEDs, paradoxical intoxication.** There is a growing body of literature supporting the notion that certain drugs can cause or aggravate certain seizures in certain types of epilepsy. This is particularly common in generalized epilepsies. For instance, carbamazepine can cause or aggravate absence seizures (Snead and Hosey et al., 1985; Liporace et al., 1994), myoclonic seizures (Shield and Saslow, 1983), seizures in patients with Lennox–Gastaut syndrome or with benign rolandic epilepsy (Corda et al., 2001). It can also aggravate or cause de novo generalized spike-wave discharges in the electroencephalogram (EEG) (Talwar et al., 1994). In patients with juvenile myoclonic epilepsy, myoclonic seizures have been shown to be potentially exacerbated by carbamazepine and phenytoin (Genton et al., 2000), and by lamotrigine (Biraben et al., 2000). In the Lennox–Gastaut syndrome, certain seizures can be aggravated by carbamazepine, phenytoin, gabapentin, vigabatrin, benzodiazepines and lamotrigine (Guerrini et al., 1999). In patients with severe myoclonic epilepsy of infancy (Dravet syndrome), seizure aggravation was reported with carbamazepine, lamotrigine and vigabatrin (Guerrini et al., 1998). The higher the number of AEDs taken by a patient, the more likely it is that one of them may actually be exacerbating certain seizures and that its elimination might lead to improved seizure control.
(b) Pharmacodynamic antagonism. Whenever a patient takes two or more AEDs, there is a pharmacodynamic interaction. In relation to seizure protection, this interaction can be purely additive, it can be supra-additive (this represents potentiation), or it can be infra-additive (this represents antagonism). In case of antagonism, one drug actually prevents or decreases the efficacy of the other drug. There is experimental and clinical evidence suggesting that antagonism may exist between AEDs. In an animal model, the combined seizure protection provided by carbamazepine and lamotrigine was found to be infra-additive (Czuczwar, S. J., personal communication, 2002). In a study of the efficacy of vigabatrin in children with infantile spasms (Elterman et al., 2001), the efficacy of vigabatrin was reduced in patients taking valproate and in those taking carbamazepine, and it was even lower in those taking valproate and carbamazepine (Shields, W. D., personal communication, 2002). Based on such evidence, it is conceivable that removing an AED involved in an antagonistic antiepileptic pharmacodynamic interaction will result in improved seizure control.

Clinical relevance of pharmacodynamic interactions: monotherapy versus combination therapy

There has been a shift in practice regarding the treatment of epilepsy with drug combinations or with one drug alone. After decades during which patients were treated with multiple drugs, monotherapy has been considered to be the gold standard for over 20 years (Deckers et al., 2001). More recently, the concept of rational polytherapy has been proposed and debated. The clinical significance of pharmacodynamic interactions and their advantages and disadvantages have been discussed in detail earlier in this chapter. There are three potential advantages of combination drug therapy:

1. better seizure control with similar or fewer side effects,
2. same seizure control with fewer side effects,
3. reduction of two or more different seizure types that respond only to different drugs.

Clinical studies of pharmacodynamic interactions between AEDs are discussed in Chapter 13. There is a paucity of clinical studies documenting the superiority of specific AED combinations. Whether or not to use combination therapy and the selection of a combination will often have to be based on an educated guess or on careful clinical observations in each individual patient (Meinardi, 1995). Considerations may include the mechanism of action of the drugs, the clinical spectrum of activity, and potential pharmacokinetic interactions. It has been suggested that drugs to be combined should have different mechanisms of action which would be complementary (Perucca, 1995; Macdonald, 1996). Although elegant, this hypothesis
has never been proven experimentally or clinically. A literature review of data in animals and in humans was used to determine whether appropriate AED combinations can be selected on the basis of their mechanism of action (Deckers et al., 2000). There was some evidence that efficacy could be enhanced by combining a sodium channel blocker with a drug enhancing GABAergic inhibition, or by combining two gamma amino butyric acid (GABA) mimetic drugs, or by combining an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist with an N-methyl-D-aspartate (NMDA) antagonist. At the present time, the basis for choosing a drug combination based on the mechanisms of actions is purely hypothetical and no specific combination can be recommended. When a patient has two or more different seizure types that cannot be controlled by one drug alone, two drugs can be selected according to their spectrum of efficacy. Although the absence of pharmacokinetic interactions between two drugs will certainly make it easier and safer to use them together, the interactions are known and predictable, and therefore largely correctable. Therefore, pharmacokinetic interactions should not be a reason to avoid a potentially beneficial drug combination. Finally, as discussed earlier, there are arguments in favor of the concept of low-dose polytherapy as opposed to the common practice of high-dose monotherapy. The rationale for this concept is that AEDs share an antiepileptic effect, but do not necessarily share their side effects.

In conclusion, rational polytherapy can rarely be predicted. In any given patient, a rational AED combination will have been identified if the patient does better in terms of seizure control versus side effects while taking drugs A and B together (at any doses) than the patient had done on drug A alone and on drug B alone at their respective optimal doses. There may be instances in which it would be appropriate to maintain a drug combination beyond the above definition. For instance, a patient may respond partially to a first drug and may experience further improvement after addition of a second drug, or the patient becomes seizure free after addition of the second drug, despite lack of response to the first drug. It is understandable in such a case that the patient and the physician may be reluctant to make any change.

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Methods for assessing pharmacodynamic interactions

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Experimental methods

Basic principles

Overall, it is much easier to assess and quantify pharmacokinetic interactions than pharmacodynamic ones. In the case of pharmacokinetic interactions, one drug will alter the pharmacokinetics of another drug. Changes in pharmacokinetic parameters can be assessed quantitatively by single dose pharmacokinetic studies, by changes in steady-state levels, or by changes in protein binding, etc. Measuring levels and calculating pharmacokinetic parameters is relatively straightforward. Assessing a pharmacodynamic interaction between two drugs requires a valid quantitative measurement of a specific drug effect for the two drugs individually, as well as a quantitative measurement of the effect of the two drugs administered together. Finally, it is necessary to determine the nature of the pharmacodynamic interaction that has occurred between the two drugs. Also, before the two drugs are administered together, one has to determine for each of the two drugs the appropriate dose to be administered for an assessment of the pharmacodynamic interaction to be possible. Once the response to the two drugs given together has been measured, the interaction has to be analyzed and categorized according to its type. As discussed and defined in Chapter 9 (see Table 9.1), there are four possible types of pharmacodynamic interactions: additive, supra-additive (potentiation), infra-additive (antagonism), and indifferent. Methods have been developed that make it possible to determine the type of interaction in experimental animal models. None of these methods can be applied directly to clinical studies.

It is important to realize that determining the type of pharmacodynamic interaction is only the first step. Whether the pharmacodynamic interaction (for instance seizure protection by two drugs) is additive or supra-additive may be of no interest whatsoever unless the therapeutic relevance of this interaction can be assessed.
For instance, does the fact that the combined seizure protection achieved by two drugs in combination is supra-additive compared to their individual effects have therapeutic relevance? Not necessarily. One could envision that the same seizure protection that is provided by the two drugs together could possibly be achieved by administering sufficiently high doses of either one of the two drugs alone. However, the limiting factor to progressive increases of the dose of the drugs (alone or in combination) will be the dose-related toxicity. Consequently, the therapeutic relevance of a pharmacodynamic interaction between two drugs providing seizure protection will depend not only on the nature of their antiepileptic interaction, but also on the type of their pharmacodynamic interaction in relation to their dose-related neurotoxicity. If the neurotoxic interaction is also supra-additive, it may be that the seizure protection afforded by the two drugs together at their subtoxic doses is no better than the seizure protection afforded by either drug alone at its subtoxic dose. In other words, what is really relevant about the pharmacodynamic interactions between two drugs is how and to what extent the therapeutic index of the combination differs from the individual therapeutic indices of the two drugs.

As early as 1955, while discussing the concepts delineated by Loewe, Weaver et al. (1955) addressed this issue quite appropriately:

Loewe (1953) has examined the characteristics of the dose–effect relationship of combined drugs acting in an additive manner and has given attention to the meaning of the common terms which are used to describe deviations from simple additive effects. He indicates that the terms synergism and antagonism, and analogous terms for supra-additive and infra-additive effects of combined drugs are usually imaginary terms and are meaningful only when they are clearly defined … He further states that it is more important to study the ratio between the intensities of various effects of the same combination, i.e., to know whether these ratios (margins of safety or therapeutic indices) assume a larger or smaller value for the combinations than for the components.

Isobolographic analysis

The concept of the isobolographic analysis has been developed about half a century ago (Loewe, 1953; Hewlett, 1969). The isobolographic analysis is currently widely used to determine the various types of pharmacodynamic interaction in experimental animal models, in particular for antiepileptic drugs (see also Chapter 11). It is a relatively simple and accurate method, which can be represented as a diagram in which concentrations or doses of drugs a and b used in a given experiment are plotted. The principle and the name of the method are best understood by analyzing additive interactions (Figure 10.1-I). The effective concentrations or doses of drugs a and b administered alone are plotted as A and B, respectively. This could be, for instance, the minimal effective dose or plasma concentration (MED,
Methods for assessing pharmacodynamic interactions

MEC), or the median effective dose or concentration (ED_{50}, EC_{50}) against maximal electroshock (MES). If the interaction between drugs a and b is purely additive, \( \frac{1}{2} \) of A combined with \( \frac{1}{2} \) of B will achieve the same effect as A or B alone. Similarly, \( \frac{3}{4} \) of A and \( \frac{1}{4} \) of B will also achieve the same effect as A or B alone. In both cases, the plot of the doses or concentrations of drugs a and b will fall on the straight line connecting A and B. Whenever plots of effective doses or concentrations of drugs a and b administered together fall on this straight line, the pharmacodynamic interaction is additive. This additive interaction implies that \( \frac{1}{2} \) of A can replace \( \frac{1}{2} \) of B, and \( \frac{3}{4} \) of A can replace \( \frac{1}{4} \) of B. Therefore, the ‘drug bolus’ consisting of \( \frac{1}{2} \)A plus \( \frac{1}{2} \)B, or \( \frac{3}{4} \)A plus \( \frac{1}{4} \)B, is equivalent in efficacy to A or B alone. Hence the term isobologram. The straight line between A and B represents the isobole for additive interaction. Any dose or concentration pair of a and b that plots above this line will be effective (responders) and any pair that plots below this line will be ineffective (non-responders).

Figure 10.1 Isobolographic analysis of different types of pharmacodynamic interactions. The abscissa and the ordinate represent the dose or concentration of drugs a and b. A and B represent the effective doses or concentrations of drugs a and b. See text for additional explanations.
If a pharmacodynamic interaction is supra-additive, the bolus of drugs a and b administered together that will be necessary to achieve efficacy may be smaller than would be expected from an additive interaction. Therefore, the line that defines the interface between responders and non-responders is a curve that bends downward below the straight isobole for additive interaction (Figure 10.1-II). For instance, \( \frac{1}{2} \) of A with only \( \frac{1}{6} \) of B may be effective. Any dose or concentration pair of a and b that plots above this downward curving line will be effective (responders) and any pair that plots below this downward curving line will be ineffective (non-responders).

Inversely, if a pharmacodynamic interaction is infra-additive, the bolus of drugs a and b administered together that will be necessary to achieve efficacy may be greater than would be expected from an additive interaction. Therefore, the line that defines the interface between responders and non-responders is a curve that bends upward above the straight isobole for additive interaction (Figure 10.1-III). For instance, \( \frac{1}{2} \) of A and \( \frac{5}{6} \) of B may be required to achieve the response provided by A or B alone. Any dose or concentration pair of a and b that plots above this upward curving line will be effective (responders) and any pair that plots below this upward curving line will be ineffective (non-responders).

Finally, an interaction can be indifferent. In this case, the drugs do not act together at all and no amount of drug b will replace any amount of drug a. Therefore, the drug combination will be effective only if the amount of drug a is \( \geq A \), or the amount of drug b is \( \geq B \) (Figure 10.1-IV). If the administered amounts of drugs a and b are smaller than A and B, respectively, there will be no response.

The isobolographic analysis can be applied in at least two different ways (Figure 10.2). One application consists of plotting doses or concentrations for individual animals receiving different doses and different ratios of drugs a and b (Figure 10.2-I). On this diagram, responders and non-responders must be identified as such. In Figure 10.2-I, one can see that there are several responders whose plots fall below the isobole for additive interaction. This is evidence that this particular interaction is supra-additive. An example of such an application is provided by a study on the anticonvulsant interaction between phenytoin and phenobarbital (Masuda et al., 1981).

The isobolographic analysis can also be applied by using a single plot for values obtained from a group of animals. For instance, once the median effective dose (ED\(_{50}\)) has been determined for drugs a and b, the ED\(_{50}\) can be determined for the combination of the two drugs. In order to do so, the two drugs must be administered together at increasing doses until the ED\(_{50}\) in the combination is determined. For this purpose, it is crucial to maintain constant ratios of doses or concentrations of drugs a to b at any level. It is probably best to choose a ratio of dose a:b that is equal to ED\(_{50a}\):ED\(_{50b}\). Such an example is provided in Figure 10.2-II. If the ED\(_{50}\) of the two
drugs in combination is equal to $1/2$ of each drug’s respective $ED_{50}$, the interaction is additive and the point will fall on the straight isobole line for additive interaction (point 1). If the interaction is supra-additive, smaller doses will be sufficient to achieve the same effect, and the $ED_{50}$ of the two drugs in combination will plot below the straight isobole (point 2). Inversely, if the interaction is infra-additive, larger doses will be necessary and the combined $ED_{50}$ values will plot above the straight isobole (point 3). Again, the dose ratio of drug a to b in combination does not have to be equal to the ratio of the respective $ED_{50}$ or equivalent values, but the ratio must be constant throughout the dosage range used to determine the $ED_{50}$ or equivalent value of the two drugs in combination.

As discussed earlier, the practical relevance of pharmacodynamic interactions may be limited to their effect on the therapeutic index. The therapeutic index of individual drugs and of drug combinations can be expressed as a ratio of a certain toxic dose or concentration divided by the effective dose or concentration, for instance $TD_{50}/ED_{50}$. The isobolographic analysis in its traditional form does not allow comparison of the therapeutic index of a drug combination with the therapeutic indices of individual drugs. In order for that, it is necessary that first, the dose or concentration ratio of the two drugs be similar when efficacy and toxicity are measured and, secondly, that the sum of the two drug doses or concentrations be used. For this purpose, a modified version of the isobolographic analysis was
developed (Bourgeois, 1986) (Figure 10.3). This modified version takes into account the dose or concentration ratio (abscissa) and the sum of the doses or concentrations of the two drugs (ordinate). The sum of the doses or concentrations in case of additive interaction would then be:

\[
a_i + b_i = A \frac{1 + r_i}{1 + r_i R}
\]  

(10.1)

where \(a_i\) and \(b_i\) are the median effective or toxic concentrations of drugs a and b, respectively, in a given combination \(i\), A and B are the corresponding effective or toxic concentrations of drugs a or b given alone, \(r_i\) is the ratio \(b_i / a_i\) (concentration ratio), and \(R\) is \(A / B\) (potency ratio). When \(A \neq B\), the line formed by all values for additive interaction at various concentration ratios is no longer straight. An example of such an application is provided in Figure 10.4 for the combination of carbamazepine and phenobarbital (Bourgeois and Wad, 1988). As can be seen, the interactions are additive for seizure protection (lower points) as well as for neurotoxicity (upper points). In this study, the therapeutic index of phenobarbital was 1.6, the therapeutic index of carbamazepine was 4.4, and the therapeutic index of the combination was 2.8 (higher than for phenobarbital but lower than for carbamazepine).
Methods for assessing pharmacodynamic interactions

Figure 10.4 Median effective brain concentrations against maximal electroshock (circles) and median toxic brain concentrations (squares) for phenobarbital (PB) alone (left) and for carbamazepine (CBZ) alone (right), as well as for the sum of the two drugs in combination. Solid lines represent expected values for purely additive interaction according to Eq. (10.1), and vertical bars represent 95% confidence limits. Both the anticonvulsant and the neurotoxic interactions are purely additive. Reproduced, with permission, from Bourgeois and Wad, 1988

A different example is provided in Figure 10.5 (Bourgeois, 1988). In this case, the anticonvulsant interaction between valproate and ethosuximide (lower points) was purely additive, whereas the neurotoxic interaction (upper points) was infraadditive. In this study, the therapeutic index of valproate alone was 1.8, the therapeutic index of ethosuximide alone was 2.4, and the therapeutic index of the combination was 3.1, superior to both individual values.

A similar diagram expressing the effective dose or concentration (ordinate) as a function of the drug concentration ratio (abscissa) was later proposed by Levasseur et al. (1998). Their mathematical analysis also includes a quantification of the intensity of the pharmacodynamic interaction.

Other methods

Besides the isobolographic analysis, various other methods have been used to assess pharmacodynamic interactions. One of them is the fractional effective concentration index (Elison et al., 1954; Kerry et al., 1975). The first step for this method is to determine the fractional effective concentration (FEC) for drugs a
and b. The FEC is the ratio between the effective amount of a drug used in combination with a second drug and the effective amount of the drug used alone. For instance, it could be the ratio between the median effective concentration (EC\textsubscript{50}) of the drug in the presence of the other drug, divided by the corresponding EC\textsubscript{50} of the drug alone (FEC\textsubscript{a} = EC\textsubscript{50}\textsubscript{a} in combination with drug b/EC\textsubscript{50}\textsubscript{a} alone). The sum of the FEC value for drugs a and b represents the FEC index. It has been suggested that an FEC index of 0.7–1.3 can be considered to represent an additive interaction (Kerry et al., 1975). FEC index values below 0.7 are indicative of a supra-additive interaction, and FEC index values above 1.3 are indicative of infra-additive interactions. An example of additive interactions by FEC index is provided in Table 10.1. This FEC index analysis is based on the same study as Figure 10.4, and addresses the seizure protection and the neurotoxicity of carbamazepine and phenobarbital, alone and in combination (Bourgeois and Wad, 1988). The isobolographic analysis had revealed a purely additive interaction for both seizure protection and neurotoxicity (Figure 10.4). Analysis of the interaction using the
Methods for assessing pharmacodynamic interactions

Table 10.1 Fractional effective concentration (FEC) and FEC indices of phenobarbital (PB) and carbamazepine (CBZ)

<table>
<thead>
<tr>
<th></th>
<th>PB</th>
<th>CBZ</th>
<th>FEC index^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES</td>
<td>39.5 ( \div ) 0.41</td>
<td>11.3 ( \div ) 25.2</td>
<td>0.86</td>
</tr>
<tr>
<td>Rotorod</td>
<td>107.5 ( \div ) 0.68</td>
<td>35.5 ( \div ) 111.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

^a FEC: EC\(_{50}\) or TC\(_{50}\) in combination/EC\(_{50}\) or TC\(_{50}\) alone.
^b FEC index: sum of FEC values for PB and CBZ. A value of 1.0 ± 0.3 indicates an additive interaction, lower values being indicative of synergism and higher values indicating antagonism.

Table 10.2 FEC and FEC indices of valproate (VPA) and ethosuximide (ESM)

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>ESM</th>
<th>FEC index^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTZ</td>
<td>225.0 ( \div ) 0.41</td>
<td>507.8 ( \div ) 826.3</td>
<td>1.02</td>
</tr>
<tr>
<td>Rotorod</td>
<td>921.7 ( \div ) 0.93</td>
<td>1348.6 ( \div ) 2001.0</td>
<td>1.60</td>
</tr>
</tbody>
</table>

^a FEC: EC\(_{50}\) or TC\(_{50}\) in combination/EC\(_{50}\) or TC\(_{50}\) alone.
^b FEC index: sum of FEC values for VPA and ESM. A value of 1.0 ± 0.3 indicates an additive interaction, lower values being indicative of synergism and higher values indicating antagonism.

FEC index also indicates additive interaction for efficacy and neurotoxicity, both FEC indices being >0.7 and <1.3 (Table 10.1). Another example is provided in Table 10.2. The data are from the same study as Figure 10.5, and are based on seizure protection and neurotoxicity of valproate and ethosuximide, alone and in combination (Bourgeois, 1988). The isobolographic analysis had revealed an additive anticonvulsant interaction and an infra-additive neurotoxic interaction (Figure 10.5). The FEC indices confirm these findings. The FEC index of 1.60 for neurotoxicity is considered to be in the infra-additive range.

Another method of analysis of pharmacodynamic interactions consists of administering an inactive dose of one drug and determining the effect of this inactive dose on the potency of the other drug. Examples and definitions of ineffective
doses may include the dose that is effective for 1% or less of the animals, i.e. ED₁ or ED₀.₁ (Bourgeois et al., 1983), or a dose that is ineffective in a group of animals (for instance 25–50 animals) (Gordon et al., 1993; Borowicz et al., 1999). The ED₁ or the ED₀.₁ can be determined by extrapolation of the probit analysis used to determine the ED₅₀ of a compound.

When drug a is administered at a sub-effective dose together with drug b, the potency of drug b can be modified, such as a significant decrease of its ED₅₀ compared to the administration of b alone. This has been shown to be the case for the effect of nicotinamide on the anticonvulsant activity of phenobarbital (Bourgeois et al., 1983). It has also been shown that inactive doses of phenytoin, valproate, carbamazepine, and phenobarbital can significantly lower the ED₅₀ of felbamate (Gordon et al., 1993), or that a sub-protective dose of melatonin can enhance the effect of carbamazepine and phenobarbital on the electroconvulsive threshold in mice (Borowicz et al., 1999). Such an effect has been considered to represent evidence of potentiation. Whether or not this is valid will be addressed in the section on ‘Methodological pitfalls’.

**Methodological pitfalls**

Considering how complex and elaborate the assessment of pharmacodynamic interactions can be, it is not surprising that there may be several methodological pitfalls. One potential pitfall has already been alluded to earlier in this chapter, mainly attributing a certain relevance to a given pharmacodynamic interaction where there may be none. A good example would be the finding of a supra-additive anticonvulsant interaction between two drugs being interpreted as an argument for the combined use of these two drugs. In fact, the finding may be totally irrelevant, unless it can be shown that the combination has a superior therapeutic index.

Another potential methodological pitfall is the use of drug doses to quantify a pharmacodynamic interaction between two drugs when there is also a pharmacokinetic interaction between the drugs. What is interpreted as a pharmacodynamic interaction may actually only be a pharmacokinetic interaction. The interaction between phenytoin and phenobarbital is a good example. It has been concluded from several studies, based on the analysis of doses, that the anticonvulsive pharmacodynamic interaction between phenytoin and phenobarbital is supra-additive (Chen and Ensor, 1954; Weaver et al., 1955; Wallin et al., 1970; Consroe et al., 1977). However, there is a pharmacokinetic interaction between the two drugs. It was shown independently in rats (Leppik and Sherwin, 1977) and in mice (Bourgeois, 1986) that brain concentrations of phenytoin following a single dose are higher in relation to the dose when phenytoin is administered with phenobarbital than when it is administered alone. If doses only are analyzed, this may lead to the
Conclusion that the interaction between the two drugs is supra-additive, because of the higher brain concentration of phenytoin when the combination is tested. In rats and in mice (Leppik and Sherwin, 1977; Bourgeois, 1986), assessment of the anticonvulsive pharmacodynamic interaction based on brain concentrations was shown to be consistent with a purely additive interaction.

Using an ineffective or sub-protective dose of one drug and measuring its effect on the potency of another drug has been presented earlier as one possible method for the assessment for pharmacodynamic interactions. In particular, it has been concluded that, if an inactive dose of a drug significantly reduces the ED$_{50}$ of another drug, this represents a supra-additive interaction. The reasoning is that adding 0 to any number should not increase that number. In the case of pharmacodynamic interactions between drugs this conclusion is open to criticism and may actually be wrong. The main reason is that the relationship between dose and response (or concentration and response) is not a straight line, but a sigmoid curve (see Chapter 9, Figure 9.1). Also, based on the isobolographic analysis, $\frac{1}{4}$ of the ED$_{50}$ of drug a can be replaced by $\frac{1}{4}$ of the ED$_{50}$ of drug b, etc. Yet, it may be that $\frac{1}{4}$ of the ED$_{50}$ of either drug is in itself ineffective. Therefore, a dose that is ineffective in itself is not necessarily ineffective when added to another drug, or when added to another dose of the same drug for that matter, even if the interaction is purely additive. Let us assume that the anticonvulsant ED$_{50}$ of a drug is 50 mg/kg and that a dose of 10 mg/kg of that drug is found to be ineffective. However, if one adds the ineffective dose of 10 mg/kg to the ED$_{50}$ of 50 mg/kg of the drug, the resulting dose of 60 mg/kg will protect >50% of the animals. Inversely, one could argue that, since 10 mg/kg is ineffective, 40 mg/kg should be just as effective as 50 mg/kg, which is obviously not true. Although the method of assessing the change in potency of one drug by an ineffective dose of another drug may not help to distinguish between a supra-additive and an additive interaction, this approach is still valid for the study of drug combinations. The reason is that this method does allow an assessment of the effect of one drug on the therapeutic index of another drug.

Clinical methods

Basic principles

The difficulties encountered in the assessment of pharmacodynamic interactions in experimental animals are compounded when interactions are to be studied clinically in patients, especially for antiepileptic drugs. The isobolographic analysis can be applied clinically under certain circumstances, but it is difficult to apply to patients with epilepsy. The interaction between anesthetics has been studied in
patients using the isobolographic analysis. For instance, the propofol–thiopental hypnotic interaction was analyzed in patients undergoing eye surgery (Vinik et al., 1999). The abolition of the ability to open the eyes on command was used as an endpoint. The $ED_{50}$ was determined by probit analysis for thiopental alone, for propofol alone, and for three different dosage ratios of the two drugs. All $ED_{50}$ values were on the straight isobole, indicating a purely additive interaction. In this study, the FEC index analysis was also used, resulting in values equal to or close to 1.0.

Populations of patients with seizures are not homogeneous and cannot be compared with groups of healthy animals in whom standardized seizures are elicited, e.g. with MES or pentylenetetrazole. Therefore, values for median effective doses or for median toxic doses, or equivalent values, cannot be determined in patients with seizures, and isobolograms are therefore difficult or impossible to create. A more reproducible and quantifiable endpoint would actually be the maximal tolerated dose (MTD) or sub-toxic dose. In the end, determining the type of pharmacodynamic interaction between two antiepileptic drugs (mainly whether it is supra-additive or not) in patients may be a moot point. As stated earlier, what is of interest is not so much the type of interaction, but the practical relevance of the interaction. Translated into clinical terms, the practical relevance is whether a certain combination of two antiepileptic drugs, compared to each drug alone, can provide better seizure protection with the same level of toxicity or the same degree of seizure protection with fewer side effects. Therefore, clinical studies should be designed to address this issue rather than whether the anticonvulsant interaction between two antiepileptic drugs is supra-additive or not.

**Trial designs**

The discussion on designs of clinical trials to study pharmacodynamic interactions between antiepileptic drugs will be based on the assumption that the studies are to be clinically relevant. They should be aimed at demonstrating that, compared with the individual drug effects, a given combination offers better seizure protection at the same level of toxicity or the same degree of seizure protection with less toxicity. Possible study designs will be divided into four groups: optimal, probably valid, questionably valid, and invalid.

**Optimal design**

Among a cohort of patients with uncontrolled seizures, a group is to be identified whose seizures are not fully controlled at the MTD of drug a in monotherapy. The MTD is a dose that causes no persistent side effects and is just below a dose that does cause persistent side effects. This group of patients should be switched to monotherapy with drug b. The dose of drug b should be increased until seizures subside, or to the MTD. Those patients who do not benefit significantly from drug
Methods for assessing pharmacodynamic interactions

b, even at the MTD, should have drug a re-introduced while maintained on drug b. The dose of drug b may be maintained at the MTD or, if necessary, it may be lowered somewhat in order to allow an increase in the dose of drug a. To what extent the combination of drugs a and b is superior will be determined by the percentage of patients receiving this combination that will have a >50% reduction in their seizure frequency. As can be seen, the essential component of an optimal study design is that all patients receive an appropriate monotherapy trial with both drugs before being treated with a combination.

Probably valid design

1 The initial step here would also be to identify patients whose seizures have failed to come under control at the MTD of drug a. At that point, drug b is added to drug a, if necessary to the MTD. In those patients who experience a >50% reduction in seizure frequency after the addition of drug b, an attempt is made to gradually taper and discontinue drug a. To what extent the combination of drugs a and b is superior will be determined by the percentage of patients whose seizure control deteriorates as drug a is tapered or discontinued and whose seizure control improves after drug a is re-introduced.

2 Patients are identified whose seizures are not controlled on monotherapy at the MTD. Some may be on drug a, some on drug b, and some on drug c. In these patients, drug d is added as a second drug and the dose of drug d is increased as necessary and as tolerated. It is conceivable that, after the addition of drug d, a substantial number of patients on drug b, for example, may experience a >50% seizure reduction whereas few or none of the patients taking drug a or c benefit. This would represent fairly good evidence that drugs b and d may have a favorable pharmacodynamic interaction profile and that they represent a desirable drug combination. An effect of drug d alone is unlikely with the present design, if a good response after the addition of drug d is not observed in patients taking drug a or c, assuming that the patient groups do not differ significantly in terms of their seizure types.

Questionably valid design

1 Clinical studies have been carried out for the use of designs outlined above as optimal or probably valid; the only difference being that patients were not on monotherapy and then on a combination of only two drugs, but took additional baseline antiepileptic drugs. Even though these baseline antiepileptic drugs remain constant, they introduce different variables and more potential for pharmacodynamic interactions.

2 Pharmacodynamic interactions between antiepileptic drugs can also be assessed by using a design based on the concept of the isobolographic analysis. As in the optimal design described above, patients are identified who have failed to
respond to the MTD of drugs a or b in monotherapy. Trough serum levels of drugs a and of drug b are determined at the MTD. The patients then receive drugs a and b in combination at doses that are adjusted to achieve 1/2 of the trough serum levels that were reached at the MTDs. Theoretically, if the antiepileptic pharmacodynamic interaction between the two drugs is supra-additive, the patients as a group should experience a reduction in their seizure frequency. However, this method does not necessarily address the issue of the clinical superiority of the combination, i.e. whether the combination has a better efficacy to toxicity ratio than either drug alone.

Invalid design

At times, conclusions regarding the value of drug combinations have been drawn from studies that were not designed to properly address this question. For instance, if patients improve with the addition of drug b after failure of drug a, this cannot be interpreted as evidence that this improvement is due to a combination of the two drugs. The improvement could just as well been entirely due to the effect of drug b only, in which case it might be maintained after discontinuation of drug a. Also, the combination cannot be assessed unless the doses of the two drugs in monotherapy have been increased to the MTD. Since the combination may be at the MTD, it is possible that improved seizure control could also have been achieved at the MTD of the two drugs in monotherapy. Finally, as in experimental studies, possible pharmacokinetic interactions between drugs have to be taken into account and they must be corrected or compensated.

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Experimental studies of pharmacodynamic interactions

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Introduction

In most patients, the therapy of newly diagnosed epilepsy is initiated with a single antiepileptic drug. Approximately 60–70% of patients may experience a reasonable seizure control with monotherapy (Sander et al., 1993; Czuczwar and Patsalos, 2001). However, monotherapy is not sufficient for the remainder of epileptic patients. Therefore, experimental background information may be helpful for an epileptologist to know what drug combinations can be considered preferentially for combination therapy or for controlled clinical trials. Animal studies evaluate the combinations of conventional antiepileptic drugs or combinations of a conventional antiepileptic drug with a novel (or potential) antiepileptic drug. The protective effect of a drug combination may be quantified with the isobolographic method on the basis of equieffective doses of individual drugs administered alone or in combination (Tallarida, 1992; Tallarida et al., 1989). An alternative method evaluates the effect of one antiepileptic drug given in sub-protective doses upon the ED50 value (the effective dose of a drug necessary to protect 50% of the animals) of another drug against experimental seizures. The ED50 value of the second drug in combination with sub-protective doses of the first antiepileptic drug is compared to the control ED50 value, estimated for the second drug alone, according to the method of Litchfield and Wilcoxon (1949).

Interactions between conventional antiepileptic drugs

As already mentioned, the experimental background may provide clues regarding which drug combinations may actually have a significant therapeutic potential. There have been many experimental studies dealing with combinations of conventional antiepileptic drugs. For instance, Bourgeois (1986; 1988a, b), Bourgeois and Wad (1984), and Chez et al. (1994) studied the interactions between conventional antiepileptic drugs in two rapid and simple screening convulsive tests – the maximal
Experimental studies of pharmacodynamic interactions

electroshock and the pentylentetrazol test. Practically, all existing conventional and novel antiepileptic drugs are effective in at least one of these tests, except for levetiracetam. According to Löscher and Schmidt (1988), maximal electroshock-induced seizures in rodents provide a good experimental model for generalized tonic–clonic convulsions while the pentylentetrazol test may be regarded as a model for myoclonic seizures in humans.

On the basis of brain concentrations of phenytoin and phenobarbital, Bourgeois (1986), using the isobolographic analysis, concluded that the interaction between these antiepileptic drugs was purely additive against maximal electroshock in mice, while their neurotoxicity was infra-additive. However, because of the very poor therapeutic index of phenobarbital in this model, the therapeutic index of phenytoin alone was still better than the therapeutic index of the combination. For seizure protection, a purely additive interaction between phenytoin and phenobarbital, based on their brain concentration in rats, was also found by Leppik and Sherwin (1977). There are other reports pointing to a synergy between these two antiepileptic drugs in rodents. However, they were based on the analysis of doses (Chen and Ensor, 1954; Weaver et al., 1955). On the other hand, an apparent synergy was found between phenobarbital and phenytoin in mice and rabbits with the use of maximal electroshock, and these results were verified with both plasma and brain concentrations of the antiepileptic drugs. However, the neurotoxicity of this combination was not evaluated (Masuda et al., 1981).

Anticonvulsant efficacy and neurotoxicity of another combination of conventional antiepileptic drugs, carbamazepine and phenobarbital, was evaluated in mice against maximal electroshock by Bourgeois and Wad (1988). Brain concentrations of these drugs were taken into consideration. No supra-additive interaction was found. An additive effect was evident for both the anticonvulsant and the neurotoxic activity. In another model of experimental epilepsy – penicillin-induced epileptic foci in cats – no potentiation could be demonstrated between carbamazepine and phenobarbital (Monaco et al., 1985). Also, only additive effects were reported when valproate was combined with phenobarbital or carbamazepine in maximal electroshock test in mice. Considering the neurotoxic effects of these combinations, additive and infra-additive interactions were evident, respectively (Bourgeois, 1988a). With the use of the same experimental approach, Chez et al. (1994) provided evidence for a supra-additive anticonvulsant interaction between valproate and diphenylhydantoin (while neurotoxicity was simply additive) that may be interpreted in terms of a potential benefit for antiepileptic treatment. Also, another combination of conventional antiepileptic drugs, valproate and ethosuximide, was found potentially beneficial in the pentylentetrazol test in mice (Bourgeois, 1988b). Although isobolographic analysis of effective brain concentrations of both drugs was indicative of an additive anticonvulsant interaction, a less
than additive neurotoxic interaction was found. These interactions resulted in a better therapeutic index for the combined treatment than for either drug alone.

A question that has been debated is whether there might be a general rule on how to combine antiepileptic drugs based on their mechanisms of action. According to Deckers et al. (2000), combining a sodium channel blocker (mechanisms of action of antiepileptic drugs are listed in Table 11.1) with a GABAergic drug seems more efficacious than two sodium channel blockers. Experimental data provided by Czuczwar et al. (1981) seem to support such a hypothesis. These authors observed a potent enhancement of diazepam’s anti-pentylenetetrazol effect in mice by diphenylhydantoin, which is completely inactive in this seizure model. Although the plasma concentrations of these antiepileptic drugs were not measured, a pharmacokinetic mechanism does not seem probable since this very potent interaction was not observed against bicuculline- or isoniazid-induced seizures in mice (Czuczwar et al., 1981). This may also point to different mechanisms of action of conventional antiepileptic drugs, which may result in a potentiation in some models of experimental epilepsy. On the other hand, some other models may require the involvement of different mechanisms.

### Table 11.1 Antiepileptic drugs – mechanisms of action

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Blockade of Na(^+) channels</th>
<th>Blockade of T-type Ca(^{2+}) channels</th>
<th>Blockade of other Ca(^{2+}) channels</th>
<th>Enhancement of GABA-mediated events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑↑</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↑↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>↑↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td></td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↑↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↑↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td></td>
<td></td>
<td>↑↑</td>
</tr>
<tr>
<td>Topiramate</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Valproate</td>
<td>↑</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td></td>
<td></td>
<td></td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Data are from (see for review) Löscher (1998), Urbańska et al. (1998), Deckers et al. (2000), and Czuczwar and Patsalos (2001). Only the mechanisms were considered which are evident within therapeutic drug concentrations.

For the influence of antiepileptic drugs on glutamate-mediated events see Table 11.3.

GABA, \(\gamma\)-amino butyric acid. ↑, effective; ↑↑, very effective.
Interactions between conventional and newer antiepileptic drugs

Shank et al. (1994) studied the protection offered by a newer antiepileptic drug, topiramate, alone and combined with standard antiepileptic drugs, phenytoin, phenobarbital, and carbamazepine against maximal electroshock-induced seizures in mice. Topiramate was combined with a conventional antiepileptic drug at fixed ratios (0.75/0.25, 0.50/0.50, and 0.25/0.75) of their respective ED$_{50}$ values. To plot a dose–response curve, multiple doses of each combination were used. The results provided evidence that the combination of topiramate with phenytoin was additive in terms of anticonvulsant activity. However, a synergy was observed when topiramate was combined with either carbamazepine or phenobarbital. The second experimental approach (effect of sub-protective doses) was used to study the interactions between felbamate and carbamazepine, phenytoin, phenobarbital, or valproate against maximal electroshock in mice (Gordon et al., 1993). It was evident that all conventional antiepileptic drugs in non-effective doses in this seizure test reduced the ED$_{50}$ value of felbamate (42.9 mg/kg) – carbamazepine (4 mg/kg) by 70%, phenytoin (6 mg/kg) by 60%, phenobarbital (4 mg/kg) by 45%, and valproate (150 mg/kg) by 69%. It is noteworthy that the protective index of felbamate, defined as its TD$_{50}$/ED$_{50}$, was significantly elevated after combinations with each standard antiepileptic drug (TD$_{50}$ is the dose of a drug necessary to cause neurotoxicity in 50% of the animals). Similarly to the former studies, a pharmacokinetic mechanism was unlikely to account for the observed interaction. Conversely, doses of felbamate sub-protective against electroconvulsions failed to affect the ED$_{50}$ values of carbamazepine, phenytoin, phenobarbital and valproate against maximal electroshock in mice (Borowicz et al., 2000c). This may emphasize the importance of dose ratios in the final quantitative analysis of an interaction between antiepileptic drugs. In fact, such a dose dependence was observed by Shank et al. (1994) with topiramate and conventional antiepileptic drugs. Swiader et al. (2000) combined topiramate (in sub-protective doses of 2.5 and 5 mg/kg in relation to the electroconvulsive threshold in mice) with conventional antiepileptic drugs. The convulsive test was maximal electro-shock. A possible pharmacokinetic interaction was identified on the basis of measurements of the free-plasma concentrations of the antiepileptic drugs. Topiramate’s ED$_{50}$ against maximal electroshock was 62.1 mg/kg. The most remarkable interaction was observed when topiramate (5 mg/kg) was co-administered with carbamazepine (its ED$_{50}$ value was reduced by 41%). In the case of phenobarbital and phenytoin, the ED$_{50}$ reductions were 30% and 28%, respectively. Much weaker effect was observed for the combination of topiramate (5 mg/kg) with valproate (its ED$_{50}$ value was decreased by only 18%). However, topiramate (5 mg/kg) elevated the free-plasma concentration of carbamazepine by 47%. Thus, a pharmacokinetic factor is apparently responsible for the
observed potentiation of the protective effect of carbamazepine. The free-plasma concentrations of the remaining antiepileptic drugs were not affected by topiramate. Although the interaction of topiramate with valproate was not remarkable (but still statistically significant) in terms of the anticonvulsant activity, the combined treatment did not disturb motor coordination or long-term memory of mice evaluated in the chimney test and passive avoidance task, respectively. In contrast, valproate alone at its ED$_{50}$ value of 248 mg/kg against maximal electroshock impaired both motor performance and long-term memory (Swiader et al., 2000). In the pentylenetetrazol test in mice, pronounced anticonvulsant activity was noted when topiramate was administered together with clobazam or phenobarbital, limited and/or variable effects being observed for its combinations with valproate, primidone, and ethosuximide (Sills et al., 1999). Another newer anti-epileptic drug, gabapentin, at a sub-protective dose of 25 mg/kg, reduced the ED$_{50}$ values of major conventional antiepileptic drugs: carbamazepine (by 28%), phenytoin (by 52%), phenobarbital (by 58%), and valproate (by 28%) against maximal electroshock in mice. In no case were the free-plasma concentrations of the conventional antiepileptic drugs affected by gabapentin. Therefore, a pharmacokinetic interaction is not probable (Czuczwar et al., 1999). Isobolographic analysis revealed distinctly supra-additive interactions for the combinations of gabapentin with carbamazepine, valproate, phenytoin, or phenobarbital, since experimentally evaluated ED$_{50}$ values were much lower than the additive ED$_{50}$ values theoretically calculated from the line of additivity for the respective combinations. A pharmacokinetic interaction was at least partially involved in the interactions between gabapentin and phenobarbital. The adverse effects of the respective drug mixtures were only additive which suggests that the combinations are potentially promising for clinical studies (Borowicz et al., 2002b). Gabapentin was also evaluated in this respect in a model of reflex epilepsy, sound-induced seizures in DBA/2 mice (De Sarro et al., 1998). At a non-protective dose of 2.5 mg/kg, gabapentin enhanced the protective activity of carbamazepine, diazepam, phenytoin, phenobarbital, and valproate. The most remarkable potentiation of the anticonvulsant effect occurred for diazepam, phenobarbital, and valproate. In addition, the therapeutic indices of the combined treatments were better than for the respective antiepileptic drugs alone. A possible pharmacokinetic mechanism may be excluded because gabapentin did not significantly affect the plasma concentration of the antiepileptic drugs. Some combinations between newer and conventional antiepileptic drugs are listed in Table 11.2.

**Interactions between newer antiepileptic drugs**

Only limited experimental data are available on this issue. De Sarro et al. (1998) studied gabapentin and its combinations with felbamate or lamotrigine. However,
Experimental studies of pharmacodynamic interactions

Table 11.2 Interactions between conventional and novel antiepileptic drugs in the maximal electroshock-induced convulsions in mice

<table>
<thead>
<tr>
<th>Conventional antiepileptic drug</th>
<th>Novel antiepileptics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Felbamate</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0</td>
</tr>
<tr>
<td>Valproate</td>
<td>0</td>
</tr>
</tbody>
</table>

Novel antiepileptic drugs were given at non-protective doses, evaluated in the threshold electroconvulsive test.

Data are from Shank et al. (1994), Borowicz et al. (2000c, 2002b), and Swiader et al. (2000). See text for the adverse potential of these combinations.

0, no interaction; ↑, positive or additive interaction; ↑↑, very potent (or supra-additive) interaction. *Pharmacokinetic interaction was found. **Isobolographic analysis was performed.

the results were not as remarkable as in the case of gabapentin combined with diazepam, phenobarbital, and valproate. Topiramate co-administered with felbamate or tiagabine demonstrated convincing efficacy against pentylenetetrazol in mice. Combinations of topiramate with gabapentin, vigabatrin, lamotrigine, or remacemide were completely without effect in this seizure model (Sills et al., 1999).

Stephen et al. (1998) tested the intriguing hypothesis of whether two drugs ineffective against pentylenetetrazol might be effective when combined. Actually, lamotrigine and topiramate, fulfilling these criteria, provided a strong protection in the pentylenetetrazol test.

Interactions of antiepileptic drugs with excitatory amino acid antagonists

*N*-methyl-\(\text{-}\)-aspartate receptor antagonists

Endogenous excitatory amino acids, mainly glutamate or aspartate, have been shown to play an important role in the induction of seizure activity (Meldrum, 1984). Also, clinical data indicate that a number of cases of human epilepsy are accompanied by elevated concentrations of excitatory amino acids in plasma (Huxtable et al., 1983; Janjua et al., 1992). In the early 1980s, intensive experimental studies were initiated on the possible anticonvulsant activity of ionotropic glutamate receptor antagonists. Results from various models of experimental epilepsy provided a good deal of data confirming this hypothesis (Czuczwar and Meldrum,
Ionotropic glutamate receptor antagonists block two major groups of receptors: those sensitive to N-methyl-D-aspartate (NMDA receptors) and those sensitive to \( \alpha\)-amino-3-hydroxy-5-methyl-isoxazole-4-propionate/kainate (AMPA/KA or non-NMDA receptors; Watkins et al., 1990). Both groups of receptors control different ion currents – excitation of NMDA receptors is associated with an influx of calcium and sodium ions into a neuron whilst non-NMDA receptors preferentially affect sodium-gated channels (Monaghan et al., 1989). Moreover, it has been suggested that some antiepileptic drugs interact with glutamate receptors (see Table 11.3).

Utilizing the method of Litchfield and Wilcoxon (1949), a number of NMDA or non-NMDA receptor antagonists were tested for their ability to interact with conventional antiepileptic drugs (Table 11.4). \( \text{D-3-(2-carboxypiperazine-4-yl)-1-propenyl-1-phosphonic acid (D-CPP-ene; a competitive NMDA receptor antagonist – 1 mg/kg) considerably enhanced the protective activity of carbamazepine, diazepam, phenytoin, phenobarbital, or valproate against maximal electroshock-induced seizures in mice without any effect upon their plasma concentrations (Zarnowski et al., 1994a). Except for carbamazepine, combinations of other antiepileptic drugs with D-CPP-ene resulted in serious impairment of motor coordination and long-term memory. A very good correlation between the experimental studies and clinical data needs to be emphasized. D-CPP-ene (as an adjuvant}

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>NMDA receptor</th>
<th>AMPA/KA receptor</th>
<th>mGluR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Felbamate</td>
<td>+</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0*</td>
<td>0*</td>
<td>ND</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>+</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Topiramate</td>
<td>0</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Valproate</td>
<td>+</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

For review see Löscher (1998), Urbańska et al. (1998), Deckers et al. (2000), and Czuczwar and Patsalos (2001).
0, no effect; +, inhibition of receptor-mediated events; ND, not determined.
*Inhibition of glutamate release was found in vitro but not in vivo.
antiepileptic drug) was also given to patients with complex partial seizures (Sveinbjörnsdóttir et al., 1993). This combined therapy induced a number of severe adverse reactions in epileptic patients, including poor concentration, ataxia, amnesia, and sedation. Interestingly, no therapeutic improvement with D-CPP-ene was noted, in contrast to findings in the animal study (Zarnowski et al., 1994a). A possible explanation for this discrepancy is that an experimental animal model for complex partial seizures in man is the amygdala-kindled seizure model in rats (Lösch et al., 1986). NMDA receptor antagonists are not very potent in this experimental model, which may result in the poor anticonvulsive effects of D-CPP-ene in patients with complex partial seizures. Memantine or procyclidine, when combined with conventional antiepileptic drugs, considerably disturbed motor coordination and long-term memory in mice, although the protection offered by the antiepileptic drugs was potentiated (Urbańska et al., 1992; Zarnowski et al., 1993; 1994a, b), Borowicz et al. (1995), and Czuczwar et al. (1998c). NS, not significant; NT, not tested.

Table 11.4 Influence of NMDA or AMPA/KA receptor antagonists on the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice

<table>
<thead>
<tr>
<th>Excitatory amino acid receptor antagonist (mg/kg)</th>
<th>Phenobarbital</th>
<th>Diphenylhydantoin</th>
<th>Carbamazepine</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGP 37849 (0.25)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>43</td>
</tr>
<tr>
<td>CGP 37849 (1.0)</td>
<td>53</td>
<td>53</td>
<td>66</td>
<td>NT</td>
</tr>
<tr>
<td>D-CPP-ene (1.0)</td>
<td>58</td>
<td>50</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>GYKI 52466 (5)</td>
<td>91(NS)</td>
<td>51</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>LY 300164 (2)</td>
<td>65</td>
<td>70</td>
<td>68</td>
<td>41</td>
</tr>
<tr>
<td>Memantine (0.5)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>55</td>
</tr>
<tr>
<td>NBQX (10)</td>
<td>59</td>
<td>53</td>
<td>74</td>
<td>59</td>
</tr>
<tr>
<td>Procyclidine (10)</td>
<td>75</td>
<td>69</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Table data indicate reductions of the ED$_{50}$ values of antiepileptic drugs (in %) after combinations with excitatory amino acid receptor antagonists. ED$_{50}$s of antiepileptic drugs alone are ascribed to 100%. Excitatory amino acid receptor antagonists were given at doses ineffective upon the convulsive threshold. Data are from Czechowska et al. (1993), Pietrasiewicz et al. (1993), Zarnowski et al. (1993; 1994a, b), Borowicz et al. (1995), and Czuczwar et al. (1998c).
no pharmacokinetic factor, at least in terms of the plasma concentration of valproate, seems to be involved (Czechowska et al., 1993). Similar results were observed, in terms of the anticonvulsant activity, when these NMDA receptor antagonists were combined with carbamazepine, phenytoin, and phenobarbital (Pietrasiewicz et al., 1993). Only combinations with phenytoin were devoid of adverse effects. The recently studied NMDA receptor antagonist CPP and its active D(−) isomer potentiated the anti-electroshock efficacy of all four conventional antiepileptic drugs with no adverse potential being observed for carbamazepine, phenytoin, and phenobarbital (Borowicz et al., 2000a). Also, the combinations with valproate were superior to valproate alone in this respect, since valproate alone at its ED50 against maximal electroshock-induced seizures produced impairment of motor coordination and long-term memory. Combination with CPP revealed only motor impairment (Borowicz et al., 2000a). It seems reasonable to state that any future therapy of seizures with NMDA receptor antagonists may result in a problem of serious side effects. This was studied in detail by Löscher and Hönack (1991) who showed that amygdala-kindled rats were much more susceptible to adverse activity of NMDA receptor antagonists than naive (non-epileptic) rats. Combined treatment with antiepileptic drugs together with NMDA receptor antagonists may help to partially overcome this problem, especially when there is a potent interaction in terms of anticonvulsant activity. Usually, the adjuvant antiepileptic drugs are used in lower doses than those necessary to produce a protective effect per se. This procedure also leads to reductions of the ED50 values of conventional antiepileptic drugs. Some of the experimental data cited above indicate that a number of combinations may be actually free from undesired adverse reactions. Moreover, low-affinity NMDA receptor antagonists possess a lower-adverse effect potential. A good example is remacemide, effective against both experimental and human seizures and well tolerated by epileptic patients (Bialer et al., 1999).

**AMPA/KA receptor antagonists**

1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride (GYKI 52466; a non-competitive antagonist of AMPA/KA receptors), at the sub-effective dose of 5 mg/kg potentiated the anticonvulsant action of carbamazepine, phenytoin, and valproate, but not that of phenobarbital, against maximal electroshock-induced seizures in mice (Borowicz et al., 1995). The GYKI 52466-induced enhancement was very significant, the respective ED50 values of these antiepileptic drugs being diminished by 64%, 59%, and 68%, respectively. The non-NMDA receptor antagonist did not affect the free-plasma concentration of the affected antiepileptic drugs. No effective combination of GYKI 52466 with the antiepileptic drugs resulted in undesirable effects. Combination of GYKI 52466
Experimental studies of pharmacodynamic interactions

(up to 10 mg/kg) with conventional antiepileptic drugs in the pentylenetetrazol test was much less remarkable. This non-NMDA receptor antagonist proved ineffective when combined with clonazepam, ethosuximide, and phenobarbital. Only a combination with valproate was quite effective (Czuczwar et al., 1998a). However, this combination resulted in a mnemonic effect. Promising effects were obtained with the competitive antagonist of AMPA/KA receptors, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)-quinoxaline (NBQX) at 10 mg/kg against maximal electroshock-induced seizures. This excitatory amino acid receptor antagonist potentiated the protective activity of conventional antiepileptic drugs, including phenobarbital. A pharmacokinetic interaction was considered unlikely. Practically, combinations of NBQX with antiepileptic drugs did not produce side effects, the only exception being one with valproate (Zarnowski et al., 1993). A very promising substance among AMPA/KA receptor antagonists is 7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo(4,5H)-2,3-benzodiazepine (LY 300164) which was studied in combination with conventional antiepileptic drugs against maximal electroshock, pentylenetetrazol, and amygdala-kindled seizures. In a sub-protective dose of 2 mg/kg, LY 300164 reduced the ED50 values of carbamazepine, clonazepam, phenytoin, phenobarbital, and valproate against maximal electroshock in mice very significantly (Czuczwar et al., 1998c; Borowicz et al., 1999). Side effects of clonazepam, phenobarbital, and valproate alone were more pronounced than those of the respective combinations of these antiepileptic drugs with LY 300164 (Czuczwar et al., 1998c; Borowicz et al., 1999). In the pentylenetetrazol test, LY 300164 increased the anticonvulsant-protective potential of valproate and ethosuximide, and these combinations were free from adverse effects (Czuczwar et al., 1998b). A very potent interaction was found for LY 300164 and benzodiazepine derivatives, clonazepam and diazepam in amygdala-kindled rats. The combination of clonazepam (in a non-protective dose of 0.001 mg/kg) with LY 300164 (in a sub-protective dose of 2 mg/kg) resulted in an anticonvulsant effect comparable to that provided by clonazepam alone at 0.1 mg/kg (Borowicz et al., 1999). Similar effects were observed when LY 300164 was combined with diazepam (Borowicz et al., 2000b). The combination of this benzodiazepine (at 1.25 mg/kg) with LY 300164 (at 2 mg/kg) provided a protection against seizures comparable to that of diazepam alone at 10–20 mg/kg. Also, the combinations were devoid of adverse effects whilst diazepam alone very potently disturbed motor coordination and long-term memory in amygdala-kindled rats (Borowicz et al., 2000b). Among the remaining conventional antiepileptic drugs, only a combination of valproate with LY 300164 (at 2 mg/kg) resulted in protective activity against amygdala kindling (Borowicz et al., 2001). In no instance did LY 300164 affect the free-plasma concentration of antiepileptic drugs. The interactions of LY 300164 with conventional antiepileptic drugs in the kindling model
of epilepsy are shown in Table 11.5. Generally, AMPA/KA receptor antagonists display less adverse potential than NMDA receptor antagonists (Parada et al., 1992; Danysz et al., 1994). This may be relevant in terms of their possible clinical use as adjuvant antiepileptic drugs in cases where monotherapy fails.

Table 11.5 Combined treatment of selective antagonists of NMDA and AMPA/KA receptors, LY 235959 and LY 300164, with conventional antiepileptic drugs in amygdala-kindled seizures in rats

<table>
<thead>
<tr>
<th>Antiepileptic drug (mg/kg)</th>
<th>Protective activity</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LY 235959</td>
<td>LY 300164</td>
</tr>
<tr>
<td>Diazepam (1.25)</td>
<td>0</td>
<td>↑↑</td>
</tr>
<tr>
<td>Phenobarbital (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phenytoin (40)</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Carbamazepine (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clonazepam (0.001)</td>
<td>0</td>
<td>↑↑</td>
</tr>
<tr>
<td>Valproate (75)</td>
<td>0</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

LY 235959 and LY 300164 were administered intraperitoneally (i.p.) in a sub-protective dose of 2 mg/kg, 15 min prior to the convulsive test. Antiepileptic drugs were also given i.p. in sub-effective doses, diazepam, clonazepam, carbamazepine, valproate – 30 min; phenobarbital – 60 min; phenytoin – 120 min before the test.

Data are from Borowicz et al. (1999, 2000b, 2001).

0, no interaction or side-effect; ↑, positive interaction; ↑↑, very potent interaction; NT, not tested.

Ligands of metabotropic glutamate receptors

In the early 1990s, experimental evidence indicated that metabotropic glutamate (mGlu) receptors (mGluRs) participate in the generation of seizure activity (Sacaan and Schoepp, 1992; McDonald et al., 1993; Tizzano et al., 1993). It was later elucidated that different ligands of mGluRs were effective anticonvulsant agents. For example, (S)-4-carboxy-3-hydroxyphenylglycine (an antagonist of mGlu1a and agonist of mGlu2 receptors), administered intracerebrally, inhibited sound-induced seizures in mice. This effect could be probably ascribed to a reduced release of glutamate because this process seems to be controlled by mGluRs (Thomsen et al., 1994). This mGluR ligand was also effective in other experimental seizure types, including pentylentetrazol-induced and electrically-induced convulsions. However, at effective anticonvulsant doses, the substance significantly impaired motor coordination (Dalby and Thomsen, 1996). A number of other agents interacting with mGluRs proved to exert anticonvulsant effects (for review see Urbańska et al., 1998). Recently, an agonist of mGlu2 receptors has been available. 2-Aminobicyclo(3,1,0)hexane-2,6-dicarboxylate (LY 354740) has a unique property among the mGluR ligands – it can easily enter the brain after peripheral administration. The
Experimental studies of pharmacodynamic interactions

substance proved effective against pentylenetetrazol- and picrotoxin-induced convulsions and potentiated the anticonvulsant efficacy of diazepam (but not that of ethosuximide or valproate) against pentylenetetrazol. Interestingly, apart from the potentiation of the activity of diazepam, LY 354740 reduced the free-plasma concentration of this antiepileptic drug (Klodzińska et al., 2000).

Blockade of all ionotropic receptors for glutamate – a new therapeutic possibility?

Löscher et al. (1993) were first to report on a clearly synergistic effect of NBQX combined with an NMDA receptor antagonist against amygdala-kindled seizures in rats. Also, Czuczwar et al. (1995) examined NMDA receptor antagonists (dizocilpine and D-CPP-ene) and AMPA/KA receptor antagonists (NBQX and GYKI 52466) in this regard, finding a strong interaction in terms of anticonvulsant activity. Some combinations were devoid of adverse effects (Czuczwar et al., 1995).

Interaction of antiepileptic drugs with voltage-dependent calcium channel inhibitors

There is no doubt that calcium channels are involved in the generation of seizure activity (Pumain et al., 1984; Speckmann et al., 1993). A hypothesis that voltage-dependent calcium channel inhibitors may be effective anticonvulsants was challenged by Desmedt in the 1970s but it was later confirmed (Desmedt et al., 1976; De Sarro et al., 1988; Jagiello-Wójtowicz et al., 1991). This was followed by attempts to test the combinations of calcium channel inhibitors with antiepileptic drugs. Flunarizine (at a sub-protective dose of 20 mg/kg) considerably decreased the ED50s of carbamazepine (by 51%) and valproate (by 54%) against electrically induced convulsions in mice. The ED50 value for phenytoin was reduced by 24%. Nimodipine was considerably weaker in this regard. None of these calcium channel blockers affected the plasma concentrations of these antiepileptic drugs and, generally, no adverse effects were observed (Czuczwar et al., 1992). Also, the anti-electroshock activity of phenytoin and carbamazepine was potentiated by nifedipine and diltiazem, but the activity of phenobarbital and valproate was not influenced (Czuczwar et al., 1990a). Interestingly, verapamil was completely inactive in this respect, both in the maximal electroshock and pentylenetetrazol test (Czuczwar et al., 1990a, b). This clearly indicates that the calcium channel inhibitor-induced hypotension is probably not involved in their interaction with antiepileptic drugs. The lack of effect of verapamil to modulate the anticonvulsant potential of antiepileptic drugs may be associated with its poor penetration through the blood–brain barrier (Hamann et al., 1983). Some conventional antiepileptic drugs
were also affected by calcium channel inhibitors in the pentylenetetrazol test in mice. These were ethosuximide and, to a lesser degree, valproate and phenobarbital (Czuczwar et al., 1990b; Gasior et al., 1996). The combination of nimodipine with ethosuximide or valproate, however, resulted in motor impairment (Gasior et al., 1996). It is noteworthy that flunarizine, although potently increasing the protective efficacy of conventional antiepileptic drugs against electrically induced convulsions (Czuczwar et al., 1992), was completely ineffective in the pentylenetetrazol test in mice (Gasior et al., 1996). Amlodipine reduced the ED$_{50}$ values of carbamazepine, phenobarbital, and valproate against maximal electroshock in mice, but the protective activity of phenytoin was not affected. Since amlodipine elevated the free-plasma concentration of carbamazepine, this effect is the consequence of a pharmacokinetic interaction. Combinations of amlodipine with conventional antiepileptic drugs caused a strong motor impairment. Also, co-administration of amlodipine with phenobarbital or valproate resulted in a potent mnemonic effect (Kamiński et al., 1999).

In the pentylenetetrazol test, this calcium channel inhibitor enhanced the protective action of ethosuximide, phenobarbital, and valproate without affecting their plasma concentrations. Again, the combined treatment produced a considerable impairment of motor coordination in mice (Kamiński et al., 2001).

Although many calcium channel inhibitors actually potentiated the anticonvulsant activity of conventional antiepileptic drugs, in many cases significant side effects were evident. In this context, experimental data may help to choose an appropriate calcium channel inhibitor for the treatment of cardiovascular diseases in epileptic patients. One has to consider that there are even certain calcium channel inhibitors, for instance niguldipine, which were shown to impair the anticonvulsant activity of carbamazepine and phenobarbital against maximal electroshock in mice or amygdala-kindled seizures in rats (Borowicz et al., 1997; 2002a). Consequently, some calcium channel inhibitors may be counteracted in epileptic patients.

Recent data by Swiader et al. (2002) indicated that flunarizine potentiated the protective activity of LY 300164 against maximal electroshock-induced convulsions in mice, presumably via a pharmacodynamic mechanism. This combination was also free of adverse effects. Among other calcium channel inhibitors, nifedipine did not modify the anticonvulsant activity of LY 300164, while nicardipine significantly raised its free-plasma concentration. Also, flunarizine was the only calcium channel inhibitor that could be shown to enhance the anticonvulsant action of another AMPA/KA receptor antagonist, GYKI 52466 (Gasior et al., 1997).

**Concluding remarks**

Experimental data may provide a good background for the add-on treatment of epilepsy. It is evident from the data presented above that some combinations of
Experimental studies of pharmacodynamic interactions

antiepileptic drugs are promising, although the results of experimental studies can only be extrapolated with caution to the clinical setting. A considerable amount of experimental data are in agreement with what is observed in epileptic patients. A good example is D-CPP-ene and its adverse potential in rodents and epileptic patients, already discussed above (Sveinbjørnsdóttir et al., 1993; Zarnowski et al., 1994a). It is also worth stressing that the psychotomimetic activity of dizocilpine (a non-competitive antagonist of NMDA receptors) found in epileptic patients (Porter, 1990) was also evident in amygdala-kindled rats (Löschner and Hönack, 1991). However, it needs to be taken into consideration that antiepileptic drugs may undergo different metabolism in experimental animals and epileptic patients. For instance, topiramate was documented to increase the free-plasma concentration of carbamazepine in mice (Swiader et al., 2000) while this effect was apparently not confirmed in epileptic patients (Bourgeois, 1996). However, most studies on the use of antiepileptic drugs are carried out acutely in rodents while epileptic patients receive a chronic antiepileptic therapy. It is widely known that carbamazepine and phenytoin are cytochrome P450 inducers when administered chronically, and this may be a reason for some discrepancies. Consequently, all experimental suggestions require careful clinical verification.

According to Majkowski (1994) and Deckers et al. (2000), the new antiepileptic drugs are currently used mainly as add-on therapy. Nevertheless, rational polytherapy with new antiepileptic drugs is likely to become increasingly widespread. It will remain a challenge for pharmacologists to provide experimental data on interactions between newer antiepileptic drugs. So far, such evidence is only fragmentary. Detailed interactions between antiepileptic drugs in both experimental and clinical conditions were also reviewed by Fröscher (1994) and Deckers et al. (2000). The experimental background for the evaluation of synergistic and additive effects of antiepileptic drugs given in combination was discussed by Czuczwar (1998) and Deckers et al. (2000).

In summary, monotherapy is recommended for the treatment of epilepsy, preferentially among newly diagnosed patients. However, in patients who are resistant to monotherapy, combination therapy may be beneficial. Experimental studies provide evidence that a combination of two antiepileptic drugs may produce antagonistic, additive, and supra-additive (synergistic) anticonvulsant effects. A drug combination producing a supra-additive seizure protection should be of clinical interest. However, if in addition to the enhanced protective efficacy against seizures there is also supra-additive toxicity, the protective index (and hence the effectiveness of the drug combination) may be equal or even inferior, when compared with each drug alone.

Two main experimental approaches for studying drug interactions exist. The isobolographic analysis may be employed when antiepileptic drugs are used at active doses against seizures. A shift of the dose–response curve for an antiepileptic drug in the presence of an adjuvant (usually in sub-protective doses) may also
indicate which combinations to choose for clinical evaluation. Existing experi-
mental evidence points to a favorable synergistic interaction between valproate and
phenytoin (or ethosuximide) or topiramate and carbamazepine (or phenobarbi-
tal), or felbamate and all major antiepileptic drugs. However, the anticonvulsant
potency of carbamazepine, phenytoin, phenobarbital, and valproate was not affected
by felbamate at sub-protective doses against maximal electroshock in mice. This
may indicate that synergism is encountered at only some drug concentration ratios.
Considerable enhancement of the protective activity of conventional antiepileptic
drugs by some calcium channel inhibitors and excitatory amino acid antagonists
has also been demonstrated. The experimental data may be helpful for choosing
drug combinations potentially beneficial in epileptic patients. However, final con-
clusions have to be based on appropriate clinical trials.

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Clinical studies of pharmacodynamic interactions

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Introduction

This chapter addresses the clinical impact of pharmacodynamic (PD) interactions of antiepileptic drugs (AEDs) and the strategies that have been used to discover these interactions. Particular attention is paid to the limitations of available studies and the chapter concludes with a summary of expert opinion about optimal study design for identifying PD interactions. For the purposes of this chapter, the definition of a PD interaction is the interaction of two drugs causing a greater or less than expected effect or side-effect in the absence of a pharmacokinetic interaction.

Polypharmacy has undergone a renaissance since the early 1980s (Goldsmith and de Bittencourt, 1995). The old arguments against combination therapy were predicated upon the observation that refractory patients placed in polytherapy were experiencing increased adverse events without better efficacy (Schmidt, 1982). Since then, the advent of monitoring AED levels and a deeper understanding of the mechanisms of AED action have led to more effective use of rational polypharmacy. A combination of drugs can now be used which suppress excitation, enhance inhibition, and work by other novel mechanisms, thus providing a previously lacking theoretical construct for the assertion that the efficacy of combinations of drugs can be additive or supra-additive. In addition, monitoring of AED levels can limit pharmacokinetic variation that often used to cause adverse events when drugs were combined. The clinician’s goal is to identify combinations that improve effectiveness, a goal that could be achieved more often if natural synergies could be identified.

For any given effect or side effect, there are four possible outcomes of PD interactions. The first is additivity, which indicates that there is no change in the effect expected from each drug. The second is supra-additivity, a state in which a given combination results in an effect which is greater than that expected from simple additivity. The third possibility is antagonism, which is a combination that does not have at least the total effect that each medicine would be expected to have on its
Clinical studies of pharmacodynamic interactions

own. Lastly, there is aberrancy, in which a combination results in completely different effects. Alternative nomenclature of positive- or negative-PD interactions has been used in some literature. These terms imply a deviation in one direction or the other away from the additive state.

Deckers et al. (2000) define effectiveness as ‘a measure encompassing both efficacy and tolerability’, and PD interactions can affect both. This chapter will address the evidence for additivity, supra-additivity, antagonism and aberrancy for various combinations as they relate to both efficacy and tolerability. Also, an attempt will be made to summarize the experiences to date with trial design quantifying PD interactions and to highlight the designs that have the best chance of providing clinically useful knowledge. Of note, the works of Deckers et al. (2000, 2003) and Bourgeois (2002) are excellent recent reviews that summarize the results of studies relevant to PD interactions.

Positive-PD interactions: efficacy

The following section will outline trials that have provided, or have attempted to provide, relevant data on PD interactions that impact on efficacy. In assessing the validity of these studies, several issues should be considered.

Should trials be sequential or parallel?

Many of the studies discussed below have been sequential – each patient must ‘fail’ on monotherapy of one or two drugs, which are then combined, to determine whether the combination succeeds where monotherapy failed. The advantage to this approach is that each patient can be pushed to individual maximal tolerated dose. This ensures that the monotherapy was a true failure, rather than a failure to achieve the proper dose. The disadvantage is that studies designed in this way are long, leading to dropouts, which may bias the outcome.

What is the impact of drug load on PD interactions?

One major problem with many studies of AED combinations is that drug load is not taken into account. Clearly, the same adverse events would not occur when two drugs are given at high doses, as when they are combined in lower doses. Deckers has suggested that toxicity may be a result of total drug load, rather than the combination of two drugs per se. He uses a prescribed daily dose/defined daily dose (PDD/DDD) calculation to determine drug load. In a review, he points out that most studies of add-on therapy do not provide information about doses of background drugs, making it difficult to determine total drug load (Deckers et al., 1997a). However, this concept of total drug load toxicity may not be true for all drugs. A drug that was pharmacodynamically benign might be able to be added to
any existing drug combination without causing problems. If a drug proves particularly tolerable, this concept can be used to evaluate combinations that would allow the average patient to exceed normal drug loads (Deckers et al., 1997b).

Is the goal of the study improved efficacy or lowering of toxicity?
In most of the trials discussed below, two drugs are combined at standard doses, to produce additive efficacy. In some cases, however, the goal of combination therapy may be a reduction in toxicity rather than improved efficacy. Most AEDs demonstrate both increase in efficacy as well as toxicity as dosage increases. Even standard dosages may produce undesirable dose-related side effects. Therefore, it may be useful to demonstrate that lower than standard doses of two drugs can be combined to produce the efficacy of either drug at higher (and presumably less well-tolerated) doses in monotherapy. This approach would only be useful if reduced toxicity could be demonstrated, since efficacy presumably is no better than monotherapy.

What type of outcome analysis should be employed?
Seizure freedom is the ultimate goal of any epilepsy therapy. Many studies have focused on this outcome measure in combination trials. Often, seizure freedom is the only outcome measure provided. While this is useful, it may be misleading. For example, by random chance, some patients may improve while others deteriorate. In this case, reporting seizure freedom only might give an appearance of benefit, where none exists.

Definitive data supporting the presence of additive or supra-additive PD interactions are difficult to find and several obstacles will be illustrated in the examples below. A caveat to the following presentation of the available data concerning additivity comes from Patsalos who suggests that there is a possibility that ‘some of these therapeutic enhancements result from pharmacokinetic interactions taking place in the central brain compartment, rather than as a result of PD interactions …’ (Patsalos et al., 2002). Nevertheless, for clinical purposes, any synergistic result is still important.

Add-on placebo-controlled trials
The most common studies of additive effects of AEDs are the randomized placebo-controlled add-on studies of the new AEDs. The design timeline is shown in Figure 12.1. The patients enter these trials on a variety of baseline drugs, typically with a maximum of two allowed. Increasing doses of the study drugs are employed, often leading to an incremental decrease in seizure frequency (see Figure 12.2) (Cramer et al., 1999). These studies suggest that the study drug does indeed have at least an additive effect on efficacy. Thus the entire generation of newer AEDs that were all
Clinical studies of pharmacodynamic interactions

231

Figure 12.1 Double-blind placebo-controlled trial schema

Figure 12.2 Fifty per cent seizure reduction in placebo-controlled add-on trials of three new AEDs (with placebo rate subtracted) (after Cramer et al., 1999)

tested using this type of study design probably have at least an additive effect on efficacy. Unfortunately, one cannot glean specific information about which combinations were most effective, because of the small number of patients on each baseline AED. It is also difficult to establish definitively that the effect is truly additive, because of problems establishing the efficacy of a baseline drug a study patient received. A very conservative interpretation of these types of study would question whether these add-on studies simply show that the new drug was effective while the older baseline drug was not.

Other studies

Dean and Penry (1998) studied the combination of carbamazepine (CBZ) and valproate (VPA) using 100 patients who had failed monotherapy with CBZ. This
study showed good success. However, it is possible that VPA monotherapy would have worked just as well, thus complicating the interpretation of these data as being supportive of an additive effect on efficacy. Of note, Harden et al. (1993) presented a smaller number of patients with a similar study design and result.

A trial of phenobarbital (PB) compared to phenytoin (PHT) and the PHT/PB combination was done in a non-randomized fashion in neonates with refractory seizures (Painter et al., 1999). This study suggested that the combination therapy made an additional 12–17% seizure free. As with the aforementioned studies, a monotherapy of the second drug was not tried, so it is not clear what the result would have been with just substituted monotherapy. A similar study design was used by Murri and Iudice (1995) in an add-on study of vigabatrin added to CBZ. There was a dropout rate of 30% but a substantial number of patients became seizure free.

Tanganelli and Regesta (1996) performed a study that used patients with newly diagnosed epilepsy, a good way to avoid the difficulties with establishing the baseline efficacy of each drug. Vigabatrin and CBZ were studied separately and in combination. The patients were randomly assigned to either drug and then titrated until they were either seizure free or experienced toxicity. Patients who became toxic before achieving adequate control were switched to the other medication. Combination therapy was attempted only for those patients who failed monotherapy. A total of 51/58 patients completed the study, and no data is available for the ones who did not complete. Approximately half of the patients responded well to their initial therapy. Of the non-responders 45% had good control with the cross over drug. The combination therapy had good results as well, with 5/14 patients (35%) becoming seizure free. There was no statistically significant difference between the efficacy of the two drugs, but the study was not powered to necessarily detect a small difference in efficacy between the drugs. This study shows an additive effect for efficacy when these two drugs are combined, because many patients who did not respond to either drug separately became seizure free with the combination. This study design was also used by Hakkarainen (1980) using CBZ and PHT. In this study of 100 patients, presented in abstract form only, 5/33 patients (15%) who failed sequential monotherapy became seizure free on combination therapy.

Walker and Koon (1988) tried a slightly different study design. They compared CBZ, VPA and the combination in series, dropping those patients who responded well from the next study arm. Again some patients became seizure free on the combination. This is relatively good evidence for an additive effect of the two drugs, but the data may be challenged because of the sequential study design.

In another classic add-on study, ethosuximide was added to VPA for control of absence seizures (Rowan et al., 1983). Five patients were involved in the study, and
all became seizure free. Two of these patients had been refractory to ethosuximide monotherapy, so these results also support at least additivity for efficacy.

The issue of using sub-toxic doses of two drugs to reduce side effects was explored in several interesting studies. An oft-cited study by Gruber et al. (1956) compared PB and PHT in what today would be considered an unusual design, a latin square (see Figure 12.3). Patients were on their own baseline medication for 3 days of the week and then were given the study drug for 4 days. Given the long half-lives of both study drugs, it is not clear if adequate washout time was given. The study results suggested that 50 mg of either drug daily was just as efficacious as 25 mg of both drugs in combination. This study design is similar to the isobolograms done when studying PD interactions in animals (Chapter XI).

In patients with newly diagnosed epilepsy, Deckers et al. (2001) compared full dose CBZ, full dose VPA, and a half drug load of both. No difference was found in overall neurotoxicity or efficacy as measured by seizure frequency. It should be kept in mind, however, that newly diagnosed patients are not as sensitive to efficacy differences between regimens, and are usually responsive to lower doses of medication. No study arm was included with half dose of either AED alone. If we assume that half dose of either AED would translate into less effectiveness than the full dose of either, this study supports the notion that these two AEDs have an additive PD effect with respect to efficacy. This type of study using the concept of drug load may be invaluable for future studies.

Using a latin square design similar to the Gruber study mentioned above, Cereghino et al. (1975) compared CBZ, PHT and PB alone and in various combinations. The groups were not assigned randomly, but instead were divided into groups the authors thought were equivalent. As in the Gruber study, the PB arms probably were not given adequate washout time. In addition one criterion for inclusion in the study was that each patient had to be refractory to CBZ treatment, thus complicating the interpretation by raising the possibility that the CBZ was not working at all in some patients. Nonetheless, in terms of total seizure frequency, the combination of
all the three drugs was the superior condition for controlling seizures, while the
group on combination PB and PHT had the most frequent seizures. Despite many
limitations, this study may show an additive effect.

Kwan and Brodie (2000) compared add-on therapy to substitution therapy in
refractory patients. In this prospective chart review, patients had similar rates of
effectiveness when converted to a sequential therapy or an add-on. The authors
observed ‘more patients became seizure free when the combination involved a
sodium channel blocker and a drug with multiple mechanisms of action compared
to other combinations.’ These data, while relatively underpowered, would support
the theory that PD interaction that results in increased efficacy will likely be a
result of targeting multiple points along the pathways of excitatory and inhibitory
action (Goldsmith and de Bittencourt, 1995).

Certain specific combinations have been suggested as being more successful than
others. Stephen et al. (1998) presented three cases where topiramate was added to
lamotrigine and the patients became seizure free. There are several studies of the
lamotrigine and VPA combination, and these provide the best evidence that there
is a supra-additive effect from certain combinations of AEDs. The first notable
study was by Brodie and Yuen (1997) (see Figure 12.4). Three hundred and forty-
seven patients with any type of refractory epilepsy on monotherapy (VPA, CBZ,
PHT) received add-on lamotrigine in addition to their previous drug. If patients
had a >50% reduction in seizures, then the first drug was withdrawn. The lamot-
rigine produced seizure reduction in a proportion of patients when it was added to
each of the tested baseline medications. When the primary drug was withdrawn,
seizure frequency declined slightly in the PHT and CBZ groups, possibly as a result

![Figure 12.4 Results of lamotrigine substitution for each of the above AEDs (after Brodie et al., 1997)]
Clinical studies of pharmacodynamic interactions

of removal of the hepatic enzyme-inducing effect of these medications, and a resulting rise in lamotrigine levels. In contrast, when the VPA was withdrawn, there was an increase in seizure frequency, despite the fact that the lamotrigine serum levels were higher as a result of dosage adjustments. This effect suggests that there may be at least an additive effect of these two drugs and possibly even PD supra-additivity. Unfortunately, this part of the study had relatively few subjects due to substantial numbers of patients who dropped out. Of course, this dropout effect may account for the apparent improvement, as those who were doing better would be more likely to remain. Another weakness of this study is the possible selection bias of the primary treatment drug.

Kanner and Frey (2000) specifically studied the combination of lamotrigine and VPA and controlled for pharmacokinetic interactions. The study evaluated 27 patients with partial epilepsy and one with generalized epilepsy who were refractory to treatment on at least three AED. All patients were on lamotrigine monotherapy at sub-toxic doses and then had VPA added. The average seizure free duration was 6.2 months on combination but only 2.1 months on monotherapy. One limitation is that the enrolled patients were selected specifically because they were refractory to lamotrigine monotherapy. These results, from a well-controlled study, again indicate the possibility that an additive or even a supra-additive PD interaction may exist between these two drugs both in efficacy and side effects.

Negative-PD interactions: efficacy

Antagonistic PD interactions for efficacy exist when a combination of two medicines does not have the efficacy that each would be expected to have on its own. In the study by Brodie and Yuen (1997) described above, a group of refractory patients who were taking CBZ or PHT as primary drugs had lamotrigine added on and then the primary drug withdrawn. As noted, during the combination period, patients had more seizures than during lamotrigine monotherapy. Although this result may reflect antagonism for efficacy, it is plausible that pharmacokinetic, rather than PD interactions resulted in a spurious result. However, had pharmacokinetic interactions not been a factor, this study design would have been ideal for identifying PD antagonism.

A few case reports have suggested that the combination of VPA and clonazepam can induce status epilepticus, a result that could be defined as the worst case scenario for antagonistic PD interaction for efficacy. However, other studies with larger numbers of patients showed no episodes of status (Rosenberry et al., 1979; Mireles and Leppik, 1985). It is possible the surprising dearth of data showing antagonistic effects of AED on efficacy may reflect a certain reality. Some have maintained that ‘PD interactions (regarding efficacy) … are probably unidirectional
and lead only to increased effects’ (Reife, 1998). However, another possibility is that the proper studies to look for this type of interaction have not been done. Even drug combinations that produce improvement in many patients may produce worsening in some. Somerville et al. (2002) looked at seizure worsening in pooled data from randomized adjunctive trials. He found that more patients worsened when tiagabine was added than when placebo was added, even though tiagabine caused a greater overall seizure reduction than placebo. This would indicate a bimodal distribution, with some patients improving, and others worsening. This indicates that PD interactions are not always unidirectional.

**PD interactions: side effects**

As noted above, side effects are often dose-related. Negative-PD interactions, also called supra-additivity for side effects, may occur when two drugs with similar side-effect profiles exceed the threshold for that side effect in combination but not individually. The possibility exists of discovering combinations of drugs that have additivity for efficacy permitting the use of doses below the threshold for side effects. A study by Lammers et al. (1995) used a quantitative assessment of adverse effects for patients on monotherapy vs. polytherapy. Interestingly, the study showed that as an aggregate measure, adverse events were no more frequent in either group. This suggests that it is possible that specific combinations of medications may offer extra efficacy without producing extra side effects. An alternative explanation for these results is that measuring the percentage of people who suffer from a given side effect may not be the best measure. Some subjects may have experienced worsening of side effects with the combination of medicines, but this would not have been detected by the measurements used in this study.

Several studies of specific AED combinations have demonstrated an increase in side effects. In the study by Kanner and Frey (2000) described above, the combination of VPA and lamotrigine caused an increase in the number of patients complaining of tremor to 55%. This combination of VPA and lamotrigine also caused a notable increase in the fraction of patients experiencing tremor in a study by Pisani et al. (1999). It is unclear whether the increase was additive or supra-additive. Another example is the studies by Tanganelli and Regesta (1996) and Murri and Iudice (1995) discussed above, in which the combination of vigabatrin and CBZ led to increase in side effects such as weight gain and ataxia. As another example of a possible combination-specific interaction, in a small case series, four patients on polytherapy that included CBZ were started on levetiracetam and experienced side effects characteristic of CBZ toxicity. All the patients responded to decreasing the dose of one of the drugs, but no levels were drawn (Sisodiya et al., 2002). This interaction has not been confirmed by other investigators.
PD interactions may also increase the likelihood of non-dose-related side effects and serious idiosyncratic reactions. Osteopenia has been reported to occur in highest incidence among patients taking more than one enzyme-inducing AED (Farhat et al., 2002). Hepatic toxicity is significantly more common in patients taking valproic acid in combination therapy than in monotherapy, and this effect becomes even more pronounced in the young. The incidence of VPA-induced hepatic failure increases from 1/2000 in children under 2 years old on monotherapy, to 1/200 in those on polytherapy. The cause of this interaction is unknown (Dreifuss et al., 1987).

Another dramatic PD interaction is the development of side effects that are not described for either drug in isolation. In one descriptive paper, three patients developed new-onset chorea, and all were on a combination of PHT and lamotrigine (Zaatreh et al., 2001). The chorea resolved in all these patients with tapering of one medication. Although this side effect has been described for AEDs, it was unusual that this combination appeared in all three cases of chorea seen at an epilepsy clinic and represents an aberrant PD interaction for side effects.

**Trial designs**

The problem of designing the ideal trial to assess PD interactions has been addressed by several authors. Pledger (1989) suggests that the most straightforward and ethical design would involve a baseline medication that had no interactions with the two drugs to be studied (X and Y). All patients would be on the baseline drug and then groups would receive X, Y or X + Y as add-on therapy. However, even the author notes that this study design would probably be prohibitively large. Deckers et al. (2003) suggest another paradigm that might be less costly. Patients would be evaluated on polytherapy while in the midst of switching monotherapies. He argues that this would provide useful clinical information, and provide information about PD interactions. Additionally since there is very little evidence for negative-PD interactions for efficacy, if a given combination is evaluated and proved not to have higher efficacy than the primary monotherapy, then the secondary therapy likely does not work. This would save the patient from an ineffective second monotherapy. Bourgeois (2002) suggests the optimal model would be to give drug X to maximally tolerated dose, then give drug Y to maximally tolerated dose as monotherapy, then a combination of both. While potentially valid, one must consider the likelihood of spontaneous regression/remission when analyzing such a trial.

Bourgeois has also discussed the impact of drug load, as it relates to PD interactions. He states that while drug load can be used in an isobologram fashion to give half doses of each drug, he considers this option suboptimal. A patient who is not tolerating maximal doses of drug X may be tried randomly in two arms of a
trial: half dose X + half dose Y; or convert to drug Y titrated up from half dose. This type of trial was attempted by Deckers et al. (2001) but no attempt was made to discover if half dose of drug Y was as effective as the combination.

Bourgeois lists other designs as most likely valid such as: failure of drug X, improvement after addition of drug Y, and then worsening after elimination of drug X; or adding drug D to drugs X, Y, or Z and obtaining significantly better results with one of the combinations.

In summary, the total database of proven PD interactions is far from complete. To date, the best data for a potentially supra-additive effect on efficacy are for the combination of lamotrigine and VPA. Studies undertaken in the future should ideally address many of the difficulties identified above. These include: using universally accepted measures of efficacy, inefficacy, and side effects; accounting for dropouts; using the concept of drug load; and performing well-controlled studies that rule out pharmacokinetic interactions. For many reasons, whether cost or ethics or unavailability of patients, we are unlikely to gain the insights into PD interactions that the perfect studies would afford.

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Clinical studies of pharmacodynamic interactions


Clinical studies of pharmacodynamic interactions between antiepileptic drugs and other drugs

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Introduction

Pharmacodynamic (PD) drug–drug interactions can occur when a patient receives concomitant treatment with two or more drugs. In general, the clinical effect resulting from PD interactions can be either advantageous or disadvantageous. A few studies in animal models have addressed the therapeutic or adverse synergistic effects of antiepileptic drugs (AEDs) (Meinardi, 1995). In humans, formal studies aiming to prove PD interactions between AEDs and other drugs are rare.

In this field, one of the most studied PD interactions is that occurring between flumazenil and benzodiazepines (BZD). Flumazenil is a specific and competitive antagonist of central BZD receptors, reversing all effects of BZD agonists. For this reason, incremental intravenous bolus injections of flumazenil are effective and well tolerated in the diagnosis and treatment of BZD overdose; treatment with flumazenil results in complete awakening with restoration of upper airway protective reflexes (Weinbroum et al., 1997). However, withdrawal symptoms and even seizures can be observed after administration of flumazenil in long-term BZD users; these symptoms may be avoided by a slow titration of flumazenil dose.

Alcohol is another substance whose PD interactions with sedative drugs have often been studied. Sedation, which is a typical adverse effect of many AEDs, is increased by the concomitant administration of alcohol in a way that has been described in different studies as either synergistic or additive (Kastberg et al., 1998).

In this chapter, we discuss in more detail the clinical data concerning PD interactions of AEDs with antidepressants (ADs), antipsychotics (APs), central nervous system (CNS) stimulants, anesthetic agents, analgesics and anti-inflammatory drugs.
PD interactions with ADs

AEDs and ADs are often co-administered. In fact, the lifetime prevalence of major depression reported in epileptic patients is remarkably higher than in the general population (8–48% vs. 6–17%, respectively) (Lambert and Robertson, 1999). It has been hypothesized that common pathogenetic mechanisms may predispose to depression in some patients with certain types of epilepsy (Jobe et al., 1999).

Experimental and clinical data suggest that AEDs and ADs have similar mechanisms of action which could result in favorable and/or unfavorable PD interactions depending on the particular agents involved. Recently, biological psychiatrists have assessed the potential usefulness of AEDs in the treatment of affective disorders. Furthermore, some data suggest that ADs can have anticonvulsant and proconvulsant properties. Finally, many drugs of these two classes share similar adverse effects which are worsened by the concomitant administration.

AEDs and affective disorders

In some patients, AEDs may precipitate mood disorders. The probability of developing such adverse events is highest with the combination of barbiturates and vigabatrin (VGB) and very low with the combination of carbamazepine (CBZ) and valproate (VPA). Brent et al. (1987) found that the prevalence of depression and suicidal ideation was higher in adolescents and children taking phenobarbital (PB) than in age-matched subjects treated with CBZ. Furthermore, a meta-analysis of clinical studies performed with new AEDs shows that, in patients taking GB, the percentage of withdrawal due to depression was significantly higher than in patients treated with placebo (Marson et al., 1997).

However, the psychiatric prognosis of patients affected by epilepsy is likely to be improved by the use of AEDs. In fact, a better seizure control can have an indirect positive effect on the predisposition to mood disorders. In addition, the established positive psychotrophic effects of some AEDs in non-epileptic psychiatric conditions suggest that AEDs could also directly improve the mood of epileptic patients (beyond their influence on seizure activity). In this context, the choice of the appropriate AED in individual patients should not merely be guided by the efficacy of the drug, but also by its AD properties and by its adverse effect profile.

Combination of AEDs and AD in the treatment of affective disorders

In an open, pivotal study, the effect of low doses of CBZ combined with low doses of amitriptyline has been evaluated in patients with major depression (Dietrich and Emrich, 1998). The particularly good results of this drug association have been postulated as a typical example of PD interaction. The authors hypothesize that the mood is regulated by two distinct groups of functional subsystems in the CNS.
While ADs affect the most important neurotransmitter systems (which are assumed to be directly involved in endogenous depression), CBZ would affect some regulatory mechanisms between temporal cortex and amygdala which couple cognition and perception with emotions. Simultaneous targeting of these two functional subsystems would cause a favorable PD interaction and a potentiation of the AD effect of these drugs.

Various new AEDs have been also used in the treatment of mood disorders. Lamotrigine (LTG) is the most widely studied and has proven efficacy in acute bipolar depression and in the long-term treatment of bipolar depression (Yatham et al., 2002). Recently, in a placebo-controlled double-blind study, LTG was added to paroxetine in depressed patients and appeared to accelerate the onset of action of the AD (Normann et al., 2002). One can therefore speculate that LTG also has favorable PD interactions with some ADs. CBZ and VPA are used for the prophylaxis of bipolar disorders in combination with lithium. It is known that in these disorders, monotherapy is associated with a high failure rate. In contrast, the combination of lithium with CBZ or VPA has been reported to be highly effective (Post et al., 1996). Some double-blind and open studies have revealed that lithium and CBZ have additive effects (Kramlinger and Post, 1989). Similar results have been observed for the combination of lithium plus VPA and, in this case, a synergistic effect has been proposed (Salomon et al., 1998). These results are of particular interest because the combination of lithium and ADs gave different results. In fact, in a multi-center study which compared the efficacy of lithium, imipramine and the combination of lithium plus imipramine, the failure rate was similar for treatments with lithium and with lithium plus imipramine (Prien et al., 1984). Some experimental data suggest that lithium and VPA have a true positive PD interaction; they are thought to down-regulate the expression of a protein involved in synaptic transmission which seems to be involved in stabilizing recurrent mood episodes. These two drugs act at different biochemical levels and they can therefore be synergistic (Lenox et al., 1996).

**ADs effects on seizure threshold**

Shortly after the introduction to the market of the tricyclic antidepressants (TCAs), seizures were reported in people taking these drugs. The most clear-cut situation in which ADs show an effect on seizure activity is overdose; in such a condition the incidence of seizures ranges from 4 to 20% with a mean overall incidence of 8.4% (Pisani et al., 1999). Maprotiline and amoxapine appear to be more frequently associated with seizures. With TCAs, seizures are reported in 3–8% of cases. Finally, the cumulative evidence from published reports shows that selective serotonin-reuptake inhibitors (SSRIs) are much less likely to cause seizures in overdose and that trazodone is the safest agent in this respect (Alldredge, 1999).
The incidence of seizures occurring with therapeutic doses of ADs varies from 0.1 to 4% (Pisani et al., 1999). This incidence differs slightly from the annual incidence of first seizures in the general population (which has been estimated to be from 0.073 to 0.086%). However, under these circumstances, a clear dose-related effect has been observed for some ADs. For example, Peck et al. (1983), through the analysis of almost one hundred studies on imipramine, found that the overall incidence of seizures was 0.33%. However, seizures occurred in 0.10% of patients when the drug was prescribed at doses of 200 mg/day or less and in 0.63% of patients treated with doses greater than 200 mg/day. The incidence of AD-related seizures for some ADs is reported in Table 13.1.

Interestingly, some AEDs may also have similar proconvulsant characteristics, particularly in overdose. For example, an increased frequency of partial seizures can be the primary manifestation of intoxication with CBZ or phenytoin (PHT) (Perucca et al., 1998). CBZ, which has the chemical structure of a TCA, may worsen epilepsy in several conditions even at therapeutic dosages. In particular, this agent may precipitate or exacerbate a variety of seizures in patients with generalized epilepsies. Similar paradoxical proconvulsant effects have also been described, although less frequently, with other traditional and new AEDs (Perucca et al., 1998).

In spite of frequent observations of seizures induced by ADs in non-epileptic patients, the few studies in which an AD has been administered to epileptic patients show that the seizure control was improved in most cases (Alldredge, 1999). This effect might be secondary to an attenuation of emotional triggers for seizures or to

### Table 13.1 Incidence of seizures induced by AD drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>Seizure incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>High (&gt;200)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Moderate (50–600)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Low (≤200)</td>
<td>0.1</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>High (&gt;200)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Moderate–low (&lt;200)</td>
<td>0.00</td>
</tr>
<tr>
<td>Bupropion</td>
<td>High (&gt;450)</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td>Moderate–low (≤450)</td>
<td>0.44</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Wide range</td>
<td>0.5</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Wide range</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20–60</td>
<td>0.2</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>&lt;100</td>
<td>0.2</td>
</tr>
<tr>
<td>Viloxazine</td>
<td>150–800</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Source: From Pisani et al. (1999), with some modifications.*
enhancing the effectiveness of concomitant AED therapy through pharmacokinetic interactions. However, direct anticonvulsant effects of ADs have been shown in animal as well as in some human studies (Alldredge, 1999). In a small double-blind cross-over study, imipramine at a dose of 25 mg/day was effective in the treatment of absences and myoclonic–astatic seizures (Hurst, 1984). In a more recent add-on open-label study, 17 non-depressed patients with drug-resistant complex partial seizures were treated with fluoxetine (Favale et al., 1995). Six patients became seizure free for 8 months, while the remaining patients experienced an average 30% reduction in seizure frequency. An effect against partial seizures has also been reported with doxepin (Pisani et al., 1999). For a more detailed review, see Alldredge (Alldredge, 1999). All of these data suggest that some TCAs and some SSRIs, at a certain dose, may exert an inhibitory action on neural excitability. It seems that the most important factor in determining the direction of a given AD in terms of inhibition or excitation is drug dosage. It would be interesting to explore possible favorable interactions between AEDs and ADs on different epileptic syndromes.

**Adverse effects**

PD interactions can also cause the appearance or the worsening of some adverse effects. Sedation may be particularly troublesome in patients taking AEDs, particularly barbiturates or BZD. This adverse effect can be aggravated by the co-administration of most of the older ADs, especially TCAs, mianserin, trazodone and mirtazapine (Lambert and Robertson, 1999). Patients with epilepsy often complain of memory disturbances and some AEDs, such as barbiturates and topiramate (TPM) are known to have deleterious effects on memory. The association of these drugs with older TCAs (especially amitriptyline, which has strong anticholinergic effects), mianserin, and trazodone has been found to produce cognitive impairment and therefore should be avoided (Lambert and Robertson, 1999).

Theoretically, monoamine oxidase (MAO) inhibitors should not be co-administered with CBZ because this may precipitate a hypertensive crisis. However, this event has not been observed in practice. In contrast, a case has been described of a toxic serotonin syndrome attributed to the concomitant use of fluoxetine and CBZ in a patient with an affective disorder (Lambert and Robertson, 1999). Finally, CBZ and, more frequently, oxcarbazepine have been associated with hyponatremia. This metabolic effect has also been documented in patients taking SSRI (Bouman et al., 1998). Therefore, attention should be paid when SSRI are co-administered with CBZ or oxcarbazepine, particularly in elderly patients also treated with diuretic drugs.

In summary ADs and AEDs share several clinical effects. The factors which determine the direction of the effect (pro- or anticonvulsant) may be the dosage of drugs and the epileptic syndrome. PD and also pharmacokinetic interactions (some AEDs induce the metabolism of ADs and in turn are inhibited by these
PD interactions with AP drugs

AP and AEDs are frequently co-administered and PD interactions concerning their effects on psychosis and seizure threshold are possible. Epidemiological studies have identified a variety of psychoses in about 7–8% of patients with epilepsy. The risk for this adverse effect seems to be higher in patients with temporal lobe epilepsy. In a prospective study of psychosis and epilepsy, children with temporal lobe epilepsy had a 10% chance of developing interictal psychoses during a 30-year follow-up compared with a mean incidence of psychosis of 0.8% in the general population. On the other hand, patients with schizophrenia appear to be more prone to seizures than the general population. This vulnerability can be related both to neuropathologic substrate of schizophrenia and to the exposure to psychotropic medications that lower the seizure threshold (Torta and Keller, 1999).

AEDs and psychosis

Neurobiological hypotheses of epileptic psychoses are focused on the neuropathologic alterations observed in epilepsy and on the neurophysiologic modifications of various neurotransmitter systems (particularly 3,4-dihydroxyphenylalanine, DOPA) induced by the epileptic discharge (Torta and Keller, 1999). In general, the overall psychiatric prognosis of epilepsy is thought to be improved by the use of AEDs. However, in many situations, interictal psychoses can be induced or aggravated by some AEDs. Mechanisms related to these adverse events are represented by forced normalization1, folate deficiency, drug toxicity and abrupt withdrawal of a drug. Ethosuximide is associated with forced normalization and psychosis both in children and in adults (Torta and Keller, 1999). Psychoses are also described with PHT when serum level is above 35 mg/l (McDanal and Bolman, 1975). Among the new AEDs, VGB and TPM are more frequently responsible for psychotic disturbances. In patients included in controlled clinical studies, the incidence of this complication was 3.4% with VGB (Ferrie et al., 1996) (which is higher than the incidence of psychosis in patients treated with placebo: 0.6%) and 3% with TPM (Shorvon, 1996).

APs effects on seizure threshold

As far as convulsant effects of APs are concerned, a report of seizures induced by chlorpromazine appeared in the literature within the first year of the introduction

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1 The term forced normalization (Landolt, 1958) indicates the appearance of a psychosis in an epileptic patient in whom the abnormal EEG became normal as a result of anticonvulsant treatment.
of this drug in clinical practice (Zaccara et al., 1990). Subsequent studies showed that phenothiazines were able to produce convulsions. In a study of hospitalized psychiatric patients, Logothetis (1967) found that the incidence of spontaneous seizures was 1.2% among 859 patients under treatment with phenothiazines. The incidence increased to 9% among patients receiving large therapeutic doses of these agents, while only 0.5% of patients treated with low or moderate doses had seizures. Patients with organic brain diseases were at higher risk. Seizures were generally observed at the onset of therapy or after a sudden increase in the dose.

To date, almost all of the APs introduced in clinical practice are known to induce seizures in predisposed subjects. In this respect, the aliphatic phenothiazines (e.g. chlorpromazine, promazine and triflupromazine) imply a higher risk of this adverse event than the phenothiazines bearing a piperazine or piperidine moiety (Zaccara et al., 1990). The degree of the epileptogenic power of a neuroleptic seems to be related to the ratio between the blockage of D2 dopaminergic receptor (which is convulsant) and the blockage of D1 receptor (anticonvulsant). It seems also to be associated with the agent’s antihistaminergic activity. In general, the more prominent the sedative properties of an individual AP, the higher its epileptic potential. However, as with ADs, the low incidence of reported cases does not allow an accurate assessment of the relative seizure risk. It has been suggested that, among traditional APs, haloperidol, fluphenazine, molindone, pimozide and trifluoperazine have a lower rate of seizures during therapeutic use and should be preferred in patients with epilepsy (Alldredge, 1999).

**Convulsant effect of atypical APs (clozapine, olanzapine, quetiapine and risperidone)**

Among the atypical APs (AAPs), clozapine carries the highest seizure risk (see Table 13.2). The occurrence of seizures appears to be dose-related, possibly

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Seizure incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines</td>
<td>High (≥1 mg/day)</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Low (≤200 mg/day)</td>
<td>0.3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>High (600–900 mg/day)</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Moderate (300–599 mg/day)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Low (≤299 mg/day)</td>
<td>1.0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Wide range</td>
<td>0.9</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Wide range</td>
<td>0.9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Wide range</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Source: Data from Logothetis (1967) and Alldredge (1999).
occurring at a dosage rate of 0.7% per 100 mg. At higher doses, seizure risk rises and reaches 5% at doses of 600–900 mg/day (Alldredge, 1999). In schizophrenic patients, the drug causes electroencephalographic (EEG) abnormalities typically characterized by background slowing in the theta and often the delta range. Bilateral spike, polyspike and slow wave discharges have also been described (Malow et al., 1994). Antiepileptic treatment is indicated in patients experiencing seizures with clozapine. Olanzapine has a binding profile similar to that of clozapine but, despite their similarity, the two drugs demonstrate a strong clinical difference concerning induction of seizures (Table 13.2). As far as quietapine is concerned, no difference in the incidence of seizures was observed between patients treated with this drug and those given placebo (incidence of 0.4% and 0.5%, respectively). Finally, as far as risperidone and sertindole are concerned, only a few patients with seizures have been reported (Alldredge, 1999; Torta and Keller, 1999).

In summary, with the exception of clozapine, the new APs are less prone to induce seizures than the traditional ones. Nevertheless, caution is recommended in using these drugs in patients with a history of seizures or with a lowered seizure threshold.

**Adverse effects**

Clozapine causes agranulocytosis in about 0.4% of patients (Lader, 1999). Similar figures have also been reported with some AEDs. Incidence values for aplastic anemia have been published for CBZ (39 cases per million) and felbamate (FBM) (127 cases per million) (Kaufman et al., 1997). These values are consistently higher than the overall incidence in the general population which is two cases per million per year (Kaufman et al., 1997). Therefore, concomitant administration of clozapine and other AEDs to patients at high risk of developing aplastic anemia (particularly FBM) should be avoided.

The association of low-potency sedative APs and sedative AEDs (e.g. barbiturates, BZD) may precipitate or aggravate sedation. All neuroleptics cause weight gain and this adverse effect is more evident for AAPs olanzapine and clozapine. Some AEDs (VPA and VGB) cause weight gain too. Therefore, the choice of the appropriate association between AEDs and APs should also take into account this aspect. Finally, one case has been described, in the literature, of catatonia-like events apparently induced by the association of VPA, sertraline and risperidone. A complex PD interaction has been advocated to explain this rare adverse effect (Lauterbach, 1998).

**PD interactions with stimulants of the CNS**

All CNS stimulants produce a dose-related excitation of the CNS which can lower seizure threshold (Zagnoni and Albano, 2002). In fact, seizures are frequently
observed during overdose with these drugs. In a retrospective study of seizures associated with poisoning or drug intoxication, CNS stimulants were involved in 29% of the cases (Olson et al., 1994). However, in some patients, amphetamines (whose effect is to increase dopaminergic transmission) may reduce seizure activity and improve EEG (Zaccara et al., 1990).

A reduced level of vigilance, which can be induced by AEDs and particularly by barbiturates, can worsen seizure frequency in some types of epilepsy (Papini et al., 1984). In addition, sedative effects of traditional AEDs can exacerbate the overactivity and aggressiveness of some epileptic patients (Viani et al., 1977). Based on these considerations, the use of amphetamines, which improve vigilance and contrast sedation, was proposed as a comedication in some epileptic disorders. According to this hypothesis, a propylhexedrine salt of PB (barbexaclone, an amphetamine-like molecule) has been used in the treatment of epilepsy. The aim of this association was to determine a favorable PD interaction characterized by potentiation of the anticonvulsant effects and antagonism of the sedative effects of PB. The safety of the use of barbexaclone in epileptic patients has been documented only by a few open studies conducted in small patient groups (Visintini et al., 1981) even though more studies document that amphetamines have beneficial effects on attention deficits in epileptic patients (Gross-Tsur et al., 1997). However, even at low doses, CNS stimulants can have proconvulsant activities. In 234 non-epileptic children with attention deficit and hyperactive disorders, seizures occurred in 2% of the stimulant-treated group (a rate higher but not particularly alarming given that an estimated 1% of unselected children have seizures). Instead, in a subgroup of patients with epileptiform discharges in the EEG, seizures were observed in 20% of cases (Hemmera et al., 2001).

**Adverse effects**

Dyskinesia is a rare adverse effect of many AEDs. Chorea and orofacial dyskinesias have been described. PHT is the AED most frequently implicated although cases have also been described with CBZ, gabapentin (GBP), FBM, VPA and LTG (Zaatreh et al., 2001). Young subjects with organic brain abnormalities are at higher risk. It has been postulated that PHT may cause chorea through enhancement of central dopaminergic pathways in the basal ganglia. Since amphetamines increase dopaminergic transmission and may cause dyskinesias, the association of amphetamine-like stimulants with some AEDs in high-risk patients can increase the risk of this adverse effect (personal unpublished observation).

In conclusion, at low doses, stimulants are co-administered with AEDs in the epileptic patient and seem to have beneficial PD interactions. However, in some patients with a lower seizure threshold or exposed to high doses, these substances have proconvulsant effects.
PD interactions with anesthetic agents

Some anesthetic agents are used in the treatment of status epilepticus and therefore have strong anticonvulsant properties. However, selected agents used during general anesthesia are reported to be epileptogenic (Zaccara et al., 1990). For example, etomidate and enflurane enhance epileptiform activity in the EEG and have been exploited for their ability to elucidate epileptogenic regions during seizure surgery. Methohexital, a short acting barbiturate, has also been used to enhance epileptiform activity on the EEG, although it paradoxically functions as an anticonvulsant.

Among anesthetic agents, lidocaine is of particular interest. This agent has a concentration-dependent effect on seizures. At concentrations between 0.5 and 5.0 mg/l, lidocaine can effectively suppress seizures in animal models of epilepsy and in clinical practice (DeToledo, 2000). In fact, it has been used in the treatment of convulsive status epilepticus and epilepsia partialis continua. Levels above 8–9 mg/l, however, selectively block inhibitory mechanisms and may induce seizures. This bimodal response has been clearly demonstrated in experimental models of epilepsy and in healthy volunteers (DeToledo, 2000).

Treatment of anesthetic-induced convulsions can be particularly difficult because of many possible unfavorable PD interactions. AEDs (particularly barbiturates) may seriously exacerbate circulatory and respiratory depression caused by anesthetics. Particular attention should be paid to depressive effects on the myocardium which are potentiated by co-administration of anesthetics and barbiturates. Since severe hypoxia, hypercapnia and lactic acidosis occur concomitantly with anesthetic-induced convulsions and may be aggravated by many AEDs, treatment with succinylcholine and simultaneous ventilation should be the immediate treatment of choice to stop convulsions rapidly. However, because this procedure has no effect on cortical electric seizure activity, a co-treatment with BZD is also required (Zaccara et al., 1990).

PD interactions with analgesic and anti-inflammatory agents

AEDs, analgesics and anti-inflammatory drugs can often be co-administered for the treatment of some forms of pain. Neuropathic pain is not a specific entity, but comprises a variety of pain states with differing sensitivities to varying pharmacological interventions (MacPherson, 2000).

AEDs in the treatment of pain

Abnormal ectopic impulse generation represents an important pathophysiologic mechanism of neuropathic pain. This abnormal impulse generation in injured nerves may depend on changes in the cell membrane Na⁺ channels. Furthermore,
hypofunction of GABA-ergic inhibitory mechanisms and/or hyperfunction of glutamatergic excitatory mechanisms has been hypothesized to explain the diffusion of pain from the peripheral pain generator into the CNS (Bonezzi and Demartini, 1999). It has been observed that CBZ is effective in reducing acute pain but seems ineffective for continuous pain (Bonezzi and Demartini, 1999). GBP is now considered a first-line medication in the treatment of several neuropathic syndromes. VPA and, more recently, LTG have given encouraging results (MacPherson, 2000).

However, several pain mechanisms may be operant in the same neuropathic disorder and, therefore, it is often useful to associate drugs with different mechanisms of action. AEDs may be associated with opioids, ADs, alfa2-adrenergic agonists and non-steroidal anti-inflammatory drugs (MacPherson, 2000).

Effect of analgesic and anti-inflammatory drugs on seizure threshold
When administered in the CNS, both morphine and other opioid peptides can evoke an epileptiform activity in the EEG. These abnormalities are probably mediated by specific opioid receptors and are antagonised by opiate antagonists, such as naloxone (Tortella et al., 1979). However, in some experimental models, morphine has an anticonvulsant effect (Nowack et al., 1987). In the current practice, opioids have a low potency to induce seizures. This does not apply to pethidine. This drug may cause agitation, restlessness and seizures which have been postulated to be due to accumulation of the N-demethylated metabolite norpethidine. However, opioid-induced neurotoxicity, which comprises cognitive failure, organic hallucinations and seizure activity, can result from therapy with any of the opioids, including morphine, fentanyl and hydromorphone (MacPherson, 2000). Seizures can also be observed after salicylate intoxication (Zaccara et al., 1990). In this circumstance, intravenous diazepam is considered the drug of choice. The proconvulsant effect of ADs has already been described.

Opioids in valproic acid overdose
Recently, a few cases have been described in which naloxone has been successfully used to reverse CNS depression associated with acute VPA overdose (Roberge and Francis, 2002). In conclusion, co-administration of AEDs with analgesics and/or anti-inflammatory drugs and/or ADs can be useful in the treatment of neuropathic pain. Since this condition has different pathogenetic mechanisms, it is often necessary to administer drugs with different actions to target pain generation mechanisms at many levels and minimize adverse effects.

Conclusions
Although many AEDs are widely used in combination with other drugs (ADs, analgesics) to treat various diseases, a scarce knowledge has been gained on the PD
interactions of these drugs. There are hints that a true synergistic effect between some AEDs and ADs or analgesics can take place in the treatment or prophylaxis of mood disorders and in the treatment of neuropathic pain, respectively. In the field of epilepsy one can speculate that, in particular cases, the combination of AEDs with other drugs might improve seizure control. In addition, the association of stimulants with AEDs could be useful to antagonize some adverse effects (i.e. sedation). Further clinical studies are needed to verify these hypotheses.

REFERENCES

Clinical studies of PD interactions between AEDs and other drugs


Part IV

Drug interactions in specific patient populations and special conditions
Antiepileptic drug interactions in children

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² Hôpital Saint Vincent de Paul, Paris, France

Introduction

Many clinical practitioners are of the opinion that the optimal treatment of epilepsy is best achieved by use of antiepileptic drugs (AEDs) that have several modes of action, and therefore the drugs that are the most effective in this regard are AEDs such as carbamazepine (CBZ), valproate (VPA) or topiramate (TPM) whose efficacy relates to several modes of action. Thus, from the pharmacodynamic point of view, these AEDs when prescribed as monotherapy in fact comprise polytherapy regimens. On the other hand, because of metabolism, many AEDs reach the brain as combinations of the parent drug and their metabolite(s) and this too can be considered a form of polytherapy. For example, CBZ, which is metabolized to a pharmacologically active metabolite CBZ-epoxide, readily enters the brain where it exerts pharmacological effects. Thus polytherapy at the brain level can in fact be distinguished from polytherapy at the oral level. The same applies to clobazam (CLB) whose metabolism is inhibited by stiripentol leading to significant increase of CLB and norCLB with far better tolerability (Perez et al., 1999; Chiron et al., 2000). This is also observed with VPA for which the proportion of toxic 4-ene-VPA is decreased (Levy et al., 1987). A further consideration is that the metabolic pathway may vary according to age. Therefore, in infants, the hydroxylation of both diazepam and nordiazepam is very limited, combined with low glucoronidation capacity which generates major hypotonia (Morselli et al., 1973).

In clinical practice, access to plasma level monitoring has demonstrated that metabolic interactions are very complex, and contribute to frequent and often insidious side effects including paradoxical increases in seizure frequency (Reynolds and Shorvon, 1981). Thus, insidious occurrence of increased plasma concentration may generate severe toxicity. This is the case for the combination of phenytoin (PHT) with phenobarbital (PB) in children, a combination that results in unpredictable plasma concentrations and carries a risk of increased toxicity to PHT with cerebellar atrophy, due to progressive accumulation of PHT. Another example of the increased toxicity of combined drugs compared to monotherapy is the combination of lamotrigine (LTG)
with VPA that produces the highest incidence of skin rash, although this combination is, from the therapeutic point of view, particularly efficacious (Brodie and Yuen, 1997). On the other hand, a supra-additive effect has been observed with LTG and VPA in combination, that could be the consequence of a pharmacokinetic, due to metabolic interaction in the liver, or a pharmacodynamic, due to some modification of the action of the molecules inside the brain, interaction, or both (Pisani et al., 1999).

Therefore, the issue of mono- versus polytherapy covers a wide range of concepts, and proper analysis requires us to take into account the whole pathway from oral administration, through liver metabolism, to the mode of action within the brain, and also pharmacokinetic differences according to age. However, because of the lack of insight into the mechanism of action of most AEDs, it is not possible to predict the benefit versus negative effects of the various combinations.

Few studies have been performed to address this issue, primarily because of its complexity and the significant number of factors that are involved. Animal studies have provided evidence of some specific AED combinations that are indeed additive, whilst others were supra-additive and still others infra-additive (Bourgeois, 1988). However, these studies were based on acute AED administration and could not take in account the effect of chronic administration, which may modify the supply of drug to the brain because of metabolic interactions in the liver that need at least several days, often a few weeks, to take place after onset of therapy. Pragmatic clinical studies have been performed, but the results obtained could be misleading if not interpreted properly. Thus, no significant difference was found between VPA mono- and polytherapy (Deckers et al., 2001). Clinical experience shows that mono- and polytherapy do not have the same value according to the type of epilepsy, and to the type of polytherapy. Thus, the type of epilepsy needs to be taken in account, and also the type of drug.

Specificity of epilepsy in pediatrics is its considerable heterogeneity with a growing number of epilepsy syndromes identified. The latter is combined with more or less specific response to drugs or to drug combinations for each given syndrome (Luna et al., 1989; Roger, 1992; Schlumberger et al., 1994). This variable response to drugs includes a risk for worsening of seizure frequency and severity that needs to be taken in account, even when addressing the issue of drug combinations (Perucca et al., 1998). The situation is complicated by the fact that a patient may switch over time from one syndrome to another as an effect of age or as a consequence of treatment. Infantile spasms in a patient with focal malformation respond to vigabatrin (VGB), but in approximately 50% of cases the child is left with focal seizures (Lortie et al., 1993). The addition of CBZ raises the risk of relapse of spasms that again disappear with cessation of CBZ (Talwar et al., 1994; unpublished data).

A very particular aspect that impacts on our knowledge of AEDs and the best use we can make of them, relates to the strategy of their development by the
pharmaceutical industry, which is guided by registration body requirements, and both ethical and marketing considerations. Drugs are first developed for adults that suffer from partial epilepsy. Then, if it appears useful to adults, the drug is tested in children, with a clear preference for what is considered as the most intractable conditions, partial epilepsy and Lennox–Gastaut syndrome. However, compounds are tested first as add-on because it is given to patients with resistant epilepsy for which it is not possible to withdraw the previous treatment. For this reason the drug reaches the market with an indication restricted to polytherapy. It is only later, and with major methodological difficulties, that studies permit the efficacy in monotherapy to be demonstrated. Often, a few years later, it appears that the AED is much better tolerated in mono- than in polytherapy. The best example is VPA for which several years were needed before the compound was widely and legally used in monotherapy, whereas it was clear that polytherapy had contributed to fatal hepatic toxicity (Dreifuss et al., 1987, 1989; Bryant and Dreifuss, 1996). Such drawbacks of polytherapy also apply to the therapeutic aspect itself: in one open study performed soon after the launch of VPA in polytherapy, patients with idiopathic generalized epilepsy still suffering from tonic–clonic seizures when treated with the combination of VPA with PB, experienced disappearance of seizures just by withdrawing PB, without any modification of the dose of VPA (Dulac et al., 1982). The growing interest for evidenced-based medicine and restrictions given to the use of drugs out of the strict legal indications may therefore contribute to a somewhat vicious use of medication because it is paradoxically only legal to use the compound in its most hazardous condition, polytherapy, before studies demonstrate efficacy in monotherapy. In the present state of knowledge, it is therefore reasonable with drugs that have no monotherapy claim, to start the medication as add-on therapy, as legally required, but then to go to monotherapy as soon as a clear benefit has been obtained. Nevertheless, there are individual cases in which the combination is more effective than monotherapy.

**Interactions between AEDs**

In this chapter we will review the characteristics of the various interactions between the various AEDs, including those that are in development, and what is presently known regarding their mechanism; we will then highlight the benefits this knowledge can offer to optimize the treatment for each type of epilepsy in children.

**Clinically relevant metabolic and pharmacodynamic interactions**

**Phenobarbital, phenytoin and carbamazepine**

PB, PHT and CBZ are potent inducers of hepatic metabolizing enzymes and consequently any comedication compound that undergoes hepatic metabolism will
need to be administered at a higher dose so as to achieve an adequate therapeutic response. PHT generates particular difficulties since it follows a similar metabolic pathway to that of PB and may therefore compete on the catabolism enzymatic activity, with unpredictable results. In particular, accumulation of PHT with toxic effects in the cerebellum and in peripheral nerves may occur insidiously. Because of the metabolism of CBZ to a pharmacologically active metabolite, CBZ-epoxide, the administration of CBZ in effect represents two compounds. Thus a CBZ-epoxide plasma level of over 2.2 mg/l combined with CBZ may be toxic in children, whereas each single component seems to be better tolerated; no major side effect was observed when patients achieved similar plasma concentrations of CBZ-epoxide when administered alone (Schoeman et al., 1984). Based on these observations, CBZ was administered in combination with the experimental compound stiripentol, a compound that inhibits the metabolism of CBZ in the liver, thus decreasing the formation of CBZ-epoxide and increasing the plasma concentration of CBZ. This rational polytherapy results in better tolerability and better therapeutic effect (Tran et al., 1996; Perez et al., 1999).

Valproate

VPA being a metabolic inhibitor requires that drugs administered in combination are administered at lower doses. This applies particularly to PB, PHT, CBZ, LTG and ethosuximide (ESM). For PHT, the total plasma concentration is reduced but the free fraction is not affected, and therefore the dose should not be altered. For CBZ, the clearance of CBZ-epoxide is reduced resulting in poor tolerability particularly in relation to cognitive function, thus necessitating CBZ dose reduction. The combination of VPA with PB results in a decrease of VPA and an increase of PB plasma concentrations. This does have some clinical relevance since it could explain the disappearance of tonic–clonic seizures that occurs upon PB withdrawal and without modification of VPA dose (Dulac et al., 1982). For the combination of VPA with LTG, the risk is that of skin rash, when this combination is introduced too rapidly. However, this combination has the advantage that lower LTG doses are needed and therefore treatment costs are reduced. In addition, this combination has been associated with a positive pharmacodynamic interaction (Pisani et al., 1999) as well as a therapeutic synergism (Brodie and Yuen, 1997). With clonazepam, reduced wakefulness may contribute to the precipitation of status epilepticus in intractable epilepsy with myoclonic seizures (Covanis et al., 1982). VPA also has intrinsic metabolites; 2-ene-VPA that has been shown to be more effective than VPA (Loscher and Nau, 1985), and 4-ene-VPA that may be involved in hepatic toxicity (Nau et al., 1984).

Most new compounds have reduced metabolic interactions with comedication. However, VGB does reduce the clearance of PHT, and thus PHT plasma concentrations may become toxic when removing VGB (Luna et al., 1989).
Oxcarbazepine

Oxcarbazepine (OXC) is associated with few metabolic interactions; with PHT, plasma PHT concentration can be increased by 40% (Sallas et al., 2003) and with LTG, plasma LTG concentration is decreased by 33% (May et al., 1999). OXC may induce the metabolism of other non-antiepileptic comedication.

Gabapentin

Gabapentin (GBP) is not metabolized, and does not affect liver enzymes and consequently GBP does not affect the metabolism of drug comedication. However, there may be an interaction with felbamate (FBM) at the level of kidney excretion, resulting in 50% increase in felbamate half-life values (Hussein et al., 1996).

Felbamate

FBM is, from the pharmacokinetic point of view, a particularly complex compound since it increases the clearance of CBZ and CBZ-epoxide, and reduces that of VPA, PB and PHT. This could lead to toxic plasma PHT concentrations. The metabolism of FBM is enhanced by enzyme-inducing drugs. The combination of FBM with VPA is useful in the treatment of Lennox–Gastaut since in one series the frequency of drop attacks was reduced by 40% (Siegel et al., 1999).

Although topiramate (TPM) is mainly excreted through the kidney, this compound is sensitive to the enzyme-inducing AEDs which enhance its hepatic metabolism two-fold (Dooley et al., 1999). The increase in behavioral disorders that have been associated with LTG comedication, are likely to be the consequence of a pharmacodynamic interaction (Gerber et al., 2000). Also, TPM may inhibit PHT metabolism. Overall, the tolerability of TPM is clearly far better as a monotherapy regimen compared to when administered in combination, particularly in combination with CBZ or VPA.

Lamotrigine

LTG is particularly sensitive to the metabolic effect of comedication, both of inducer and inhibitor compounds: its elimination half-life is reduced by PB and CBZ but increased by VPA. When starting LTG in combination with VPA, the plasma concentration tends to rise more quickly than when it is given alone, and this increases the risk for skin rash. Indeed, before this pharmacokinetic effect was identified, we experienced a 10% rate of skin rash when adding LTG to VPA (Schlumberger et al., 1994), that decreased to 1% when the dose was titrated more slowly (Besag et al., 1995). The combination of LTG with CBZ is poorly tolerated in terms of vigilance, and produces the effects of overdosage with CBZ (Besag et al., 1995).
Pragmatic aspects of treatment

First-line treatment

At this stage, there is no longer any place for polytherapy. A number of AEDs have now been shown to be effective as monotherapy for various types of epilepsy, in which they may therefore be administered as first-line drug. This is the case for CBZ (Glauser, 2000), VPA (Dulac et al., 1982), OXC (Serdaroglu et al., 2003), and LTG (Ueberall, 2001) which are effective in partial epilepsy. This similarly applies to VGB in infantile spasms, not only those due to tuberous sclerosis (Chiron et al., 1997) but whatever the etiology (Appleton et al., 1999; Elterman et al., 2001). For childhood absence epilepsy, the effects of VPA and ESM seem to be interchangeable (Sato et al., 1982). For juvenile absence epilepsy, the risk of generalized tonic–clonic seizures in combination with absences is an indication not to restrict to ESM monotherapy and, for LTG, no controlled trial has confirmed the effect as monotherapy in absence epilepsy. For idiopathic generalized epilepsy with tonic–clonic and/or myoclonic seizures, controlled trials with VPA monotherapy are only available in adults (Turnbull et al., 1982). The occurrence of repeat tonic–clonic seizures between 2 and 5 years of age in a previously normal child is most likely to be the first expression of myoclonic–astatic epilepsy, that contraindicates the use of CBZ, and indicates VPA, although VPA is likely to soon prove to be insufficient in monotherapy (Dulac et al., 1998).

Epilepsy resistant to a first-line monotherapy

Epilepsy resistant to a first-line monotherapy requires a switch to a second monotherapy. However, it remains unclear whether there should be an immediate switch with withdrawal of the previous AED, or a progressive addition of a second AED followed by removal of the first as soon as benefit from the second AED is confirmed. In practice, before new data are available, it seems reasonable to decide according to each specific condition: for epilepsy syndromes or seizure types for which the presently administered drug is determined to be worsening, or does not seem appropriate because it is known to comprise a sizeable risk of worsening; for those for which a given AED seems more appropriate; and for the conditions in which the first AED did not give any clear benefit; a simple switch over a couple of weeks should be undertaken. In cases with apparently partial effects, the addition of the second AED should be chosen before returning to monotherapy, because removing the previous AED could generate withdrawal effects if the new AED is not sufficiently effective. In addition, one needs to take into account the potential metabolic interactions between the first and second AED and therefore adapt the dose of the previous drug, and one needs also to adapt the pharmacokinetics of drug withdrawal to the type of AED and to the duration of previous
treatment: even if ineffective; a previous treatment with PB, VGB, PHT or CBZ lasting several months could generate dependency, and therefore require very slow withdrawal.

Epilepsy resistant to a second AED

The use of a third AED in the treatment of epilepsy resistant to a second AED in adults is known to be associated with little benefit. Therefore, for partial epilepsy, provided that the diagnosis of the type of epilepsy is correct, that the treatment is properly given and at a proper dose and that there is no underlying progressive disease (Aicardi, 1988), it seems reasonable to consider surgery at this point (Kwan and Brodie, 2000). In children, no such data are available. Typically, controlled add-on trials for partial epilepsy with a new AED report rates of seizure freedom of approximately 5–15%: 10% for VGB (Luna et al., 1989), 14% for TPM (Ritter et al., 2000), and 14% for OXC (Rey et al., 2004), but only 3% for gabapentin (Appleton et al., 2001). However, for generalized epilepsy, the potential benefit depends on the type of syndrome. In absence epilepsy, combining LTG with VPA was associated with significant benefit (Pisani et al., 1999), and the same applies to myoclonic–astatic epilepsy (Dulac et al., 1998).

Treatment according to the type of epilepsy or epilepsy syndrome

Cryptogenic or symptomatic partial epilepsy

In cryptogenic or symptomatic partial epilepsy, whatever the age, monotherapy has a place of choice, with no significant difference of benefit with VPA or CBZ in terms of efficacy following a first seizure (Verity et al., 1995). However, tolerability seems to be slightly better with the former (Chaigne and Dulac, 2003). In addition, there is a mild restriction about the use of CBZ according to age and the type of epilepsy. In infancy, the risk of secondary development of infantile spasms, following partial epilepsy, is such that unless there is focal lesion usually not combined with infantile spasms, such as Sturge–Weber disease, the use of CBZ should be avoided. When, in childhood, cryptogenic or symptomatic focal epilepsy is combined with major spike wave activity, CBZ could contribute to the generation of continuous spike waves in slow sleep (Corda et al., 2001). Nevertheless, in the chronic condition, CBZ is more efficacious than VPA in preventing the recurrence of focal seizures. Lack of response to this first AED indicates the need to switch to the alternate AED. However, the indication could depend the topography of the epilepsy focus. Thus, OXC may be more efficacious in temporal lobe epilepsy, TPM seems more efficacious in motor seizures generated by the motor strip, whereas LTG seems useful in frontal lobe seizures, namely when combined with VPA.
For patients with transient effect of CBZ, the addition of stiripentol may produce remarkable effects (unpublished data).

**Infancy**

**Dravet syndrome**

In infancy, Dravet syndrome may worsen with the addition of CBZ, PB (Thanh et al., 2002), LTG (Guerrini et al., 1998), or VGB (Lortie et al., 1993). Bromide is widely used in Germany and in Japan. Treatment strategy for this disorder clearly improved with the introduction of a new concept of polymedication. Indeed, neither VPA nor PB succeed in preventing status epilepticus that contributes largely to worsening of the condition (Casse-Perrot et al., 2001). The combination of CLB with stiripentol has been shown to prevent the occurrence of status epilepticus in young children, and to significantly reduce seizure frequency (Chiron et al., 2000). A pragmatic study has shown that this combination should be administered as soon as possible in the course of the disease (Thanh et al., 2002). The addition of TPM also reduces seizure frequency, although the occurrence of status epilepticus cannot be prevented, and although in many instances this drug does not permit withdrawal of VPA (Coppola et al., 2002). Nevertheless, it would become possible to withdraw stiripentol and CLB in the second decade, thus reducing the polytherapy to a combination of VPA and TPM.

**Infantile spasms**

In infantile spasms, monotherapy either with VGB or steroids seems to be the treatment of choice. When the first drug is not efficient, the alternate may prove effective. No controlled study has questioned an eventual benefit from the combination of both. Patients with previous psychomotor retardation but no neuroradiological abnormality were found not to respond to VGB or steroids alone, although half these patients became spasm-free with the combination of both over several months (Villeneuve et al., 1998). In intractable cases, low doses of LTG combined with VPA seem to be of benefit in a small proportion of patients (Cianchetti et al., 2002). In contrast, this is not observed when LTG is combined with CBZ (Veggiotti et al., 1994). Clinical practice shows that felbamate may be effective, but no data could show specific benefit of a combination of this compound compared to its administration as monotherapy. However, since for regulatory purposes initial studies were performed as add-on, the AED is registered for add-on administration. A number of patients with infantile spasms exhibit focal seizures, either in combination with the spasms or as residual phenomena after the disappearance of the spasms with the therapy. In these cases, not only is the combination of CBZ ineffective, but it could also precipitate the relapse of spasms (Talwar et al., 1994). LTG could be helpful in these cases, after the age of 2 years (Veggiotti et al., 1994).
Benign partial seizures in infancy and benign myoclonic epilepsy in infancy

Benign partial seizures in infancy and benign myoclonic epilepsy in infancy are easily controlled by monotherapy with, respectively, VPA or either VPA, ESM or a benzodiazepine, primarily CLB.

Childhood

Absences

In childhood, absences usually respond to monotherapy with either VPA or ESM. The older concept that PB should be added because of the risk of occurrence of tonic–clonic seizures is no longer valid since it is clear that very few patients with childhood absence epilepsy do exhibit tonic–clonic seizures and PB may worsen the absences. A majority of patients non-responsive to either VPA or ESM may respond to add-on LTG. Whether they would respond to monotherapy LTG remains to be determined, and usually it is after a few months of the combination with VPA that a progressive reduction to monotherapy could be attempted. However, because the dose required for duotherapy with VPA is lower, one tends to maintain the combination. The dose of both ESM and LTG should be halved, and the introduction of LTG should be undertaken slowly because of VPA comedication. A combination of all three AEDs, VPA, ESM and LTG may occasionally be helpful.

Benign partial epilepsy

Benign partial epilepsy responds well to various monotherapies. The real need with this condition is to make a clear diagnosis in order to reduce, as much as possible, the indication for any AED medication which, in practice, is required in less than one-third of such patients (Ambrosetto and Tassinari, 1990). It is clear that when a treatment is needed, VPA, sulthiame, CBZ and CLB are all very efficacious. The only restriction is that associated with CBZ, which has a small risk of contributing to the occurrence of continuous spike waves during slow sleep (Corda et al., 2001), as has also been reported with LTG (Battaglia et al., 2001).

Myoclonic–astatic epilepsy

Myoclonic–astatic epilepsy is resistant to any monotherapy. VPA is usually administered when the first, tonic–clonic seizure presents between 2 and 5 years of age (Kaminska et al., 1999). Seizure recurrence or the additional occurrence of myoclonic seizures would necessitate the addition of LTG, with the restrictions and cautions mentioned earlier. Because of the long time lag to reaching proper dosage, it is preferable to start adding this compound as soon as the diagnosis becomes likely, based on the recurrence of tonic–clonic seizures with generalized spike

265 Antiepileptic drug interactions in children
waves in this age range, before myoclonic–astatic seizures do occur. The addition of ESM may be useful, in case of very rapid increase of seizure frequency, before the dose of LTG can reach sufficient levels, and when myoclonic seizures or absences persist. In this setting, LTG dosage needs to be reduced by half because of VPA comedication. TPM may be useful in some cases, but the combination with VPA should be avoided because of potential side effects. Indeed speech, which is often affected in this type of epilepsy, is sensitive to TPM, and this is a very specific effect of this AED (Aldenkamp et al., 2000). The addition of clonazepam to VPA may eventually precipitate status epilepticus (Covanis et al., 1982). CLB does not seem to carry this risk. Thus, many patients end up being treated with three AEDs.

Lennox–Gastaut syndrome

Lennox–Gastaut syndrome is rarely controlled with a single AED. As soon as the syndrome is suspected, LTG should be added to VPA. Indeed, LTG has been shown to be effective in this condition, as add-on therapy, with a sizeable number of patients becoming seizure-free (Motte et al., 1997). Since absences are one component of the syndrome, there is likely a pharmacodynamic interaction of both AEDs as in absence epilepsy (Perucca et al., 1998). Persistent seizures are then an indication to add FBM, with the usual biological, hepatic and hematological follow-up monitoring constraints. Although TPM was also shown to significantly reduce seizure frequency in this condition (Sachdeo et al., 1999), no patient became seizure-free, thus polytherapy with this AED would come later in the treatment algorithm. The use of PHT in the polytherapy is more rare, with the aim of reducing the frequency of generalized, namely tonic seizures.

Continuous spike waves in slow sleep

Continuous spike waves in slow sleep are rarely controlled by benzodiazepine or sulthiame monotherapy (Rating et al., 2000). Adding ESM may occasionally be useful. The addition of other conventional AEDs, namely CBZ, PB or PHT is more often deleterious than useful. Even the occurrence of additional focal seizures is not an indication for this type of medication, since it may aggravate the condition (Perucca et al., 1998). Few patients have benefited from TPM (Mikaeloff et al., 2003). At this point, steroids are the most helpful. Whether a benzodiazepine should then be maintained in combination with steroids is not clear.

Combining AEDs with non-AED drugs

Combining AEDs with non-AED drugs needs special attention. In infants treated with VPA, the administration of acetylsalicylic acid should be limited to situations in which there is absolute need. Indeed, this combination is associated with a high
risk of liver failure (Dreifuss et al., 1989). Macrolides should not be given with CBZ, because they reduce its clearance and may produce insidious toxicity (Mesdjian et al., 1980). Among old generation AEDs, CBZ, PHT and PB induce the activity of several enzymes involved in drug metabolism leading to decreased plasma concentration and reduced pharmacological effect of drugs, which are substrates of the same enzymes. This occurs with immunosuppressive drugs including cyclosporine (Yusof 1988; Baciewicz and Baciewicz, 1989; Wasfi and Tanira, 1993; Cooney et al., 1995), tacrolimus (Thompson and Mosley, 1996), sirolimus (Fridell et al., 2003), glucocorticoids, tricyclic antidepressants such as imipramine, amitriptyline, some antipsychotic agents such as haloperidol, chlorpromazine, clozapine (Facciola et al., 1998; Lane et al., 1998), antiarrhythmic agents including disopyramide, lidocaine, propranolol (Vu et al., 1983), doxycycline and acetaminophen (Douidar and Ahmed, 1987). In contrast, the new AEDs OXC, GBP, LTG, levetiracetam, and TPM are not hepatic enzyme-inducing drugs and are not reported to be involved in such drug interaction. However, an interaction between cyclosporine and OXC (Rosche et al., 2001) was suspected in a single case study with decrease of the cyclosporine plasma concentration. Regarding enzyme inhibition the clearance of CBZ was decreased by clozapine (Langbehn and Alexander, 2000), and that of PHT was decreased by cimetidine (Rafi et al., 1999) leading in both cases to increase in the plasma concentration of the AED. Similarly, the plasma concentration of PHT is significantly increased by fluconazole (Cadle et al., 1994). Prediction of drug interaction is difficult because enzyme induction or inhibition may coexist and many other factors are involved in determining whether a clinically significant drug interaction will occur or not. Furthermore most of these data are only case reports. Thus, available data should not be regarded as exhaustive.

Interactions with AEDs and chemotherapeutic drugs (CTDs), although poorly documented, do also occur. The coadministration of AED and a CTD may lead either to reduced activity or increased toxicity of an AED. Lowered plasma concentrations of PHT were reported with seizure recurrence during administration of cisplatin or vinca alkaloid, and a 25% decrease in VPA plasma concentration was observed with high-dose infusion of methotrexate in children. Increased toxicity due to higher plasma-PHT concentration was reported when this AED was coadministered with 5-fluouracil. Although this comedication may not be relevant in children, it points out that one should be cautious when CTDs and AEDs have to be administered concomitantly. The effect of drug interaction may also lead to a reduced activity or an increased toxicity of a CTD: the clearance of vincristine was increased by 63% with the coadministration of enzyme-inducing AEDs, however, the impact on the efficacy of vincristine was not investigated. A faster clearance was observed for teniposide with a lower efficacy in children who received PHT, PB or CBZ. Increased toxicity was reported with the coadministration of VPA, cisplatin
and etoposide. Pharmacokinetic interactions may be suspected when AED and CTD drugs share a common metabolic pathway (Vecht et al., 2003).

**Conclusion**

Although the rule of monotherapy as the strategy of choice clearly applies to the majority of pediatric patients suffering from epilepsy, it remains difficult to maintain it for patients with pharmaco-resistant epilepsy. In addition, there is clear advantage of comedication in a restricted number of specific types of epilepsy. This may be the strict rational polytherapy. However, too few structured studies have been performed to validate this concept. In all cases, any study design of this type should take into account the epilepsy syndrome. Finally, there is a sizeable number of patients for whom polytherapy is by no means rationally designed, but imposed by the story of the epilepsy, because there can be a significant increase in seizure frequency at any attempt to reduce the polytherapy. Furthermore, episodes of status epilepticus may even occur, if a vigorous reduction of AEDs is attempted. In these patients, polytherapy can be considered a failure, and its reduction should be tried at regular intervals in order to diminish the risk of insidious side effects of the combination.

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Antiepileptic drug interactions in children


Antiepileptic drug interactions in the elderly

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Introduction

The elderly ($\geq 65$ years) are the fastest growing segment of the population in developed countries. In the USA, older adults presently comprise 13% of the population and are projected to increase to 20% within the next 20 years. Similar demographics exist for many European countries. With advancing age comes increasing morbidity, medication use, and adverse drug reactions. Over two-thirds of older adults have one or more chronic medical problems (Hoffman et al., 1996). As a consequence more elderly take medications than others and the elderly take more drugs per person. In the USA, almost 90% of community-dwelling elderly take one or more medications (Guay et al., 2003). Antiepileptic drugs (AEDs) are frequently prescribed in the elderly due to the high prevalence of AED-treatable neuropsychiatric disorders in this age group. For example, epilepsy is twice as common in those $\geq 65$ years (1.5%) than in younger adults (Hauser, 1997). An estimated 1.6% of community-dwelling elderly take one or more AEDs (Nitz et al., 2000).

AED use is even greater among elderly nursing home residents. Based on two national surveys, approximately 10–11% of elderly nursing home residents take at least one AED and within this group 14–19% are on two or more AEDs including combinations known to interact (Schachter et al., 1998; Garrard et al., 2000).

Factors contributing to AED interactions in the elderly

There are several factors associated with AED therapy in the elderly that substantially increase the risk of clinically significant drug interactions. These include multiple medication use including many drugs with a high potential for interactions, altered sensitivity to drug action, and age-related changes in drug disposition.

Pharmacoepidemiology

The probability of an interaction increases significantly with the number of medications a person takes (Nolan and O’Malley, 1989). Community-dwelling elderly take...
3.1–7.9 prescription and non-prescription medications whereas nursing home residents take an average of 7.2 maintenance and pro re nata (PRN) medications (Beers et al., 1993; Stewart, 2001). The most common types of medication used include cardiovascular, gastrointestinal, central nervous system (CNS), analgesic, and vitamin agents, all of which have the potential to interact with other medications (Guay et al., 2003).

The AEDs most commonly prescribed for older patients also have the greatest potential for drug interactions. In a survey based on 1995 data, the vast majority of community-dwelling elders on an AED were on one or more of the following: phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), and valproic acid (VPA) (Nitz et al., 2000). More recent studies in nursing home residents reveal a similar pattern although there is greater use of gabapentin (GBP) and clonazepam (Schachter et al., 1998; Garrard et al., 2003). Between 14% and 19% of nursing home elderly, who receive at least one AED, receive two or more AEDs, with the most frequently occurring combinations being PHT and CBZ, PB or VPA (Schachter et al., 1998; Garrard et al., 2000). All these AED combinations are known to interact with each other.

The types of co-medication used by community-dwelling elderly taking AEDs have not been characterized, but AED use in nursing home elderly has been extensively studied. Elderly nursing home residents on an AED take more medications than other elderly residents. In one study, those receiving an AED were on 5.6 maintenance medications versus 4.6 for all other elderly residents (Lackner et al., 1998). The most commonly prescribed co-medications in this study included CNS drugs, cardiovascular agents, and anticoagulants, all of which have the potential to interact with AEDs (Figure 15.1).

**Age-related alterations in pharmacodynamics**

The elderly exhibit altered pharmacodynamics resulting in greater sensitivity to both pharmacological and toxicological drug effects. This can produce either a more narrow therapeutic range or a shift downward in the lower and upper limits of the range. Older persons on AEDs appear to be more sensitive to drug effects even when concentrations are controlled. Ramsay et al. analyzed the effect of advancing age on occurrence of adverse effects in a controlled clinical trial comparing the safety and efficacy of CBZ and VPA (Ramsay et al., 1994). They found that patients over 65 years of age experienced side effects at CBZ and VPA concentrations of 50% and 20%, respectively, lower than in younger patients. In the face of increased sensitivity to pharmacological and toxicological effects, elderly patients are more likely to experience a clinically significant pharmacodynamic drug interaction with certain drug combinations. For example, elderly taking both PB for epilepsy and a benzodiazepine for sleep are more likely to have cognitive impairment than with either drug taken alone (Michelucci and
A pharmacodynamic interaction resulting in decreased effectiveness of AED therapy occurs when medications that lower seizure threshold are added to a patient’s regimen, as may occur with antipsychotics (Lader, 1999).

Age-related alterations in pharmacokinetics

The most common AED interactions in older patients are associated with either an increase or decrease in one or both interacting drugs. The elderly are particularly susceptible to pharmacokinetic interactions due to age-related changes in drug disposition (Mayersohn, 1992) (Table 15.1). Medical conditions common in the elderly such as cardiovascular, renal or gastrointestinal diseases further alter drug disposition. Advanced age is associated with increased gastric pH, diminished gastrointestinal fluids, slower intestinal transit, and reduced absorptive area. Each of these changes can affect either or both the rate and extent of absorption. Age-related reduction in intestinal and hepatic blood flow, intestinal drug transport and metabolism, and hepatic metabolism can also affect the systemic bioavailability of some drugs. Gastric pH and intestinal transit time may exhibit intra-patient day-to-day variability while other processes tend to slowly decline. Transporter proteins, such as P-glycoprotein, which are located in intestinal enterocytes, facilitate efflux of certain drugs thereby reducing bioavailability. It is not known if advancing age alters the activity of transporter enzymes. Age-related alterations in absorption are most likely to affect slowly absorbed AEDs, particularly those administered as solid dosage.
forms, extended release formulations, or drugs absorbed by active transport (GBP). A recent report described highly variable PHT concentrations collected from 56 elderly nursing home residents on constant maintenance doses of PHT with no changes in interacting co-medication. Although there is no direct evidence, an alteration in bioavailability is the most likely explanation for this phenomenon (Birnbaum et al., 2003). The addition of drugs that affect AED absorption can compound the effects of age-related changes in gastrointestinal function. For example, calcium-containing products are commonly used in elderly patients, particularly women. These products can chelate with PHT resulting in decreased bioavailability (Cacek, 1986).

Older persons undergo a gradual reduction in serum albumin: by age 65 years, many individuals have low normal albumin concentrations or are frankly hypalbuminemic (Wallace and Verbeeck, 1987). Albumin concentration may be further reduced by conditions such as malnutrition, renal insufficiency, and rheumatoid arthritis. As serum albumin levels decline, the greater the likelihood that drug binding will decrease. This has the effect of lowering the total serum drug concentration while unbound serum drug concentration remains unchanged. The elderly

### Table 15.1: Age-related changes in physiology

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<tr>
<td>Glomerular filtration</td>
<td>Decreased by 1%/year; age: ≥40 years</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Adapted from Cloyd and Conway (2002).
are more susceptible to protein-binding interactions due to lower serum albumin
levels and the use of multiple medications, many of which are highly bound to
serum proteins. Protein-binding competitive displacement interactions, which are
the most common, occur when the unbound concentration of the displacer drug
or its binding affinity is greater than that of the displaced drug (MacKichan, 1992).
Displacer drug concentrations are often higher in elderly patients due to reduced
clearance. Hence elderly patients are likely to have a displacement interaction and
the extent of displacement will be greater than in younger patients. Protein-binding
interactions complicate interpretation of total serum AED concentrations.
Measurement of unbound AED concentrations may be useful in assessing the clin-
ical significance of this type of interaction.

Several studies have shown that both hepatic and renal drug clearances decline at
a rate of 10% per decade of life beginning at the age 40 years (Mayersohn, 1992).
Age-related decreases in clearance result in higher drug concentrations when stan-
dard doses are used in older persons. Most interactions with drugs that inhibit clear-
ance are concentration dependent. When a standard dose of an inhibiting drug is
given to an elderly patient, its concentration will be higher and, hence, its inhibition
of the affected drug’s clearance will be greater than in a younger adult. If the elderly
patient is also taking a standard dose of the affected drug, the greater decrease in its
clearance results in a further increase in concentration that was already elevated as
compared to a younger adult on the same dose. As a result drug interactions that are
clinically important in younger adults will have an even greater impact in the elderly;
and drug combinations not known to interact in younger adults may be clinically
important in older patients. Even when dosage adjustments are made to the inhibitor
and the affected drug, the concentration of the latter can still increase if the inhibitor
concentration approaches or exceeds its $K_i$. In this situation, the increased pharma-
codynamic sensitivity in the elderly can result in an adverse drug interaction
although the rise in the concentration of the affected drug is limited.

Drug interactions occurring as a result of induction of hepatic metabolism
follow a similar pattern. In most cases, induction of hepatic metabolism is concen-
tration dependent although there is some controversy as to whether the elderly
respond to inducers to the same extent as younger adults (Mayersohn, 1992). Con-
sequently, standard doses of the inducer may result in higher concentrations that,
in turn, may cause a greater extent of induction.

Finally, management of pharmacokinetic interactions must consider both initiation
and discontinuation of drug therapy. If appropriate dosage adjustments have been
made to control drug concentrations in the presence of an interaction, the concentra-
tion of the affected drug will fall or rise once the inhibitor or inducer is withdrawn. As
the elderly are likely to have a more narrow therapeutic range for many medications,
the clinical impact of withdrawing an interacting drug can also be significant.
AEDs versus other drug combinations

The elderly frequently take numerous medications for a variety of medical conditions. The use of polypharmacotherapy leaves the elderly patient at an increased risk for adverse events. There are many medications that are frequently prescribed for ailments that the elderly experience and unfortunately this chapter cannot address every possible drug interaction.

Antihypertensives

Carbamazepine

Diltiazem and verapamil are inhibitors of cytochrome P450 (CYP) 3A4, which is the major metabolic elimination pathway for CBZ (Ma et al., 2000). This inhibition may lead to increased CBZ blood concentrations and neurotoxicity (Macphee et al., 1986; Eimer and Carter, 1987; Beattie et al., 1988; Bahls et al., 1991; Shaughnessy and Mosley, 1992). CBZ is a potent inducer of CYP3A4 (Luo et al., 2002). As a result, any medications that are metabolized via that pathway are likely to be affected. CBZ also induces CYP1A2, CYP2C9, and to a variable degree CYP2C19. Patients will likely require increased doses of affected antihypertensives to decrease blood pressure adequately.

Phenobarbital

PB is a significant enzyme inducer of CYP3A4, CYP2C8, CYP2C9, and CYP2C19 (Gerbal-Chaloin et al., 2001; Raucy et al., 2002; Edwards et al., 2003). Any antihypertensive medication that is metabolized via these metabolic enzymes is likely to fall victim to increased metabolism. Hence, if an elderly patient is on PB they may require higher doses of their antihypertensive to get a therapeutic response. Conversely, if PB therapy is initiated, the existing antihypertensive medication may lose its efficacy.

Phenytoin

Diltiazem has been demonstrated to cause PHT toxicity, most likely due to enzyme inhibition although the exact mechanism is unclear (Bahls et al., 1991; Clarke et al., 1993). Careful monitoring for PHT toxicity is recommended if diltiazem is prescribed. As PHT may cause an induction in metabolism, antihypertensives that are metabolized by CYP P450 may be affected.

Other

There are no known drug interactions with antihypertensives with the following AEDs: felbamate (FBM), GBP, lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), VPA, and zonisamide (ZNS).
Antihyperlipidemics

Carbamazepine

CBZ is a substrate and inducer of CYP3A4 (Luo et al., 2002). A recent study demonstrated that CBZ significantly increases the clearance of simvastatin. This resulted in an 80% decrease in patient exposure to simvastatin (Veor et al., 2004). While there are no published reports of drug interactions with other antihyperlipidemetics it may be inferred depending on their metabolic pathway including atorvastatin and lovastatin (Wang et al., 1991; Mazzu et al., 2000; Paoletti et al., 2002). CBZ co-medication may increase a patient’s dose requirement in order to get an adequate therapeutic response.

Phenobarbital

Atorvastatin, lovastatin, and simvastatin are substrates of CYP3A4 (Wang et al., 1991; Mazzu et al., 2000; Paoletti et al., 2002). PB co-medication may increase a patient’s dose requirement in order to get an adequate therapeutic response.

Phenytoin

Atorvastatin, lovastatin, and simvastatin are substrates of CYP3A4 (Wang et al., 1991; Mazzu et al., 2000; Paoletti et al., 2002). PHT co-medication may increase a patient’s dose requirement in order to get an adequate therapeutic response.

Other

There are no known drug interactions with antihyperlipidemetics with the following AEDs: FBM, GBP, LTG, LEV, OXC, TGB, TPM, VPA, and ZNS.

Anticoagulants/antiplatelets

Carbamazepine

Warfarin is metabolized via several CYP P450 enzymes (Kaminsky and Zhang, 1997). If a patient is stabilized on CBZ and warfarin therapy is initiated, the patient will require a larger warfarin dose than patients not receiving CBZ will require (Ross and Beeley, 1980; Kendall and Boivin, 1981; Massey, 1983). If a patient is stabilized on both CBZ and warfarin and the CBZ is discontinued, the patient is very likely to experience an increase in their internationalized normalized ratio (INR) that would place the patient at an increased risk of bleeding (Denbow and Fraser, 1990).

Felbamate

There are no known documented drug interactions between anticoagulants and FBM, but FBM inhibits CYP2C19, which may increase the effect of warfarin, resulting in an increased risk of bleeding (Glue et al., 1997).
Oxcarbazepine

There are no known documented drug interactions with anticoagulants or antiplatelets, but OXC inhibits CYP2C19 and induces CYP3A4, which may alter the metabolism of warfarin (Trileptal, 2001). Caution should be taken if adding OXC to a medication regimen that includes warfarin.

Phenobarbital

The clearance of warfarin is increased when a patient is also on PB (Udall, 1975; Mungall et al., 1985). Management of this interaction is similar to the interaction of warfarin with CBZ. If PB is added to a medication regimen including warfarin, the practitioner needs to monitor for a decrease in INR and efficacy. If PB is removed from a stable medication regimen including warfarin, the practitioner needs to monitor for an increased INR and an increased risk of bleeding. The dose of warfarin will need to be appropriately decreased.

Phenytoin

The interaction between PHT and warfarin is unpredictable, with reports of increased and decreased effects of warfarin (Nappi, 1979; Levine and Sheppard, 1984; Panegyres and Rischbieth, 1991). The initiation of PHT may cause warfarin to be displaced from protein-binding sites, followed by an increase in the metabolism of warfarin (Levine and Sheppard, 1984). Caution must be used when managing a patient on warfarin and PHT. Ticlopidine inhibits CYP2C19 that may cause inhibition of the metabolism of PHT, resulting in toxicity (Klaassen, 1998; Donahue et al., 1999). Aspirin may cause protein-binding displacement of PHT at doses that exceed 650 mg every 4 h (Leonard et al., 1981). There is no evidence that aspirin dosed at 81–325 mg per day should cause a clinically significant interaction.

Topiramate

There are no known drug interactions between TPM and anticoagulants or antiplatelets. TPM is a weak inhibitor of CYP2C19 and an inducer of CYP3A4 (Benedetti, 2000). Caution should be taken when prescribing TPM with clopidogrel, ticlopidine, and warfarin, as the presence or absence of drug interactions is not established.

Valproate

Aspirin may displace VPA from protein-binding sites and inhibit metabolism (Goulden et al., 1987). Patients should be monitored for VPA toxicity while taking aspirin. VPA may displace warfarin from protein-binding sites in vitro (Depakote, 2002). Caution should be taken when prescribing VPA with warfarin.
Antiepileptic drug interactions in the elderly

Other

There are no known drug interactions between anticoagulants/antiplatelets and the following AEDs: GBP, LTG, LEV, TGB, or ZNS.

Analgesics

Carbamazepine

Fentanyl is a substrate of CYP3A4 and the addition of CBZ may reduce its effectiveness (Labroo et al., 1997; Duragesic, 2001). There is no documented interaction between CBZ and valdecoxib. Valdecoxib is metabolized via CYP3A4, CYP2C9, and glucuronidation (Bextra, 2002). It is an inhibitor of CYP2C19 and a weak inhibitor of CYP3A4 and CYP2C9 (Bextra, 2002). It may be hypothesized that CBZ may induce the metabolism of valdecoxib, reducing its effectiveness, or valdecoxib may inhibit the metabolism of CBZ, resulting in toxicity. The drug interaction between propoxyphene and CBZ has been reported numerous times in the literature (Kubacka and Ferrante, 1983; Yu et al., 1986; Oles et al., 1989; Allen, 1994; Bergendal et al., 1997). Propoxyphene appears to inhibit the metabolism of CBZ resulting in toxicity. This combination should be cautiously used. CBZ increases the metabolism of tramadol that may decrease its efficacy at usual doses (Ultram, 2000).

Lamotrigine

Only one interaction with analgesics has been reported with LTG. One study examined the pharmacokinetics of a single dose of LTG following multiple doses of acetaminophen. The investigators found that it appears that acetaminophen increases the clearance of LTG (Depot et al., 1990). It is not clear if this interaction is clinically significant.

Phenobarbital

There is no documented drug interaction between celecoxib and PB. Celecoxib is metabolized via CYP2C9 and PB induces CYP2C9 (Tang et al., 2000; Raucy et al., 2002). It is possible that PB will reduce the efficacy of celecoxib. There is no documented drug interaction between valdecoxib and PB. Valdecoxib is metabolized via CYP3A4, CYP2C9, and glucuronidation (Bextra, 2002). It is an inhibitor of CYP2C19 and a weak inhibitor of CYP3A4 and CYP2C9 (Bextra, 2002). PB may induce the metabolism of valdecoxib, reducing its effectiveness, or valdecoxib may inhibit the metabolism of PB resulting in toxicity. Propoxyphene may cause up to a 20% increase in PB blood concentrations (Hansen et al., 1980). Patients should be monitored for toxicity.

Phenytoin

PHT induces the metabolism of acetaminophen, resulting in increased clearance and a decrease in the duration of analgesia (Miners et al., 1984). Aspirin may cause
displacement of PHT from its protein-binding sites at high doses (>650 mg every 4 h), however lower-dose aspirin (<650 mg every 4 h) should not be very problematic (Leonard et al., 1981). There is no documented drug interaction between valdecoxib and PHT. Valdecoxib is metabolized via CYP3A4, CYP2C9, and glucuronidation (Bextra, 2002). It is an inhibitor of CYP2C19 and a weak inhibitor of CYP3A4 and CYP2C9 (Bextra, 2002). PHT may induce the metabolism of valdecoxib, reducing its effectiveness, or valdecoxib may inhibit the metabolism of PHT resulting in toxicity. Propoxyphene inhibits CYP2C9 and may increase PHT serum concentrations resulting in increased toxicity (Levy, 1995).

Valproate

Aspirin may displace VPA from protein-binding sites and inhibit metabolism (Goulden et al., 1987). Patients should be monitored for VPA toxicity while taking aspirin.

Other

There are no known drug interactions between analgesics with the following AEDs: FBM, GBP, LEV, OXC, TGB, TPM, and ZNS.

Gastrointestinal agents

Carbamazepine

Cimetidine is a modest inhibitor of CYP3A4 (Martinez et al., 1999). The addition of cimetidine may result in CBZ toxicity.

Gabapentin

Concomitant use of antacids (Maalox®) has been shown to decrease the absorption of GBP by 20% (Neurontin, 2002). The manufacturer recommends taking antacids and GBP at least 2 h apart.

Phenobarbital

There are no known drug interactions between gastrointestinal agents and PB. Interactions may be possible depending on the metabolism of the gastrointestinal agents and the pathways that PB induces.

Phenytoin

Antacids, when taken simultaneously with PHT, may create an insoluble complex resulting in decreased or erratic absorption of PHT (Carter et al., 1981; McElnay et al., 1982). To avoid any potential interaction, it is recommended that patients take antacids and PHT at least 2 h apart. Cimetidine appears to cause a decrease in the clearance of PHT resulting in toxicity (Algozzine et al., 1981; Hetzel et al., 1981; Bartle et al., 1983; Frigo et al., 1983). The mechanism of the drug interaction is
likely to be the inhibition of CYP2C19 (Furuta et al., 2001). Caution should be taken when prescribing cimetidine with PHT. There is potential for a drug interaction between omeprazole and PHT (Prichard et al., 1987). Omeprazole is a potent inhibitor of CYP2C19 that may cause inhibition of PHT metabolism resulting in toxicity (Furuta et al., 2001). Careful monitoring is warranted.

Valproate

One study, of six subjects, demonstrated decreased clearance of a single dose of VPA when cimetidine was also administered (Webster et al., 1984). It is not known if cimetidine interacts with multiple doses of VPA, but caution should be taken if prescribing cimetidine and VPA.

Other

There are no known drug interactions with gastrointestinal agents and the following AEDs: FBM, LTG, LEV, OXC, TGB, TPM, and ZNS.

Endocrine/metabolic agents

Carbamazepine

There is no documented interaction between hormone replacement therapy and CBZ but it is well known that CBZ increases the metabolism of hormones (Ramsay and Slater, 1991). It would be expected that women who choose hormone replacement therapy might require higher doses of hormones for control of menopausal symptoms. There is no documented interaction with pioglitazone and CBZ. Pioglitazone is metabolized via CYP3A4 and may undergo increased metabolism secondary to CBZ induction (Actos, 2002).

Felbamate

There is no documented interaction between hormone replacement therapy and FBM. There was one study that examined the effect of FBM on oral contraceptives and it was found that FBM decreases hormone blood levels (Saano et al., 1995). It is unknown if FBM would also adversely affect blood levels of hormone replacement therapy.

Lamotrigine

There is no documented interaction between hormone replacement therapy and LTG but it has been demonstrated that oral contraceptives increase the clearance of LTG by as much as 50% (Jaben et al., 2003). LTG clearance may be increased by hormone replacement therapy.

Oxcarbazepine

There is no documented interaction between hormone replacement therapy and OXC. There is one study that examined the effect of OXC on oral contraceptives that
found OXC decreases hormone blood levels (Fattore et al., 1999). It is unknown if OXC would also adversely affect blood levels of hormone replacement therapy.

**Phenobarbital**

Both glypizide and tolbutamide are CYP2C9 substrates (Kidd et al., 1999; Kirchheiner et al., 2002). There is no documented interaction with PB and glypizide or tolbutamide. PB may cause some enzyme induction altering the metabolism of both agents (Gerbal-Chaloin et al., 2001). Close monitoring of therapeutic response and glucose levels is warranted. There is no documented interaction between hormone replacement therapy and PB. There is evidence that PB induces the metabolism of hormones and monitoring of therapy is recommended (Ramsay and Slater, 1991). There is no documented drug interaction between pioglitazone and PB. Pioglitazone is metabolized via CYP3A4 and may be susceptible to increased metabolism secondary to PB co-medication (Actos, 2002; Luo et al., 2002; Edwards et al., 2003). There is no documented drug interaction between rosiglitazone and PB. Rosiglitazone is metabolized via CYP2C8, a metabolic pathway induced by PB (Baldwin et al., 1999; Gerbal-Chaloin et al., 2001).

**Phenytoin**

There is no documented interaction between PHT and glypizide or tolbutamide. Both glypizide and tolbutamide are CYP2C9 substrates (Kidd et al., 1999; Kirchheiner et al., 2002). PHT may cause some enzyme induction altering the metabolism of both agents. Close monitoring of therapeutic response and glucose levels is warranted. There is no documented drug interaction between hormone replacement therapy and PHT. However, there is evidence that PHT increases the clearance of oral contraceptives (Coulam and Annegers, 1979; Mattson et al., 1986). It may be extrapolated that PHT will increase the clearance of other hormone replacement therapy. There is no documented drug interaction between pioglitazone and PHT. Pioglitazone is metabolized via CYP3A4 and may be susceptible to increased metabolism secondary to PHT co-medication (Actos, 2002; Luo et al., 2002).

**Topiramate**

There is no documented drug interaction between hormone replacement therapy and TPM. There is one study that documented a 14–33% increase in clearance of ethinyl estradiol when administered with TPM (Rosenfeld et al., 1997). The formulation ethinyl estradiol used in this study is an oral contraceptive. It may be extrapolated that TPM may increase the clearance of other estrogen supplements.

**Other**

There are no known drug interactions between endocrine/metabolic agents and the following AEDs: GBP, LEV, TGB, VPA, and ZNS.
Respiratory agents

There are no established interactions between inhaled respiratory medications and the AEDs.

Phenobarbital

There is a study of six adults that demonstrated an increased clearance of theophylline when they were also receiving PB (Landay et al., 1978). It is unknown what the significance of this drug interaction is in the elderly. It may be inferred that they would require larger doses of theophylline while being treated with PB.

Phenytoin

There are several case reports and studies that have demonstrated that PHT increases the clearance of theophylline (Miller et al., 1984; Sklar and Wagner, 1985; Adebayo, 1988). Patients on PHT may require increased doses of theophylline to get an adequate response.

CNS agents

Carbamazepine

There are numerous antidepressants whose metabolism is increased by CBZ, including tricyclic antidepressants, bupropion, mirtazapine, and sertraline (Leinonen et al., 1991; Wellbutrin, 1999; Sitsen et al., 2001; Pihlsgard and Eliasson, 2002). Several antidepressants may cause an elevation of CBZ blood concentrations including fluoxetine, fluvoxamine, and nefazodone. Fluoxetine has been shown to cause inhibition of CBZ in one study of six subjects (Grimsley et al., 1991), while another study of eight subjects showed no change in CBZ pharmacokinetics (Spina et al., 1993). Fluvoxamine was hypothesized to cause inhibition of metabolism of CBZ in three cases (Fritze et al., 1991), while a study of seven subjects showed no change in CBZ pharmacokinetics when fluvoxamine was added (Spina et al., 1993). Nefazodone is a CYP3A4 inhibitor (Rotzinger and Baker, 2002). The metabolism of CBZ is decreased when nefazodone is added to a patient’s regimen (Laroudie et al., 2000). Patients should be monitored for signs of CBZ toxicity and increased blood concentrations if nefazodone is prescribed to a patient also on CBZ. The metabolism of olanzapine, an atypical antipsychotic, is increased by CBZ by approximately 40%, which may not be clinically significant since olanzapine has a wide therapeutic range (Lucas et al., 1998; Olesen and Linnet, 1999; Linnet and Olesen, 2002). When CBZ was added to a regimen containing haloperidol, the clearance of haloperidol increased by 60% (Jann et al., 1985). The resulting increase in clearance may lead to treatment failure due to insufficient efficacy (Hesslinger et al., 1999). The metabolism of risperidone may be increased by CBZ (Ono et al., 2002). Alternatively risperidone may modestly increase plasma concentrations of CBZ and its metabolite CBZ-epoxide (CBZ-E) (Mula and Monaco, 2002). Monitoring the efficacy
of both agents is warranted. There are two case reports of quetiapine being added to a CBZ regimen that was thought to cause toxicity secondary to an increase in CBZ-E (Fitzgerald and Okos, 2002). The metabolism of quetiapine may be increased by CBZ (DeVane and Nemeroff, 2001). CBZ increases the metabolism of ziprasidone but it is not clear if the increase is clinically significant (Miceli et al., 2000).

Donepezil, a reversible inhibitor of acetylcholinesterase, used to treat dementia, is metabolized by CYPZD6, CYP3A4 and glucuronidation (Aricept, 2002). Galantamine, also a reversible inhibitor of acetylcholinesterase used to treat dementia, is metabolized via CYP2D6 and CYP3A4 (Reminyl, 2003). It is expected that CBZ may increase their clearance.

Lamotrigine

There are two case reports of patients receiving LTG to which sertraline was added to therapy resulting in toxicity secondary to increased LTG blood concentrations (Kaufman and Gerner, 1998). It was hypothesized that a glucuronidation pathway interaction may be the cause of the reaction, but further research is needed. Patients on LTG and sertraline should be monitored for signs of toxicity secondary to LTG.

Phenobarbital

There are no well-documented drug interaction studies done between antidepressants and PB. Since it is established that PB induces CYP2C9, CYP2C19, and CYP3A4, interactions may be inferred by looking at the metabolic pathway of the antidepressant being prescribed (Glue et al., 1997; Raucy et al., 2002; Edwards et al., 2003). The metabolism of clozapine is increased by co-medication with PB (Facciola et al., 1998). It has also been reported that PB may increase the metabolism of haloperidol (Linnoila et al., 1980). An increase in metabolism may result in a loss of efficacy without adequate dose adjustments. It is expected that PB may increase the clearance of donepezil and galantamine (Aricept, 2002; Reminyl, 2003).

Phenytoin

There are several case reports of the addition of fluoxetine to a regimen with PHT resulting in PHT toxicity (Jalil, 1992; Woods et al., 1994). An in vitro study examining the effect of fluoxetine on PHT metabolism demonstrated that fluoxetine inhibited CYP2C9 resulting in impaired metabolism of PHT (Nelson et al., 2001). Fluvoxamine inhibits CYP2C19, which may result in PHT toxicity, and doses may need to be appropriately adjusted (Schmider et al., 1997; Hemeryck and Belpaire, 2002). Tricyclic antidepressants may cause inhibition of CYP2C9 and CP2C19 resulting in an increased risk of PHT toxicity (Shin et al., 2002). Monitoring of blood concentrations and dose adjustments of PHT may be necessary. Sertraline has been associated with increased PHT toxicity in a report of two elderly patients (Haselberger et al., 1997). In vitro data also demonstrated that sertraline has the potential to inhibit CYP2C9 (Schmider et al., 2000).
et al., 1997; Nelson et al., 2001). The addition of PHT to quetiapine resulted in a five-fold increase in the metabolism of quetiapine (Wong et al., 2001). Patients should be monitored for a loss of efficacy if PHT is added to a regimen containing quetiapine. It is expected that PHT may increase the clearance of donepezil and galantamine (Aricept, 2002; Reminyl, 2003). It has been reported that PHT decreases the efficacy of levodopa therapy in patients with Parkinson’s; as a result, larger doses of levodopa may be necessary (Mendez et al., 1975).

Valproate

There are no well-documented clinically significant drug interactions between CNS medications and VPA.

Other

There are no documented drug interactions between CNS agents and the following AEDs: FBM, GBP, LEV, OXC, TGB, TPM, and ZNS.

Conclusion

AED interactions in the elderly are common and often lead to serious adverse events. A growing number of elderly are taking AEDs, usually in combination with other medications. Older patients appear to be more sensitive to adverse effects even when drug concentrations are controlled. Age-related changes in drug disposition and the use of multiple medications greatly increase the risk of clinically significant interactions in older patients. A number of AEDs either induce or inhibit drug metabolizing enzymes and, in turn, their metabolism is affected by many co-medications. Clinicians and older patients need to recognize that the addition or discontinuation of medications can place the patient at risk of an adverse event due to a drug interaction. An understanding of the principles that determine interactions and the pharmacokinetics of specific AEDs and other medications permits prospective assessment of the risk of an interaction when a drug is added or stopped. This allows clinicians to avoid interactions by selecting an alternate medication or rationally managing an interaction when it cannot be avoided. Several of the newer AEDs do not appear to interact with other medications, while others are affected by enzyme induction of inhibition but do not appear to alter the disposition of co-medications. Thus, the newer AEDs may be particularly useful in older patients.

REFERENCES


Antiepileptic drug interactions in the elderly


Antiepileptic drug interactions in pregnancy

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Scope of the problem

Women with epilepsy require chronic antiepilepsy drugs (AEDs) to prevent seizures, maintain their function and health. Unlike most young women they are unable to discontinue their medications if they become pregnant, for to do so increases their risk of seizures, personal injury, miscarriage and developmental delay in the offspring. With a prevalence of between 0.6% and 1.0% and an estimated 40% of those with epilepsy being women of childbearing years one can see that the potential public health impact is significant. Most women with epilepsy have healthy children but there is an increased risk for congenital malformations, fetal loss, developmental delay and neonatal hemorrhage. Maternal epilepsy is a contributor but the use of AEDs is a significant confounder. To make matters more complicated 86% of pregnant women take medications during pregnancy. A survey by the World Health Organization of 14 778 women in 22 countries reported that of the 86% of women taking medications during pregnancy the average number of prescriptions was 2.9 (range of 1–15). This study did not evaluate over-the-counter medications. The preponderance of prescriptions, 73%, were written by obstetricians (Collaborative Drug Use in Pregnancy, 1991).

When evaluating AED use in pregnancy one is hampered by the lack of knowledge of specific co-medications, even though it is clear that this is a common event. While monotherapy with AEDs is a goal of epilepsy management, it is not always an obtainable one. Polytherapy is also more common with the “newer” post-1993 introduction AEDs, because all were initially approved for use as adjunctive therapy. The pregnancy outcome of greatest interest is congenital malformations. While there are substantial data on this outcome, most are in the form of case series and case reports, and accurate rates and risks cannot be determined. Other adverse outcomes are at least as common in terms of incidence (developmental delay, fetal loss), but have received significantly less attention.

Let us review some of the clinically important issues surrounding pregnancy and AED exposure.
Antiepileptic drugs and hormonal contraceptives

A discussion of pregnancy needs to be preceded by reviewing the problems of contraception. Oral contraceptives have not been associated with exacerbation of epilepsy (Mattson et al., 1986). The effectiveness of hormonal contraceptives can, however, be reduced by enzyme-inducing AED (carbamazepine, phenytoin, phenobarbital, felbamate, topiramate). Hormonal contraceptives come in three formulations:

- oral (estrogen–progesterone combinations or progesterone only);
- subcutaneous (levonorgestrel) or intrauterine (progestasert) implants;
- injectable (depoprovera).

All three forms can be adversely impacted by enzyme-inducing AED.

AEDs may lower concentrations of estrogens by 40–50%. They also increase sex hormone-binding globulin (SHBG), which increases the binding of progesterone and reduces the unbound fraction. The result is that hormonal contraception is less reliable with enzyme-inducing AEDs.

The low- or mini-dose oral contraceptives are therefore to be used with caution. As it is the progesterone not the estrogen that inhibits ovulation, using higher-dose estrogens alone may not be effective. The more rapid clearance of the oral contraceptive when used in conjunction with an enzyme-inducing AED will reduce the likelihood of unwanted side effects from higher-dose tablets.

Failure of implantable hormonal contraceptives has also occurred (Shane-McWhorter et al., 1998). Mid-cycle spotting or bleeding is a sign that ovulation is not suppressed. If this occurs alternative or supplementary methods of contraception are required. Contraceptive failure may not always be predictable, even when mid-cycle spotting does not occur. Failure of basal body temperature to rise at mid-cycle can be used to document ovulatory suppression.

Medroxyprogesterone injections should be given every 10 instead of 12 weeks to women on enzyme-inducing AED. This shorter cycle is less likely to result in unintended pregnancy (Crawford, 2002a).

For multiparous women with epilepsy, intrauterine devices may be an excellent contraceptive choice. Alternatively non-enzyme-inducing AEDs may need to be considered (valproate, lamotrigine, gabapentin or zonisamide). A recent report suggests that topiramate at doses of <200 mg a day lacks enough enzyme induction to effect hormonal contraceptives. Higher doses however do reduce ethinyl estradiol concentrations by 18% on 200 mg, 21% with 400 mg and 30% with 800 mg of topiramate a day (Doose et al., 2002).

The importance of the potential impact of enzyme-inducing AEDs cannot be underestimated. In a survey of 294 general practices in the General Practice Research Database, 16.7% of women aged 15–45 with epilepsy were taking an oral
contraceptive. Two hundred were on an enzyme-inducing AED and 56% on low estrogen (<50 μg) hormonal contraceptives (Shorvon et al., 2002).

There has been at least one circumstance in which oral contraceptives effect AED concentration. Sabers and colleagues (2003) have demonstrated a marked reduction in lamotrigine concentrations when oral contraceptives are also taken. The average plasma concentration in 22 women on lamotrigine monotherapy and an oral contraceptive was 13 μmol/l. In a similar group of women on lamotrigine monotherapy with no oral contraceptive use, the plasma concentrations averaged 28 μmol/l: a significant reduction in AED concentration of over 50%. It has been suggested that oral contraceptives may induce the metabolism of glucuronidated drugs such as lamotrigine.

Maternal complications associated with AED
Seizures not infrequently worsen during pregnancy. One-quarter to one-third of woman with epilepsy (WWE) will have an increase in seizure frequency during pregnancy. This increase is unrelated to seizure type, duration of epilepsy, or seizure frequency in a previous pregnancy. In a recent series of 215 pregnancies in WWE an increase in seizures during the first trimester occurred in 30% of monotherapy- and 43% of polytherapy-treated women. One in 8 or 12.5% had to be hospitalized for their seizures during the pregnancy (Cahill et al., 2002).

Plasma concentrations of anticonvulsant drugs decline as pregnancy progresses, even in the face of constant and in some instances increasing doses (Tomson et al., 1994; Rodriguez-Palomares et al., 1995; Tomson et al., 1997). Although reduction of plasma drug concentration is not always accompanied by an increase in seizure frequency, virtually all women with increased seizures in pregnancy have subtherapeutic drug levels (Dansky et al., 1982; Janz, 1982; Schmidt, 1982; Schmidt et al., 1983; Otani, 1985). The decline of anticonvulsant levels during pregnancy is largely a consequence of decreased plasma protein binding (Perruca, 1982; Yerby et al., 1985; Tomson et al., 1994), reduced concentration of albumin and increased drug clearance (Dam et al., 1979; Nau et al., 1981; Janz, 1982; Philbert and Dam, 1982). The clearance rates are greatest during the third trimester.

Kaarkuzhali and colleagues (2002) found that a majority of their pregnant patients on carbamazepine, phenytoin or phenobarbital required numerous dose adjustments during pregnancy to maintain therapeutic levels. Fifty percent of the pregnancies had breakthrough seizures when the levels fell below the therapeutic range. It is therefore imperative to monitor AED levels at least monthly and adjust dosage to maintain therapeutic levels (Levy and Yerby, 1985). Table 16.1 summarizes some of the pharmacokinetics of anticonvulsant drugs during pregnancy.

Less is known about the kinetics of the newer AEDs in pregnancy. A report demonstrates that lamotrigine clearance increases by >50% during pregnancy
and that the clearance changes occur relatively early in pregnancy. Eleven of 12 pregnancies required increased doses of lamotrigine to maintain therapeutic levels during pregnancy (Tran et al., 2002).

**Polycystic ovaries**

A great deal of confusing literature has been written about the effect of AEDs on the development of polycystic ovaries (PCO). Ovarian cysts are found in approximately 6.6% of women of childbearing age. Most of these cysts (over 80%) will disappear within 3 months (Borgfeldt and Andolf, 1999). Multiple or PCO are more commonly found in women taking hormonal contraceptives with progesterone, and women who are infertile. The rates vary but average between 10% and 20% (Borgfeldt and Andolf, 1999).

The polycystic ovarian syndrome (PCOS) is a specific disturbance of neuroendocrine function defined as no or irregular menses (oligomenorrhea), elevated levels of male sex steroid hormones (hyperandrogenism) without evidence of other disturbances such as hyperprolactinemia, thyroid dysfunction or 21-hydroxylase deficiency. It is uncommon as occurs in approximately 6.5% of women of reproductive age (Asuncion et al., 2000). It is associated with sustained release of gonadotropic-releasing hormone (GnRH) and lutenizing hormone (LH), and affected women are often overweight, have elevated serum lipids and are less sensitive to insulin. PCOS is also seen in higher than expected rates in mothers (24–52%) and sisters (32–66%) of women with this disorder leading some to believe that it is a genetic disorder (Govind et al., 1999; Kahsar-Miller et al., 2001).

Isojarvi and colleagues (1993) demonstrated an excess of menstrual abnormalities in WWE taking valproic acid (VPA) compared to other AEDs. They also stated that

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Percent decrease</th>
<th>Normal</th>
<th>Maternal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>40</td>
<td>22</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>?</td>
<td>90</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>55</td>
<td>51</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>56</td>
<td>9</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Primidone</td>
<td>55</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Derived phenobarbital</td>
<td>70</td>
<td>75</td>
<td>80</td>
<td>?</td>
</tr>
<tr>
<td>VPA</td>
<td>50</td>
<td>9</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>

**Table 16.1** Pharmacokinetic data for first generation AEDs
80% of women taking valproate before the age of 20 developed PCO. Despite this observation other researchers have not found a consistent association between specific AED or epilepsy types and PCOS (Chappell et al., 1999; Bilo et al., 2001; Genton et al., 2001). Women with bipolar disorder are often treated with valproate and do not have an increase in PCOS (Rasgon et al., 2000).

**Fetal complications associated with AED**

A number of adverse outcomes of pregnancy are known to occur more often in infants of mothers with epilepsy (IME). Of the three major variables – maternal epilepsy, maternal seizures during gestation, and AEDs – it is not always possible to determine which is the most significant. For the outcome congenital malformations, AEDs appear to be a significant risk factor. A recent epidemiological study in Iceland suggests that untreated women with epilepsy have approximately the same rate of malformations in their offspring as do treated mothers, 4.8 vs. 5.9%, respectively. This suggests that a portion of the increased risk is secondary to maternal epilepsy itself (Olafsson et al., 1998). On balance however, malformation rates are twice that seen in the general population, and the proportion of women with epilepsy who are untreated is so small that it is clinically insignificant.

Congenital malformations are defined as a physical defect requiring medical or surgical intervention, and resulting in a major functional disturbance. Congenital anomalies in contrast are defined as deviations from normal morphology that do not require intervention. It is uncertain whether these aberrations represent distinct entities or a spectrum of physiological responses to insult to the developing fetus: malformations at one extreme and anomalies at the other. For the purposes of this review, congenital malformations and anomalies will be discussed separately.

IME, exposed to anticonvulsant drugs in utero, are twice as likely to develop malformations as infants not exposed to these drugs. Malformation rates in the general population range from 2% to 3%. Reports of malformation rates in various populations of exposed infants range from 1.25% to 11.5% (Fedrick, 1973; Nakane et al., 1980; Philbert and Dam, 1982; Kelly, 1984a; Steegers-Theunissen et al., 1994; Jick and Terris, 1997; Olafsson et al., 1998; Kaneko et al., 1999; Vajda et al., 2002). These combined estimates yield a risk of malformations in a pregnancy of a WWE of 4–6%. Cleft lip, cleft palate, or both, and congenital heart disease account for many of the reported cases. Orofacial clefts are responsible for 30% of the increased risk of malformations in these infants (Kelly, 1984a; Friis et al., 1986; Abrishamchian et al., 1994).

The increased rate of malformations in the offspring of mothers with epilepsy appears to be related to AED exposure in utero. Evidence to support this association comes from four observations.
Comparisons of the malformation rates in the offspring of mothers with epilepsy treated with AEDs as opposed to those with no AED treatment reveal consistently higher rates in the children of the treated women (South, 1972; Speidel and Meadow, 1972; Lowe, 1973; Monson et al., 1973; Annegers et al., 1978; Nakane et al., 1980).

Mean plasma AED concentrations are higher in mothers with malformed infants than mothers with healthy children (Dansky et al., 1980).

Infants of mothers taking multiple AEDs have higher malformation rates than those exposed to monotherapy (Nakane, 1979; Lindhout et al., 1984).

Maternal seizures during pregnancy do not appear to increase the risk of congenital malformations (Fedrick, 1973).

Majewski and co-workers (1980) described increased malformation rates and central nervous system injury in IMEs exposed to maternal seizures. More recently, Lindhout and co-workers (1992) described a marked increase in malformations amongst infants exposed to first trimester seizures (12.3%) compared to fetuses that were not subject to any maternal seizures (4.0%). Malformations were more often observed in infants exposed to partial seizures than to generalized tonic–clonic seizures. Nonetheless, most investigators have found that maternal seizures during pregnancy had no impact on the frequency of malformations, development of epilepsy or febrile convulsions (Annegers et al., 1978; Nakane et al., 1980).

A variety of congenital malformations have been reported in children of mothers with epilepsy, and every anticonvulsant medication has been implicated in their development. Cleft lip and/or palate, and congenital heart disease account for a majority of reported cases (Elshove and Van Eck, 1971; Anderson, 1976; Annegers et al., 1978). Orofacial clefts are relatively common malformations in the general population, occurring with a frequency of 1.5 per 1000 live births. IME have a rate of orofacial clefting of 13.8 per 1000, a nine-fold increase in risk (Kelly, 1984a; Kallen, 1986a). Early observations that persons with clefting of the lip or palate were twice as likely to have family members with epilepsy as controls suggested that orofacial clefts were associated with epilepsy (Friis et al., 1981). Subsequent studies of the prevalence of facial clefts in the siblings and children of 2072 persons with epilepsy found observed or expected ratios increased only for maternal epilepsy. The risk was greater if AEDs were taken during pregnancy (4.7) than if no AED treatment was used (2.7). The authors concluded that there was no evidence that epilepsy itself contributed to the development of orofacial clefts (Friis et al., 1986). Israeli researchers have found that children with cleft lip or palate are four times as likely to have a mother with epilepsy as the general population, and mothers with epilepsy are six times as likely to bear a child with an orofacial cleft as non-epileptic women (Gatoh et al., 1987). Orofacial clefts account for 30% of the excess of congenital malformations in IMEs.
Congenital heart defects are the second most frequently reported teratogenic abnormality associated with AEDs. IME have a 1.5–2% prevalence of congenital heart disease, a relative risk (RR) of three-fold over the general population (Kallen, 1986b). Anderson (1976) prospectively studied maternal epilepsy and AED use in 3000 children with heart defects at the University of Minnesota. Eighteen IMEs were identified. Twelve of these had ventricular septal defects; 9 of the 18 children had additional non-cardiac defects, 8 of which were orofacial clefts.

No AED can be considered absolutely safe in pregnancy, but for the vast majority of drugs no specific pattern of major malformations has been identified (Kallen, 1986b). This lack of a particular or characteristic pattern of defects has been cited as evidence that AEDs are not teratogenic. When phenobarbital is given during pregnancy for conditions other than epilepsy, no increase in malformation rates has been demonstrated (Shapiro et al., 1976). Phenobarbital has been demonstrated to be relatively teratogenic in mono- and polytherapy. Five of 79 phenobarbital monotherapy-exposed pregnancies were associated with major malformations (proportion 6.3%; 95% confidence interval (CI): 2.1–14.2%). When compared to the background rate (1.62%), there was a significantly increased risk for major malformations, with a RR of 3.8 (95% CI: 1.7–9.0%). A two-fold increase in risk was found when phenobarbital was compared to three other frequently used AED monotherapies (RR 2.2; 95% CI: 0.9–5.2%) (Holmes et al., in press).

Mechanisms of teratogenicity
A hypothesis that metabolites of AEDs are responsible for malformations has been developed on the basis of the following observations:

1. an arene oxide metabolite of phenytoin or other AED is the ultimate teratogen;
2. a genetic defect in epoxide hydrolase (arene oxide detoxifying enzyme) system increases the risk of fetal toxicity;
3. free radicals produced by AED metabolism are cytotoxic;
4. a genetic defect in free radical scavenging enzyme activity (FRSEA) increases the risk of fetal toxicity.

Epoxides
A large number of drugs can be converted into epoxides, in reactions that are catalyzed by the microsomal monooxygenase system (Jerina and Daly, 1974; Sims and Grover, 1974). Arene oxides are unstable epoxides formed by aromatic compounds. Various epoxides are electrophilic and may elicit carcinogenic, mutagenic and other toxic effects by covalent binding to cell macromolecules (Nebert and Jensen, 1979; Shum et al., 1979). Epoxides are detoxified by two processes:

1. conversion to dihydrodiols catalyzed by epoxide hydrolase in the cytoplasm,
2. conjugation with glutathione (GSH) in the microsomes.
Epoxide hydrolase activity has been found in the cytosol and the microsomal subcellular fraction of adult and fetal human hepatocytes. Epoxide hydrolase activity in fetal liver is lower than that of adults (Pacifici et al., 1983). One-third to one-half of fetal circulation bypasses the liver, resulting in higher direct exposure of extrahepatic fetal organs to potential toxic metabolites (Pacifici and Rane, 1982).

**Phenytoin teratogenicity**

**Formation of arene oxides by phenytoin**

Arene oxides are obligatory intermediates in the metabolism of aromatic compounds to transdihydrodiols. Phenytoin forms a transdihydrodiol metabolite (Chang et al., 1970). This metabolite is also formed by neonates exposed to phenytoin in utero (Horning et al., 1974). In vitro studies have shown that an oxidative (NADPH/02 dependent) metabolite of phenytoin binds irreversibly to rat liver microsomes (Martz et al., 1977). This binding is increased by an inhibitor of epoxide hydrolase (trichloroproponene oxide, TCPO) and decreased by GSH (Martz et al., 1977; Pantarotto et al., 1982; Wells and Harbison, 1985). Using human lymphocytes to assess cell defense mechanisms against toxicity, Spielberg et al. (1981) showed that cytotoxicity was enhanced by inhibitors of epoxide hydrolase.

**Phenytoin birth defects and lymphocyte cytotoxicity**

Strickler et al. (1985) examined lymphocytes of 24 children exposed to phenytoin during gestation and lymphocytes from their families using the Spielberg test of cytotoxicity (Spielberg et al., 1981). Lymphocytes were incubated with phenytoin in a mouse microsomal system. A positive response was defined as increase in cell death over baseline. Cells from 15 children gave a positive response. Each positive child had a positive parent (as many mothers as fathers), and a positive response was highly correlated with major birth defects. The authors concluded that a genetic defect in arene oxide detoxification increased the risk of the child having major birth defects (Strickler et al., 1985).

**Phenytoin birth defects and epoxide hydrolase activity**

In 1985, Buchler reported epoxide hydrolase activity in skin fibroblasts of a pair of dizygotic twins exposed to phenytoin in utero. The infant who had more features of the fetal hydantoin syndrome (FHS) showed lower epoxide hydrolase activity. Although this finding supports the epoxide hydrolase hypothesis, it should be noted that a full report of the experimental details has not yet appeared.

The evidence that epoxide metabolites of phenytoin are teratogenic can be summarized as follows. Phenytoin has an epoxide metabolite that binds to tissues.
Inhibition of the detoxifying enzyme epoxide hydrolase increases the rate of orofacial clefts in experimental animals, lymphocyte cytotoxicity, and the binding of epoxide metabolite to liver microsomes.

These facts cannot completely explain the teratogenicity seen in phenytoin or other AEDs. The lymphocyte cytotoxicity seen with epoxide metabolites correlates with major but not minor malformations (Dansky et al., 1987). Dysmorphic abnormalities have been described in siblings exposed to ethotoin in utero. Ethotoin is not metabolized through an arene oxide intermediate (Finnell and DiLiberti, 1983). Embryopathies have been described with exposure to mephenytoin, which also does not form an arene oxide intermediate (Wells et al., 1982). Trimethadione is clearly teratogenic but has no phenyl rings and thus cannot form an arene oxide metabolite. Therefore, an alternate mechanism must exist.

**Free radical intermediates of AEDs and teratogenicity**

Some drugs are metabolized or bioactivated by co-oxidation during prostaglandin synthetase (PGS)-catalyzed synthesis of prostaglandins. Such drugs serve as electron donors to peroxidases, resulting in an electron-deficient drug molecule, which by definition, is called a free radical. In the search for additional electrons to complete their outer ring, free radicals can covalently bind to cell macromolecules, including nucleic acids (DNA, RNA), proteins, cell membranes and lipoproteins to produce cytotoxicity.

Phenytoin is co-oxidated by PGS, thyroid peroxidase and horseradish peroxidase producing reactive free radical intermediates that bind to proteins (Kubow and Wells, 1989). Phenytoin teratogenicity can be modulated by substances that reduce the formation of phenytoin-free radicals. Acetylsalicylic acid (ASA) irreversibly inhibits PGS, caffeic acid is an antioxidant, alpha-phenyl-N-t-butyl nitronitrone (PBN) is a free radical spin-trapping agent. Pretreatment of pregnant mice with these compounds reduces the number of cleft lip or pathies secondary to phenytoin in their offspring (Wells et al., 1989).

GSH is believed to detoxify free radical intermediates by forming a non-reactive conjugate. N-acetylcysteine (NACl) a GSH precursor, decreases phenytoin-induced orofacial clefts and fetal weight loss in rodents (Wong and Wells, 1988). 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) inhibits GSH reductase, an enzyme necessary to maintain adequate cellular GSH concentrations, and increases phenytoin embryopathy at doses at which BCNU alone has no embryopathic effect (Wong and Wells, 1989). The metabolism of phenytoin or other AEDs to free radical intermediates may be responsible for the teratogenicity seen in IMEs. Twenty-six children with myelomeningocele and their parents were studied by Graf and colleagues (1995). They were found to have significantly lower antioxidant enzymes, particularly GSH peroxidase, than controls.
Neural tube defects and AEDs

Antiepileptic drugs as a group do not produce any specific pattern of major malformations. A possible exception to this is the association of sodium valproate and carbamazepine with neural tube defects (NTDs). Robert and Guibaud (1982) were the first to make this association while working in a birth defects registry in the Rhone Alps region of France. They reported NTDs in IME exposed to VPA. Other studies have revealed an association between carbamazepine exposure in utero and NTDs (Rosa, 1991; Little et al., 1993). Subsequent evaluations of these exposures identify spina bifida aperta (SB) as the specific NTD associated with the VPA or carbamazepine exposure (Lindhout et al., 1992). Methodologic problems make frequency estimates imprecise since most published data are case reports, case series or very small cohorts from registries that were not designed to evaluate pregnancy outcomes. The prevalence of SB with valproate exposure is approximately 1–2% (Lindhout and Schmidt, 1986) and with carbamazepine 0.5% (Rosa, 1991; Hiilesmaa, 1992). A recent prospective study in the Netherlands, however, found IME exposed to valproate had a 5.4% prevalence rate of SB. Average daily valproate doses were higher in the IME with SB (1640 ± 136 mg/day) than in the unaffected IME (941 ± 48 mg/day). Another group of investigators has found that valproate doses of 1000 mg/day or plasma concentrations of <70 µg/ml are unlikely to cause malformations (Kaneko et al., 1999). Both groups recommend that valproate dose be reduced whenever valproate must be used in pregnancy (Omtzigt et al., 1992; Kaneko et al., 1999). It has also been suggested that multiple daily doses or the use of extended release formulations may reduce the peak plasma concentrations and thus reduce the risk of malformations.

NTDs are uncommon malformations occurring in 6/10,000 pregnancies. Spina bifida and anencephaly are the most commonly reported NTD and affect approximately 4000 pregnancies annually resulting in 2500–3000 births in the US each year (Mullinare and Erickson, 1997; Honein et al., 2001). The types of NTD associated with AED exposure are primarily myelomenigocele and anencephaly, which are the result of abnormal neural tube closure between the third and fourth weeks of gestational age.

Previous thinking about NTD visualized the fusion of the neural tube as one in which the lateral edges met in the middle and fused both rostrally and caudally similar to a bi-directional zipper. Recent studies have suggested there are multiple sites for neural tube closure (Van Allen et al., 1993; Golden and Chenroff, 1995) and that different etiologies may result in different types of abnormality.

There are differences in specific sites and timing of each individual closure region. The majority of human NTD can be explained by failure of one or more closure sites. Anencephaly with frontal and parietal defects is due to failure at closure site two. Holocrania which also involves defects of the posterior cranium to the
foramen magnum is due to failure of closure of areas two and four. Lumbar spina bifida results from failure of closure one. The development of closure sites appears to be under genetic control and also affected by environmental factors. In twins, concordance rates are only 56% for anencephaly and 71% for spina bifida. In Great Britain there is a male preponderance of lumbar spina bifida and female preponderance of holocrania and anencephaly. Even VPA appears to have species differential effects being associated with spina bifida in humans and exencephaly in mice (Seller, 1995).

A number of risk factors are associated with NTDs. A previous pregnancy with NTD is the strongest association, with a RR of 10. There are strong ethnic or geographic associations with NTDs. Rates per 1000 are 0.22 for Whites, 0.58 for persons of Hispanic descent and 0.08 for persons of African descent. The incidence of NTDs in Mexico is 3.26/1000, for Mexican-born persons living in California 1.6/1000 and for US-born persons of Mexican descent 0.68/1000 (Harris and Shaw, 1995). Diabetic mothers have 7.9 times the rates of NTDs in their offspring (Becerra et al., 1990). Deficiencies of GSH, folate, vitamin C, riboflavin, zinc, cyanocobalamin, selenium and excessive exposure to vitamin A have been associated with NTD. Higher rates are seen in children of farmers, cleaning women and nurses (Matte et al., 1993; Blatter et al., 1996). Pre-pregnancy weight has also been demonstrated to be a factor. Werler and colleagues (1996) compared RR for NTD in control women weighing 50–59 kg and found the RR increased to 1.9 in women weighing 80–89 kg and 4.0 for those weighing over 110 kg. AEDs may be a necessary but not sufficient risk factor for the development of NTDs.

**Folate deficiency as a potential mechanism of AED teratogenicity**

Folate is a coenzyme necessary for the development of white and red blood cells, and proper function of the central nervous system. Normal concentrations are typically measured in the serum (plasma folate = 6–20 ng/ml) and erythrocytes (red blood cell folate, RBCF = 160–640 ng/ml). Low levels of folate are associated with hyperhomocysteinemia and concentrations required to prevent this are 6.6 ng/ml for SF and 140 ng/ml for RBCF.

Deficiencies of folate have been implicated in the development of birth defects. Dansky et al. (1987) found significantly lower blood folate concentrations in women with epilepsy with abnormal pregnancy outcomes. Co-treatment of mice with folic acid, with or without vitamins and amino acids, reduced malformation rates, and increased fetal weight and length in mice pups exposed to phenytoin in utero (Zhu and Zhou, 1989). Biale and Lewenthal (1984) reported a 15% malformation rate in IMEs with no folate supplementation, whereas none of 33 folate-supplemented children had congenital abnormalities. Eight trials have demonstrated that pre-conceptual folate reduces the risk of recurrence of neural tube defects in women with a previous affected pregnancy (Table 16.2).
Unfortunately pre-conceptual folate supplementation may not be protective for women with epilepsy. Craig and colleagues (1999) reported a young woman whose seizures were controlled for 4 years by 2000 mg of VPA a day. Though she took 4.0 mg of folic acid a day for 18 months prior to her pregnancy she delivered a child with a lumbosacral NTD, a ventricular and atrial septal defect, cleft palate and bilateral talipes. Two Canadian women delivered children with NTD despite folate supplementation. One taking 3.5 mg of folic acid for 3 months prior to conception and 1250 mg of VPA aborted a child with lumbosacral spina bifida, Arnold Chiari malformation and hydrocephalus. A second woman who took 5.0 mg of folic acid had one spontaneous abortion of a fetus with an encephalocele and two therapeutic abortions of fetuses with lumbosacral spina bifida (Duncan et al., 2001). These cases might have been predicted given the demonstrated failure of folate to reduce
NTD and embryotoxicity in vitro and in vivo in rodent models (Hansen and Grafton, 1991; Hansen et al., 1995). In fact not all research supports the association with folate deficiency and malformations. Mills et al. (1992) found no difference between serum folate levels in mothers of children with NTD and controls. A number of other studies also failed to demonstrate a protective effect of pre-conceptual folate (Laurence et al., 1981; Winship et al., 1984; Vergel et al., 1990; Bower and Stanley, 1992; Kirke et al., 1992; Friel et al., 1995). These studies are problematic due to small sample sizes, failure to document folate supplementation and recall bias in the retrospective investigation.

There is evidence to suggest that women with similar folate intake may have different serum concentrations due to differences in folate metabolism. Absorption does not account for the difference in plasma concentration between cases and controls (Davis et al., 1995).

**New AED in pregnancy**

A number of new AEDs have been marketed since 1993. Gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide are all now available in the US. The numbers of reported exposed pregnancies with these drugs is very low, and unfortunately not large enough for one to determine if there is an increased risk of adverse outcome with fetal exposure to these compounds. We know that lamotrigine and levetiracetam concentrations decline during pregnancy and expect that this is also true for the other new AEDs (Tomson et al., 1997). This is what we know to date.

**Gabapentin**

Despite its extensive use for a variety of conditions little has been published about its effect on pregnancy outcomes. A large post-marketing surveillance study of 3100 English patients taking this drug identified 11 pregnancies and no malformations (Wilton and Shakir, 2002). Dr. Georgia Montouris (2002) has collected 51 pregnancies from 39 women with epilepsy. The malformation rate was 4.5%. Eighty-seven percent of the pregnancies were live births, there were 11.3% miscarriages and 2% therapeutic abortions.

**Lamotrigine**

The International Lamotrigine Pregnancy Registry has identified 334 pregnancies reported in women taking lamotrigine in the first trimester. One hundred and sixty eight of these were with monotherapy, 166 with polytherapy. There is a significant difference in malformation rates when lamotrigine is used in monotherapy (1.8%), polytherapy with VPA (10%) and polytherapy without VPA (4.3%) (Tennis and Eldridge, 2002).
Lamotrigine clearance increases early in pregnancy and continues to accelerate through all three trimesters in most women taking this medication. In at least one case report the apparent clearance increased by $<700\%$ (Pennell et al., 2002).

Lamotrigine crosses the placenta and at delivery fetus and mother have similar plasma concentrations. Elimination in infants appears to be rather slow. Seventy-two hours postpartum infant plasma levels are 75\% that of the mother. Median milk/plasma (M/P) ratios are 0.61 (Ohman et al., 2000).

**Oxcarbazepine**

In the first 12 reported cases of pregnancy with oxcarbazepine there have been nine live births and three spontaneous abortions (Friis et al., 1993). In a prospective study of 11 pregnancies one child with spina bifida exposed to oxcarbazepine in polytherapy was reported. The manufacturer has been notified of five cases of fetal malformations in the post-marketing period. One was a cardiac defect and there were three cleft palates and one facial dysmorphism. Three of the five were exposed to AED polytherapy. The drug has been available in Europe for 10 years, but an accurate denominator is not available thus we are unable to calculate rates. In a recent prospective report of 42 pregnant women taking oxcarbazepine, 25 on mono-therapy and 17 on polytherapy, no malformations were seen in the monotherapy group. A child with a ventricular septal defect was exposed to oxcarbazepine and phenobarbital (Rabinowicz et al., 2002). Oxcarbazepine crosses the placenta with equivalent maternal and fetal cord levels (Myllynen et al., 2001).

**Topiramate**

We have little information of the number of pregnancies with topiramate exposure. In the clinical trials there were 28 reported pregnancies with one malformation and two children with anomalies. All of these were polytherapy cases. Post-marketing surveillance has collected 139 reports of pregnancy. These included 87 live births, 23 therapeutic abortions, 29 cases lost to follow-up and five cases of hypospadias. Topiramate crosses the placenta with cord and maternal plasma levels being equivalent at delivery. M/P concentration ratios average 0.86. Infant elimination appears to be substantial with little measurable drug found in plasma of breast fed infants 2–3 weeks postpartum (Ohman et al., 2002).

**Zonisamide**

There have been 26 reported pregnancies with zonisamide exposure. Two of the 26 (7.7\%) had congenital malformations. One child was also exposed to phenytoin and the other to both phenytoin and VPA (Kondo et al., 1996).

Zonisamide also freely crosses the placenta with transfer rates of 92\%. Though data is available from only two children M/P ratios are 0.8 and elimination half-life ranges from 61 to 102 h (Kawada et al., 2002).
Syndromes of anomalies

In distinction to malformations, which are deformities of anatomy requiring medical or surgical intervention to maintain a functionally healthy person, anomalies are abnormalities of structure, which, while varying from the norm, do not constitute a threat to health. Patterns of anomalies in IMEs have been noted with certain AED exposure. Five clinical syndromes have been reported in IMEs: fetal trimethadione syndrome, FHS, a primidone embryopathy, a fetal valproate syndrome and a fetal carbamazepine syndrome.

Fetal trimethadione syndrome

In 1970, German and colleagues described a case of a WWE treated with trimethadione who had had four unsuccessful pregnancies. After trimethadione was discontinued, she went on to have two healthy children. Her physician then surveyed trimethadione-exposed infants delivered at New York Hospital between 1946 and 1968. The records of 278 women with epilepsy were reviewed and, of these, 14 had taken trimethadione during pregnancy. Only 2 of these 14 children were normal. One had multiple hernias and diabetes; 8 had developmental defects; 3 were spontaneously aborted and only 3 of the 14 actually survived infancy.

The peculiar facial characteristics of these children were delineated by Zackai et al. (1975), who noted that not only were these children short in stature and suffering from microcephaly, they had V-shaped eyebrows epicanthal folds, low set ears, anteriorly folded helices, and irregular teeth. Other abnormalities were often frequent: inguinal hernias, hypospadias and simian creases. Feldman et al. (1977) reviewed 53 pregnancies in which trimethadione was used. In 46 of these (87%), there was fetal loss or the development of a congenital malformation. Follow-up studies of the surviving children have reported significant rates of mental retardation (Goldman et al., 1986).

FHS

The most famous and controversial of the dysmorphic syndromes associated with AEDs is the FHS. It was first reported by Loughnan et al. (1973), who described seven infants exposed to hydantoin in combination with a barbiturate, in utero. The children displayed hypoplasia and irregular ossification of the distal phalanges. In 1974, Barr and co-workers reported distal digital hypoplasia (DDH) in eight children exposed to phenytoin and phenobarbital. The syndrome was given its name by Hanson and Smith (1975), who reported five IMEs who had been exposed to hydantoin in utero. The infants had multiple systemic abnormalities of the face, cranium, and nails, DDH, intrauterine growth retardation, and mental deficiencies. Only one of the five was exposed to phenytoin monotherapy. Of the others, three were exposed to phenobarbital, one to mephobarbital and one to a
combination of phenobarbital, phensuximide and mephenytoin. Despite the multiplicity of exposures, the authors noted the resemblance to the fetal alcohol syndrome and described their cases as suffering from FHS.

Subsequent work by Hanson’s group found that approximately 11% of infants exposed to hydantoin in utero demonstrated the complete syndrome, and an additional 30% would have some anomalous components (Hanson et al., 1976). Many of the features of the syndrome appear to be subjective, but some investigators believe that DDH is a unique and relatively constant feature (Kelly et al., 1984b).

The prevalence and significance of the dysmorphic features of FHS remain unclear. Researchers at the University of Virginia followed 98 women with epilepsy who took phenytoin during pregnancy and found that 30% of their offspring had DDH with no other features of FHS (Kelly et al., 1984b). Gaily et al. (1988a) reported a prospective study of 121 IMEs at the University of Helsinki, 82 of whom were exposed to phenytoin. None of the children had FHS. Hypertelorism and DDH were the only dysmorphic features associated with phenytoin exposure. In our own experience following 64 IMEs, no children with FHS were seen. Dysmorphic features could be seen with any drug exposure (Yerby et al., 1992).

Hanson (1986) feels that there are three components to the syndrome:

1. abnormal growth,
2. abnormal performance,
3. dysmorphic cranial facial features.

An unexpected sequela of the syndrome may be an increased risk of cancer. Four cases of neuroblastoma associated with the FHS have been described since 1976, although all children were also exposed in utero to primidone or phenobarbital. There have also been reports of carcinoma, ganglioneuroblastoma, Wilms’ tumor, a melanotic neuroectodermal tumor and a malignant mesenchymoma in children with FHS (Ehrenband and Chaganti, 1981).

The contention that FHS results in abnormal performance or mental deficiency is not supported by subsequent research. Of 103 IMEs exposed to phenytoin, only 1.4% displayed mental deficiency on the Wechsler Preschool and Primary Scale of Intelligence or Leiter International Performance Scale, not significantly different from the general population (Gaily et al., 1988b).

Gaily’s work suggests that there is a genetic component that permits expression of the FHS. Children of mothers with epilepsy who are not exposed to AEDs in utero have frequencies of dysmorphic abnormalities intermediate to those children exposed to AEDs and controls. Dizygotic twins exposed to hydantoins in utero have been shown to display discordant dysmorphism (Phelan et al., 1982; Buchler, 1985). If the first child in a family has FHS, the chance of a second such child is 90%, compared to the 2% chance of having a second child with FHS if the
first is normal (Van Dyke *et al.*, 1988). Such observations suggest that hydantoin exposure may be a necessary but not sufficient cause of infant dysmorphism.

Krauss and co-workers (1984) described four siblings with features of FHS. The first two were exposed to both phenytoin and primidone in utero. In an attempt to prevent further fetal injury, Krauss discontinued the phenytoin and the patient was treated with primidone monotherapy. Two subsequent pregnancies resulted in children with similar dysmorphic features to their elder siblings.

**Primidone embryopathy**

Five years before Krauss’ report, Rudd and Freedom (1979) had described craniofacial abnormalities in children exposed to primidone in utero. These children had hirsute foreheads, thick nasal roots, antverted nostrils, long philtrum, straight thin upper lips and hypoplastic nails. These children were also likely to be small for their gestational age and have psychomotor retardation and heart defects (Gustavson and Chen, 1985).

**Fetal valproate syndrome**

Reports of dysmorphic children exposed to valproate in utero had previously been made by other investigators (Dalens *et al.*, 1980; Clay *et al.*, 1981), but it was DiLiberti *et al.* (1984) who described a specific fetal valproate syndrome. They reported seven infants exposed to VPA in utero who had facial abnormalities characterized by interiorepicanthal folds, a net nasal bridge, an upturned nose, a long upper lip, a thin vermilion border, a shallow philtrum and downturned mouth. These children also had abnormalities of their distal digits, and they tended to have long thin overlapping fingers, toes and hyperconvex nails. Subsequent reports of valproate-exposed infants having radial ray aplasia have also been made.

The prevalence of this syndrome has not yet been established. Jaeger-Roman *et al.* (1986) described it in 5 of 14 children exposed to valproate monotherapy. In this same group, 43% of the children were distressed at labor, and 28% had low Apgar scores and other major malformations. High doses of valproate were associated with drug withdrawal, hypotonia, and motor and language delay. In a review of 344 women who took valproate during the first trimester of pregnancy, Jeavons (1984) described a 19.8% rate of abnormal deliveries, but no evidence of a dose–response effect with valproate exposure.

Felding and Rane (1984) described an infant with severe congenital liver disease after in utero exposure to VPA and phenytoin. Ardinger and co-workers (1988) reported craniofacial dysmorphism in 19 children exposed to valproate in utero and confirmed the features described by DiLiberti. They also found a large proportion of these infants had postnatal growth deficiency and microcephaly, particularly if the children were exposed to polytherapy. The association of valproate with spina bifida is discussed further on.
Benzodiazepine syndrome

Infants exposed to benzodiazepines in utero are at greater risk for intrauterine growth retardation, dysmorphic features and neurological dysfunction. Seven of 37 infants exposed to benzodiazepine drugs in utero were described as hypotonic and hyperexcitable, with dystonic postures and choreoathetotic movements (Laegreid et al., 1987). Delayed hand–eye coordination, psychomotor slowing and a learning disability were also noted. Four infants had major malformations and dysmorphic faces with wide-set eyes, epicanthal folds, upturned noses, dysplastic oracles, high-arched palates, webbed necks and wide-spaced nipples (Laegreid et al., 1987). In a survey of 278 women whose infants had congenital malformations, children with a history of diazepam exposure in the first trimester had a four-fold increase in cleft lip and/or palate (Safra and Oakley, 1975).

Carbamazepine syndrome

The most recently described syndrome of anomalies associated with AED exposure is the carbamazepine syndrome. One group of investigators has described craniofacial defects (upslanting palpebral fissures, epicanthal folds, short nose, long philtrum), hypoplastic nails, and microcephaly, in 37 IMEs exposed to carbamazepine monotherapy (Jones et al., 1989). The authors used the Bayley Scale of Infant Development, the Stanford-Binet IV, and the Wechsler Scale of Preschool and Primary Intelligence in their evaluations and found a 20% rate of developmental delay in 25 children of mothers taking carbamazepine monotherapy. They used an unconventional one standard deviation from the mean to define delay, however.

A case of DDH in an IME exposed to carbamazepine monotherapy had been described earlier (Niesen and Froscher, 1985), but that child was otherwise normal.

Low birth weight has been reported with in utero exposure to carbamazepine monotherapy (Kallen, 1986b). A reduction in fetal head circumference has been noted in IMEs exposed to carbamazepine (Hiilesmaa et al., 1981). While smaller than control children, the head sizes were still within the normal range. Subsequent studies on the same clinical population failed to find differences in head circumference as the children matured (Granstrom, 1987).

Newer AED and anomalies

There have been case reports of anomalies associated with exposure to the newer (introduced after 1993), AEDs, but no drug-specific syndrome of anomalies described. Three children exposed to lamotrigine and VPA have been reported to have dysmorphic facial features of broad nasal bridge, low set ears and hypertelorism. One child was karyotyped as 47, XXX and another simply had epicanthal folds (GlaxoSmithKline, 2002).
Clinical and laboratory evidence clearly supports the association of certain anticonvulsants with teratogenic effects, especially facial and distal digital anomalies. However, the existence of drug-specific syndromes is doubtful. Facial dysmorphism is difficult to quantify and clearly is not drug specific. Infants of epileptic mothers with similar dysmorphic features have been described in the pre-anticonvulsant era (Baptist, 1938; Philbert and Dam, 1982). Follow-up of these infants into adult life has yet to be accomplished, and therefore the significance of these anomalies is unclear. Gaily et al. (1988a) followed a cohort of IMEs to 5½ years of age. These children had more minor anomalies characteristic of FHS than control children but so did their mothers. Only hypertelorism and digital hypoplasia were associated with phenytoin exposure. Certain anomalies, particularly epicanthal folds, appeared to be associated with maternal epilepsy, not with AED exposure.

The hypothesized association of dysmorphic features with mental retardation (Kelly, 1984a) has not been confirmed (Hutch et al., 1975; Granstrom, 1982). In the few cases that have been followed into early childhood, the dysmorphic features tend to disappear as the child grows older (Janz, 1982). Mental deficiency was found in only 1.4% of IMEs followed to 5½ years of age (Gaily et al., 1988b). Exposure to AEDs below toxic concentrations or to maternal seizures did not increase the risk of lower intelligence. No association between features of FHS and mental retardation could be demonstrated.

The primary abnormalities in these syndromes involve the midface and distal digits. A retrospective study spanning 10 years of deliveries in Israel found hypertelorism to be the only anomaly seen more often in IME than in controls (Neri et al., 1983). This was associated with all AEDs except primidone. A prospective study of 172 deliveries of IMEs evaluated eight specific AEDs and other potential confounding factors and found no dose-dependent increase in the incidence of malformations associated with any individual AED. Furthermore, no specific defect could be associated with individual AED exposure (Kaneko et al., 1988). It has been suggested that, since a variety of similar anomalies of the midface and distal digits are seen in a small proportion of children exposed to anticonvulsants in utero, a better term for the entire group of abnormalities would be fetal anticonvulsant syndrome or AED embryopathy (Dieterich et al., 1980; Vorhees, 1986; Huot et al., 1987).

**Neonatal complications associated with AED**

A unique neonatal hemorrhagic phenomenon has been described in the IME. It differs from other hemorrhagic disorders in infancy in that the bleeding tends to occur internally during the first 24 h of life. It was initially associated with exposure to phenobarbital or primidone, but has subsequently also been described in children
exposed to phenytoin, carbamazepine, diazepam, mepobarbital, amobarbital and ethosuximide (Van Creveld, 1957; Mountain et al., 1970). One group of investigators suggests that vigabatrin may also increase the risk of neonatal hemorrhage (Howe et al., 1999). Prevalence figures are as high as 30% but appear to average 10%. Mortality is high, over 30%, because bleeding occurs within internal cavities and is often not noticed until the child is in shock.

The hemorrhage is the result of a deficiency of vitamin K-dependent clotting factors II, VII, IX and X. Anticonvulsants can act like warfarin, and inhibit vitamin K transport across the placenta. This results in the increase in an abnormal prothrombin induced by vitamin K absence of factor II (PIVKA-II). Maternal coagulation parameters are invariably normal. The fetus, however, will demonstrate increased levels of PIVKA, diminished clotting factors, and prolonged prothrombin and partial thromboplastin times. PIVKA-II has been demonstrated in 54% of infants exposed to AEDs in utero compared to 20% of controls \( (P < 0.01) \), and maternal vitamin K concentrations are lower in WWE than those untreated though PIVKA is rarely detectable in mothers (Cornelissen et al., 1993).

This phenomenon can be prevented by maternal ingestion of oral vitamin K in the last month of gestation (Deblay et al., 1982; Crawford, 2002b). I use 10 mg/day of oral vitamin K. Routine intramuscular administration of vitamin K at birth is not adequate to prevent hemorrhage within the first 24 h of life.

The prevalence of AED-associated neonatal hemorrhage is unclear. One report states it is 1.6 times as common in IME as controls (Speidel and Meadow, 1972). A more recent prospective study followed 667 IME and 1334 controls and found neonatal bleeding in 5 of 667 (0.7%) IME and 5 of 1334 (0.4%) of controls. While more prevalent there was no statistical difference between the groups. The authors concluded that there was no increased risk for neonatal bleeding in the IME (Kaaja et al., 2002). I would point out that the sample size for a low frequency outcome such as this may need to be larger and there was clearly a trend for more bleeding in the IME.

**Developmental complications associated with AED**

**Developmental delay**

IME have been reported to have higher rates of mental retardation than controls. This risk is increased by a factor of two- to seven-fold according to various authors (Speidel and Meadow, 1972; Hill et al., 1974). None of these studies controlled for parental intelligence, although differences in IQ scores at age 7 between groups of children exposed (full-scale IQ, FSIQ = 91.7) or not exposed (FSIQ = 96.8) to phenytoin reached statistical significance, the clinical significance of such difference is unknown (Hill and Tennyson, 1982).
We have found that IME display lower scores in measures of verbal acquisition at both 2 and 3 years of age. Though there was no difference in physical growth parameters between IME and controls, IME scored significantly lower in the Bailey Scale of Infant Development’s mental developmental index (MDI) at 2 and 3 years. They also performed significantly less well on the Bates Bretherton early language inventory \((P \leq 0.02)\) and in the Peabody Picture Vocabulary’s scales of verbal reasoning \((P \leq 0.001)\) and composite IQ \((P \leq 0.01)\), and they displayed significantly shorter mean lengths of utterance \((P \leq 0.001)\) (Leavitt et al., 1992).

Polytherapy-exposed infants performed significantly less well on neuropsychometric testing than those exposed to monotherapy. Socioeconomic status had the strongest association with poor test scores, but maternal seizures during pregnancy was also a significant risk factor (Losche et al., 1994).

Leonard et al. (1997) has in part addressed the question of whether maternal seizures or in utero exposure to AEDs are responsible for the developmental delay seen. A group of children of mothers with epilepsy followed to school age were found to have a rate of intellectual deficiency of 8.6%. The Wechsler Intelligence Scale for Children revealed significantly lower scores for children exposed to seizures during gestation (100.3), than for children whose mother’s seizures were controlled (104.1) or controls (112.9). All AEDs are clearly not created equal and Koch and co-workers (1999) have demonstrated that primidone, particularly when used in polytherapy, is associated with lower Wechsler score of intelligence.

**Conclusion**

The potential interactions of AEDs in pregnant women with epilepsy can be characterized by those effecting the mother, and those effecting the fetus. While pregnancy, maternal seizures and AEDs pose risks for successful pregnancy outcome, the majority of patients can and do have healthy children. Physicians cannot eliminate risk, but can reduce it. Pre-conceptual folic acid is an approved intervention but may not prevent all malformations. Though there are no head to head studies of the safety of AEDs in pregnancy some principles have been clearly established. Monotherapy is safer than polytherapy. Phenobarbital is no safer than, and probably more hazardous than, other AEDs in monotherapy. VPA has in addition to the underlying increased risk for malformations an additional risk for development of NTDs. The newer AEDs have theoretical advantages over older ones in terms of malformations but the sample sizes collected to date are not adequate to determine relative safety. Malformations are not the only adverse outcome that one should be concerned about. Developmental delay is, in terms of magnitude, as significant as birth defects. There is no drug-specific syndrome of anomalies but a tendency for all AEDs to cause facial dysmorphism, which is a relatively transient condition.
Given the nature of the data available to date clinical judgement in determining the most effective AED for the seizure type and using the lowest effective dose is still the best approach.

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Antiepileptic drug interactions in pregnancy


Krishnamurthy KB, Sundstrom DT, Beaudoin JM, et al. Pregnant women with epilepsy taking older anticonvulsant medications must have drug levels checked frequently to avoid seizures. Epilepsia 2002; 43(Suppl. 7): 232–233.


Antiepileptic drug interactions in pregnancy


Antiepileptic drug interactions in handicapped and mentally retarded patients

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Departments of Child Neurology and Public Health, University of Turku, Turku, Finland

Introduction

Epilepsy in the mentally retarded differs from epilepsy in the mentally normal patient in relation to etiology, seizure types, epilepsy syndromes, choice of antiepileptic drugs, identification of their side effects and treatment outcome. Consequently, a successful antiepileptic drug therapy is a demanding task in terms of choice of drug therapy, combinations of drugs and side effects in mentally retarded patients compared with mentally normal people. Adverse effects and interactions between different antiepileptic drugs are a potential risk in the presence of many and difficult-to-treat seizure types, leading to frequent polytherapy. There is also an increased risk of interactions between antiepileptic drugs and other drugs because of the increased incidence of co-morbidity among these patients.

In patients who are handicapped or mentally retarded, there is no evidence that pharmacokinetic drug interactions per se are quantitatively or qualitatively different from those seen in otherwise normal epilepsy patients. However, it is the context of the treatment of their epilepsy that puts a different emphasis on the potential for interactions. These patients are characterized by an increased incidence of co-morbidity that may require treatment with other medications. Their epilepsies are generally more refractory to treatment and antiepileptic drug combinations are more likely to be used. Also, central nervous system (CNS) toxicity of drugs may be more prominent in mentally retarded patients, and this may include neurotoxic pharmacodynamic interactions between antiepileptic drugs as well as pharmacodynamic interactions between antiepileptic drugs and other psychotropic drugs. As a group, these patients may be particularly vulnerable to the problems associated with polytherapy. The main purpose of this chapter is not to provide an exhaustive discussion of possible pharmacokinetic interactions that are discussed elsewhere in this book, but to emphasize the context in which pharmacokinetic and pharmacodynamic interactions are likely to occur during the treatment of epilepsy in handicapped and mentally retarded patients.
Epidemiology of epilepsy in the mentally retarded

Epilepsy occurs in approximately 15% of patients with mild mental retardation (IQ 50–69) (Blomquist et al., 1981; Drillien et al., 1966; Hagberg et al., 1981) and 30% of those with severe mental retardation (IQ < 50) (Corbett, 1993; Drillien et al., 1966; Gustavson et al., 1977a, b). In institutionalized patients with mostly severe or profound mental retardation, the prevalence of epilepsy ranges from 35% to 60% (Iivanainen, 1974; Illingworth, 1959; Mariani et al., 1993). The age at the onset of the epilepsy does not differ from that in the general population (Forsgren et al., 1990; Goulden et al., 1991; Richardson et al., 1980). However, children with severe mental retardation were found to have a significantly earlier seizure onset than those with a mild mental retardation (Steffenburg et al., 1996).

Table 17.1 shows several lesional, developmental, chromosomal and metabolic conditions in which epilepsy is associated in up to 100% of the cases. The etiology of severe mental retardation is reportedly prenatal in 55–78%, perinatal in 8–15%,

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence (%)</th>
<th>Author(s) and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy and MR</td>
<td>28–38</td>
<td>Goulden et al. (1991), Sillanpää (1978)</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>96–100</td>
<td>Hirano and Pavlakis (1994)</td>
</tr>
<tr>
<td>Polymicrogyria</td>
<td>90</td>
<td>Kuzniecky et al. (1993)</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>90</td>
<td>Barkovich and Kjos (1992), Fois et al. (1988)</td>
</tr>
<tr>
<td><strong>Chromosomal anomalies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf–Hirschhorn syndrome</td>
<td>70</td>
<td>Jennings and Bird (1981)</td>
</tr>
<tr>
<td>Prader–Willi syndrome</td>
<td>15–20</td>
<td>Bray et al. (1983)</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>2–10</td>
<td>Becker et al. (1996), Nielsen and Pedersen (1969), Zupping et al. (1967)</td>
</tr>
</tbody>
</table>

**Metabolic disorders**

- Peroxisomal diseases          80
- Krabbe's disease               50–75
- Biotinidase deficiency        50–75
- Disorders of urea cycle       60

MR, mental retardation.

Table 17.1: Occurrence of epilepsy in certain syndromes with MR
postnatal in 1–12% and unknown in 13–22% (Goulden et al., 1991; Gustavson et al., 1977b; Hagberg and Kyllerman, 1983; Linna, 1989). In patients who have a mild mental handicap, the corresponding figures are 23–43%, 7–18%, 4–5% and 43–55%, respectively. In many patients, the etiology is still unknown but probably prenatal (Blomquist et al., 1981; Hagberg and Kyllerman, 1983).

Problems in diagnosing epilepsy

The diagnosis of epileptic seizures may be difficult in mentally retarded patients, because they cannot in many cases express themselves and therefore fail to tell about their perceived symptoms (Table 17.2). Also, in these patients, motor automatisms are not easily distinguished from stereotypic movements, nor are nocturnal seizures easy to separate from parasomnias. Table 17.3 lists the most important non-epileptic conditions which may lead to a misdiagnosis of epilepsy.

Intractability of seizures

The main groups of reasons for intractability of seizures are related to actions by the physician, to the patient, to the epilepsy itself and to the drugs (Table 17.4). The type of epilepsy may be a priori intractable. Epileptic and non-epileptic seizures may be intermingled in the same patient. Certain antiepileptic medications, at therapeutic or at toxic doses, may cause or aggravate seizures. Remote symptomatic etiology, abnormal neurological status, occurrence of status epilepticus and poor short-term effect of drug therapy have been shown to be independent predictors of intractability (Kwan and Brodie, 2000; Sillanpää, 1993).

Table 17.2 Failure to recognize epileptic seizures in the mentally retarded

| Seizures with vertigo          |
| Seizures with paresthesias    |
| Seizures with visceral disturbances |
| Seizures with headache        |
| Seizures with loss of emotional control |
| Partial seizures with other clinical manifestations |
| Supplementary sensorimotor area seizures |
| Simple partial seizures       |
| Absence seizures              |
| Drop attacks                  |
| Automatisms                   |
Most of the untoward effects are not as readily recognized in mentally retarded as in mentally normal patients. These patients may also be at higher risk for certain adverse effects of antiepileptic therapy, such as reduced bone density (Andress et al., 2002; Tolman et al., 1975). Pharmacokinetics of antiepileptic drugs may be affected in many ways. Administration of the drugs may be complicated by the reluctance of the patient to take the pills, or decreased absorption due to slow bowel movements and constipation. Elimination of drugs metabolized by the liver may also be altered due to changes in genetic capacity, especially in inborn errors of neurometabolism.

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**Table 17.3** Differential diagnosis of non-epileptic seizures in the mentally retarded

<table>
<thead>
<tr>
<th>Cardiovascular mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile syncope</td>
</tr>
<tr>
<td>• Breath-holding spells</td>
</tr>
<tr>
<td>– Cyanotic infantile syncope</td>
</tr>
<tr>
<td>– Reflex anoxic seizures</td>
</tr>
<tr>
<td>• Syncope in older children</td>
</tr>
</tbody>
</table>

**Paroxysmal movement disorders**

<table>
<thead>
<tr>
<th>Infantile jitteriness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign myoclonus of early infancy</td>
</tr>
<tr>
<td>Hyperekplexia</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Paroxysmal dystonia/choreoathetosis</td>
</tr>
<tr>
<td>Shuddering attacks</td>
</tr>
<tr>
<td>Stereotypic movements</td>
</tr>
<tr>
<td>Alternating hemiplegia of childhood</td>
</tr>
<tr>
<td>Masturbation</td>
</tr>
<tr>
<td>Stool withholding activity and constipation</td>
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</tbody>
</table>

**Psychological disorders**

<table>
<thead>
<tr>
<th>Psychogenic or pseudoseizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Münchhausen by proxy</td>
</tr>
</tbody>
</table>

**Migraine and migraine equivalents**

| Recurrent abdominal pain       |
| Basilar migraine               |

**Sleep disorders**

| Arousal disorders              |
| REM sleep disorders            |

REM, rapid eye movement.
involving the liver. Epilepsy in mental retardation commonly presents with several seizure types, drug resistance, concomitant psychiatric symptoms and syndromes with various enzyme abnormalities, which increase the risk of interactions. Often, polytherapy in mentally retarded patients with epilepsy can be reduced successfully (Bennett et al., 1983). In a 10-year study in 244 institutionalized patients, the percentage of patients receiving monotherapy could be increased from 36.5% to 58.1% with no observed loss in seizure control (Pellock and Hunt, 1996). Whenever polytherapy is reduced, it is important to keep in mind that existing pharmacokinetic interactions are reversible upon removal of the drug responsible for the interaction.

**Table 17.4 Intractability of epilepsy in the mentally retarded**

<table>
<thead>
<tr>
<th>Physician related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect diagnosis</td>
</tr>
<tr>
<td>Misclassification of epilepsy</td>
</tr>
<tr>
<td>Failure to recognize all seizure types</td>
</tr>
<tr>
<td>Failure in choice of drug</td>
</tr>
<tr>
<td>Failure to recognize seizure freedom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compliance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epilepsy related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe early infantile encephalopathies</td>
</tr>
<tr>
<td>Minor motor seizures</td>
</tr>
<tr>
<td>Complex partial seizures</td>
</tr>
<tr>
<td>Atonic seizures</td>
</tr>
<tr>
<td>Multiple seizure types</td>
</tr>
<tr>
<td>Organic etiology of epilepsy</td>
</tr>
<tr>
<td>Progressive etiology of seizures</td>
</tr>
<tr>
<td>Non-epileptic seizures</td>
</tr>
<tr>
<td>Concomitant non-epileptic seizures</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Drug related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems in ingestion of drug</td>
</tr>
<tr>
<td>Lack of good early effect of therapy</td>
</tr>
<tr>
<td>Side effects of single drug therapy</td>
</tr>
<tr>
<td>Side effects of polytherapy</td>
</tr>
<tr>
<td>Drug interactions</td>
</tr>
<tr>
<td>Deviating drug kinetics</td>
</tr>
</tbody>
</table>

Phenobarbital

Phenobarbital (and other barbiturates) has been used for almost one century for its good anticonvulsive efficacy. Phenobarbital (and primidone, the main active
metabolite of which is phenobarbital) is considered to typically affect cognition, behavior and affect in mentally normal people. Combination of valproate with phenobarbital therapy results in elevated phenobarbital levels, due to inhibition of phenobarbital hydroxylation, with subsequent somnolence and even coma or hyperkinesis, aggressive bursts and insomnia (Bruni et al., 1980). Inversely, phenobarbital accelerates the metabolism of valproate, thus lowering valproate levels in relation to the dose. The metabolism of cimetidine, used against peptic ulcer, which is not so uncommon in the mentally retarded, may be induced by phenobarbital with subsequent decreased blood levels (Somogyi and Gugler, 1982). Because of its potential adverse effects, phenobarbital cannot be recommended as the first or second choice of drug for epileptic seizures associated with mental retardation.

**Phenytoin**

Along with phenobarbital, phenytoin was for decades the most important tool against seizures in the mentally retarded. Phenytoin therapy is not easily managed because of its saturation kinetics, marked differences in attaining steady-state levels in the blood and in other features of metabolism, and certain pharmacokinetic interactions which may in some cases result in toxic levels of phenytoin. Combined with primidone, phenytoin may cause phenobarbital intoxication by causing a marked rise in the ratio of phenobarbital to primidone (Fincham and Schottelius, 1989).

The most serious groups of side effects include neurological adverse effects. Brain damage, which is commonly associated with mental retardation, and phenytoin in polytherapy further increase the risk for neurological adverse effects at therapeutic or even low levels of plasma phenytoin (Iivanainen, 1998). A chronic and in the mentally retarded often irreversible syndrome of phenytoin encephalopathy was seen in 28% (Iivanainen et al., 1977).

Phenytoin can no longer be recommended as the first or second drug of choice against epileptic seizures associated with mental retardation. This is particularly true when the patient has primary locomotion disorder or evidence of cerebellar disease.

**Valproate**

Valproate is a major antiepileptic drug with a broad spectrum, which is an advantage because it can cover several types of seizure so typical of the many mentally retarded. Seizure freedom is achieved by 20–70% of children with mental retardation and infantile spasms (Friis, 1998), and one-fifth of those with Lennox–Gastaut syndrome (Covanis et al., 1982; Henriksen and Johannessen, 1982) become seizure-free on a high-dosage valproate monotherapy. Valproate may have a clinically significant displacing effect on phenytoin and can cause phenytoin intoxication due to high free levels of phenytoin, even in the presence of therapeutic total levels (Wilder and
Valproate can significantly elevate levels of phenobarbital (also derived from primidone), ethosuximide and lamotrigine. The risk of death from liver failure is highest in children who are less than 2 years of age, especially among those with mental retardation, genetic metabolic disorders, brain injury or a family history of severe hepatic disease and/or who are receiving valproate in polytherapy (Bryant III and Dreifuss, 1996).

**Carbamazepine**

Carbamazepine is effective against focal and generalized seizures. It is not effective against atypical absence, atonic and myoclonic seizures, and may even cause or increase these seizures, which are common in mentally retarded patients. Neurotoxicity is for the most part dose related. Though negative behavioral effects are in general fewer on carbamazepine than on phenytoin, phenobarbital or primidone, they may occur in mentally retarded patients and particularly in those with brain damage and those with pre-existing behavioral problems (Alvarez et al., 1998; Friedman et al., 1992; Reid et al., 1981).

Carbamazepine levels are lower but carbamazepine-epoxide concentrations are higher in combination therapy with phenobarbital, phenytoin, primidone and valproate than in monotherapy. But carbamazepine and epoxide levels do not appear to be affected by newer anticonvulsants. Increasing displacement of carbamazepine from plasma proteins increases free fraction of carbamazepine during valproate co-medication (Haidukewych et al., 1989). In case of co-medication with felbamate, lamotrigine, phenobarbitone, phenytoin, primidone, pregabide and valnoctamide, carbamazepine-epoxide concentrations may reach toxic levels. Carbamazepine combined with valproate appears to have synergistic effects in frontal and temporal focal seizures (Gupta and Jeavons, 1985).

**Oxcarbazepine**

Oxcarbazepine is similar to carbamazepine in its mode of action and efficacy against epileptic seizures. Few data are available on its efficacy in people with mental retardation. Given as adjunctive therapy for difficult-to-treat patients with mental retardation, a 50% or greater decrease in seizure frequency has been achieved in 50–60% of patients (Gaily et al., 1997; Sillanpää and Pihlaja, 1988/1989; Singh and Ramani, 2001). The tolerability of oxcarbazepine is better and interactions are less frequent than those observed with carbamazepine, with the exception of higher frequency of hyponatremia. Electrical status epilepticus in sleep may occur during oxcarbazepine therapy in the mentally retarded. Oxcarbazepine has not shown any significant autoinduction or interactions with other drugs (Baruzzi et al., 1994), and may therefore be a useful drug for polytherapy in the treatment of difficult-to-treat seizures.
Benzodiazepines

Benzodiazepines are in most cases used as an adjunctive therapy, for example in children with Lennox–Gastaut syndrome or other epilepsy types with mental retardation. Clinically relevant interactions of benzodiazepines are rare, if any. In some patients, however, adjunctive therapy with clonazepam may cause toxic levels of phenytoin (Isojärvi and Tokola, 1998). The incidence of tolerance is higher in patients with clonazepam-treated West syndrome or Lennox–Gastaut syndrome than in epilepsy with typical absence seizures (Specht et al., 1989). Interactions with other drugs are based on pharmacodynamic influences. A combination with other CNS-depressant drugs may increase depression (Haefely, 1989).

Vigabatrin

Vigabatrin proved to be an efficient drug against difficult-to-treat seizures in people with mental retardation (Pitkänen et al., 1993) and particularly in children with infantile spasms, with a 50% or greater decrease in seizure frequency in two-thirds (Chiron et al., 1991). Vigabatrin does not cause excessive behavioral disturbances in mentally retarded patients (Pitkänen et al., 1993). Hyperactive agitation or aggression, on the other hand, have been observed in up to 15–26% of pediatric patients (Dulac et al., 1991; Uldall et al., 1991). Myoclonic jerks may be provoked by vigabatrin, necessitating discontinuation of the drug (Dean et al., 1999).

The good efficacy of vigabatrin on seizures (Kälviäinen et al., 1995) is shadowed by recent observations of visual field constriction, which occurs in one-third (Kälviäinen and Nousiainen, 2001), is caused by accumulation of vigabatrin in the retina (Sills et al., 2001), and appears irreversible (Nousiainen et al., 2001). The benefits, however, outweigh the risks and the therapy can be continued under strict clinical control (Paul et al., 2001). This is particularly true for infantile spasms due to tuberous sclerosis (Harding, 1998). Vigabatrin has not been found to be involved in any pharmacokinetic interaction.

Lamotrigine

The antiepileptic efficacy of lamotrigine is similar to that of other major antiepileptic drugs in placebo-controlled studies. In a retrospective evaluation of 44 institutionalized patients with mental retardation (Gidal et al., 2000), lamotrigine, added to other antiepileptic drug therapy, decreased seizure frequency by 50% or more in 55% of the patients with mental retardation (Beran and Gibson, 1998). Addition of lamotrigine to carbamazepine may accentuate or cause carbamazepine side effects, such as dizziness, diplopia and sedation which are subjective symptoms, and may present as behavioral disturbances in the mentally retarded (Besag et al., 1998a). The most important effect of other antiepileptic drugs is inhibition of lamotrigine metabolism by valproate and the acceleration of lamotrigine metabolism by
enzyme-inducing antiepileptic drugs. Methsuximide lowers lamotrigine to a clinically significant extent and this must be considered in the dosing of lamotrigine (Besag et al., 1998b). Several other papers have reported favorable effects on seizure frequency (Buchanan, 1995), cognition and behavior (Meador and Baker, 1997), and quality of life (Nadarajah and Duggan, 1995) and less successful involvement of behavior (Beran and Gibson, 1998; Davanzo and King, 1996).

**Gabapentin**

Gabapentin has been shown to be effective as an adjunct on refractory partial-onset seizures. Eleven (42%) of 26 children with mental retardation experienced a 50% or greater decrease in seizure frequency on gabapentin add-on therapy. The response did not differ from that of mentally normal study subjects (Khurana et al., 1993; Mikati et al., 1998). Gabapentin has an effect on focal seizures but not on myoclonic, atonic or absence seizures. With regard to adverse effects, 16% of 110 mentally retarded people showed aggressiveness, 15% had increase in seizure frequency, and 9% had ataxia or lethargy (Mayer et al., 1999). Mikati et al. (1998) reported behavioral adverse changes in 58% of 26 mentally retarded children. In one study, gabapentin was shown to extend the elimination half-life of felbamate by a 50% (Hussein et al., 1996). No other interactions involving gabapentin have been described.

**Tiagabine**

Tiagabine, another GABAergic antiepileptic drug, is in many respects similar to gabapentin. According to a meta-analysis (Marson et al., 1997), the chance for at least 50% reduction in seizure decrease was three-fold with add-on tiagabine than without. No separate data on mentally retarded patients are so far available. Lack of clinically relevant cognitive adverse effects may encourage tiagabine trials in mentally retarded individuals. On the other hand, dizziness, asthenia, nervousness, abnormal thinking, depression, aphasia and abnormal abdominal pain are significantly more common compared with placebo. Three patients with tiagabine-associated encephalopathy have been reported (So et al., 2001). The elimination of tiagabine is accelerated by enzyme-inducing antiepileptic drugs, but tiagabine does not seem to affect the pharmacokinetics of any other drugs.

**Topiramate**

The meta-analysis of six pooled double-blind, placebo-controlled studies on the effectiveness of topiramate on partial-onset seizures (Reife et al., 2000) showed that the seizure frequency had decreased by at least 50% in 43% of 527 patients, compared with 12% on placebo. In 98 patients with Lennox–Gastaut syndrome,
Topiramate decreased the frequency of both drop attacks and generalized tonic-clonic seizures in every third patient, whereas the same effect occurred in only every eighth patient on placebo (Glauser et al., 2000). Interactions affecting other drugs are negligible due to predominantly renal excretion and low protein binding, but the half-life of topiramate is shortened by enzyme-inducing antiepileptic drugs such as carbamazepine, phenytoin, phenobarbital and primidone. Side effects during topiramate therapy include dizziness, fatigue, visual disturbance, diplopia, ataxia, psychomotor slowing, weight decrease and, in rare cases, renal stones, and hypohidrosis.

**Felbamate**

When felbamate was launched, it soon appeared effective in patients with, among other conditions, the Lennox–Gastaut syndrome and infantile spasms (The Felbamate Study Group, 1993). Dangerous adverse effects, mainly aplastic anemia and liver failure, have greatly restricted its use. Felbamate has also several interactions with other drugs. It increases significantly carbamazepine epoxide, phenobarbital, phenytoin and valproate plasma levels and decreases total carbamazepine concentrations. Both carbamazepine and phenytoin induce felbamate metabolism and hence increase its clearance. For the moment, felbamate can only be used in well-selected patients under strict and individualized control.

**Zonisamide**

Few data are available on the efficacy of zonisamide in patients with mental retardation and refractory seizures. Inuma et al. (1998) reported a more than 50% decrease in seizure frequency in 67% of mentally normal and in 41% of retarded patients. Adverse effects were as common in the retarded as in the mentally normal children (27% vs. 30%). The most common untoward effect was aggravation of seizures, which was more common in the mentally normal than in the retarded (28% vs. 18%), and drowsiness. No data on antiepileptic drug interactions were reported. Zonisamide does not induce or inhibit other drugs but its half-life is shortened in humans by enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin and valproate (Sackellaes et al., 1985).

**Levetiracetam**

Levetiracetam, a novel broad-spectrum antiepileptic drug, is effective against focal and generalized seizures. In three multicenter, double-blind, placebo-controlled studies (Ben-Menachem and Falter, 2000; Cereghino et al., 2000; Shorvon et al., 2000), about one-third of 904 patients with partial-onset, drug-refractory seizures achieved an at least 50% overall decrease in seizure frequency. The tolerability was
good. According to existing data, no interactions can be anticipated in clinical use (Patsalos, 2000). The place of levetiracetam in the treatment of seizures in the handicapped and mentally retarded patient remains to be established.

Outcome of epilepsy in the mentally retarded

The outcome of drug therapy may be difficult to assess in the mentally retarded, for example in patients with infantile spasms. Video electroencephalograph (EEG) monitoring may be needed for this purpose. Most of the few population-based studies dealing with the prognosis of epilepsy in the mentally retarded show a less favorable seizure outcome (seizure freedom in 38–46%) than in mentally normal patients (65–89%) (Aicardi, 1986; Brorson and Wranne, 1987; Wakamoto et al., 2000). In another recent long-term follow-up prospective study (Sillanpää, to be published), 34% of patients with epilepsy and mental retardation and 67% of patients with uncomplicated epilepsy became seizure-free. The prognosis is better, the higher the intelligence level (Goulden et al., 1991; Rowan et al., 1980; Sillanpää, to be published). Additional predictors of poor outcome are symptomatic etiology, association of cerebral palsy and perinatal brain injury.

Conclusion

Epilepsy is a common concomitant disorder in people with mental retardation. The diagnosis of epilepsy may be more difficult, because epilepsy in the mentally retarded often presents with several seizure types. The differential diagnosis between epileptic and non-epileptic events may also at times cause difficulties. In many patients, epileptic and non-epileptic seizures may co-occur. The effects of medication are difficult to evaluate, not least due to impaired abilities of these individuals to express themselves about perceived side effects. Video EEG monitoring may be needed. The responses to antiepileptic drugs may be different from that in mentally normal individuals. Numerous attempts in individual patients to attain seizure freedom or an acceptable level of seizure frequency mostly result in polytherapy and increasing adverse effects. These side effects may result from a different susceptibility of the brain to the drugs, to pharmacokinetic interactions, or to a greater susceptibility to pharmacodynamic interactions. To avoid or minimize these effects, the drugs should be as few as possible and a conversion to monotherapy with a broad-spectrum drug should be preferred when feasible. This seems to be particularly important in patients with mental retardation. The impact of the newer antiepileptic drugs may consist of a better tolerability with fewer interactions.
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Antiepileptic drugs and sex steroids

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Background

In 1972 Kenyon sent a letter to the British Medical Journal describing a patient with epilepsy treated with phenytoin (PHT) who became pregnant despite taking usual amounts of oral contraceptive (OC) pills (Kenyon, 1972). She astutely attributed the contraceptive failure to an inductive effect of the PHT on the metabolism of the sex steroid hormones. This observation was soon confirmed by others (Coulam and Annegers, 1979; Janz and Schmidt, 1974) and the underlying mechanisms were further elucidated (Back, 1980). All the older antiepileptic drugs (AEDs), carbamazepine (CBZ), phenobarbital (PB), PHT and primidone (PRM) except valproate (VPA) (Crawford 1986; Sonnen, 1983) were found to have similar effects (Mattson et al., 1986; Schmidt, 1981). In contrast most of the new AEDs with the exception of felbamate (FBM), oxcarbazepine (OXC) and topiramate (TPM) do not change the metabolism of the OCs. Parenteral formulations (intramuscular (i.m.) depot, subcutaneous implant and dermal patch) of contraceptive female sex hormones have also been reported to be subject to increased clearance.

The effect of the AEDs on testosterone metabolism has also indicated changes occur although the evidence of clinical effects is less easily assessed than an unplanned pregnancy. Conversely, except for lamotrigine (LTG) the OCs do not appear to change the pharmacokinetics of AEDs.

Frequency and importance of interactions

Following the initial case report by Kenyon, three other cases of OC failure were cited by Janz and Schmidt (1974). By 1983 Sonnen found that 52 cases had been reported. He concluded that the incidence was probably much higher because 12 women in his own small population had experienced an unplanned pregnancy while using OC pills when taking AEDs (Sonnen, 1983). Although the effect of
CBZ, PB and PHT became established, the exact risk of an unplanned likelihood could only be estimated. The probability approximates that of condom use, a five-to ten-fold increase relative to use of OCs in women not receiving enzyme-inducing drugs (Mattson et al., 1986). Considering the very large usage of OCs, the occurrence of an unplanned pregnancy may be relatively low but the consequences can be of great importance.

The increased clearance of LTG by OCs can result in loss of seizure control or conversely, when OCs are discontinued, overdose of LTG may occur. AED-induced clearance and increased sex-hormone-binding globulin (SHBG) may result in lower free testosterone with resultant decrease in libido, potency and spermatogenesis.

**Awareness of the issues**

On the basis of accumulating reports of OC drug failure the Epilepsy Foundation of America and the American College of Obstetricians and Gynecologists invited us to write a position paper on the problem of unplanned pregnancy associated with the use of AEDs (Mattson et al., 1986). The review with recommendations for management was published in the *Journal of the American Medical Association*, a publication with the widest physician distribution in the USA. It was estimated that failure rates of OC in patients on CBZ, PB, PB and PRM were approximately five-fold the expected numbers. In contrast VPA use, a non-enzyme inducer, was not associated with increased risk of pregnancy (Crawford, 2002; Sonnen, 1983). Breakthrough bleeding, an effect of low estrogen levels, was advised to be a warning sign of insufficient steroid effect. Increasing the strength of the oral steroid was recommended if continuation of an enzyme-inducing AED was deemed clinically advisable. A decade later Krauss et al. (1996) conducted a large survey of licensed neurologists and obstetricians and found approximately a quarter of those surveyed had a patient who had an unplanned pregnancy due to presumed OC failure. A majority did not know which specific AEDs were involved in interactions and did not make an effort to change the dose of the OC. Only 4% of neurologists and none of the obstetricians knew the interactions of all of the AEDs available at that time. Four years later Morrell et al. (1996) in a survey of health care professionals found only a small majority was aware of increased failure rates of OCs with AED use and only 27% could correctly identify the responsible drugs. At about the same time a survey in the UK revealed about half of women receiving AEDs and OC did not receive education about a possible interaction (Crawford, 2002). It may be that the efforts to educate health care professionals and women about these interactions, the consequences and the options are now being heard. Aggressive marketing and educational efforts have been made by a number of organizations and especially by pharmaceutical companies that have introduced new AEDs not having interactions with sex steroid hormones.
Mechanism of interactions and contraceptive failure

Most pharmacokinetic studies have suggested the estrogens and progestins in the OC pill were cleared approximately twice as rapidly in women patients receiving enzyme-inducing AEDs compared to normal controls.

The primary mechanism of action of the contraceptive sex hormones is thought to be due to inhibition of release of luteinizing hormone (LH) by the progestin and prevention of ovulation. The critical concentration of hormones needed to have this effect is not predictable, but the evidence that doubling of hormone clearance has been associated with contraceptive failure indicates a concentration below which failure is possible or likely.

The concentration of contraceptive sex hormones in the blood and brain is determined by a number of pharmacokinetic factors (Emery, 2000). After oral intake, a significant first-pass effect occurs especially for the estrogen component (usually ethinyl estradiol or mestranol). Some conjugation with sulfates and glucuronides occurs in the gut as well as hepatic hydroxylation to inactive polar metabolites (Back et al., 1980). Enterohepatic recirculation of these products may result in change back to ethinylestradiol and reabsorption into the blood. These multiple variables make uncertain the final quantity reaching the general circulation. The major hepatic biotransformation of the estrogen is by the CYP3A4 isoenzyme system. Mestranol is converted to ethinylestradiol, the active drug, by demethylation thought to involve the CYP2C9 isoenzyme. Even in normal women from different populations bioavailability of ethynylestradiol (ethinyl) was found to vary up to ten-fold (Fotherby et al., 1981). (It is unclear if compliance could be assured.) The synthetic progestins used in older OC combination pills are norethindrone and levonorgestrel. More recent formulations have included other progestins, norgestimate (converted in part to levonorgesterol), degestrel and gestodene. The synthetic progestin, medroxyprogesterone, has been and continues to be used extensively although primarily in parenteral formulations. The progestin metabolism is less well defined than the estrogens but conjugation, oxidation and reduction all occur and can be induced by the AEDs (Emery, 2000).

CBZ, PB, PRM (that is metabolized to PB) and PHT have inductive effects on the CYP isoenzymes as well as conjugation involved in sex steroid metabolism. Although having lesser inductive effect, FBM, OXC and TPM can all increase clearance of sex steroid hormones in contraceptive preparations. In contrast, VPA as well as many of the newer AEDs, gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), tiagabine (TGB) and vigabatrin (VGB) have no effect on sex steroid clearance.

The progestins undergo both oxidation and reduction as well as conjugation after entering the circulation. First-pass effect is much more extensive for norethindrone.
than levonorgesterol. Since the older enzyme-inducing AEDs increase clearance of these sex steroids the amount circulating in the blood and brain may reach levels too low for the progestin to inhibit ovulation, especially in formulations containing 50 μg of ethinylestradiol or less (and comparable but higher doses of the pro-drug, mestranol) and 1 mg of levonorgesterol. After entering the circulation the sex steroids are protein bound. The progestins are extensively bound to SHBG. This is relevant because the enzyme-inducing AEDs increase the amount of SHBG, which in turn effectively reduces the free, pharmacologically active, circulating progestin. This represents a second mechanism for OC failure.

Specific AED interactions with OCs

Among the older AEDs, CBZ, PB, PRM and PHT have specifically been found to increase clearance of the OC sufficiently to reduce sex hormone levels by approximately 50% (Back et al., 1980; Coulam and Annegers, 1979; Crawford et al., 1986; 1990; Janz and Schmidt, 1974; Kenyon, 1972; Mattson, 1985; Schmidt, 1981; Wilbur and Enson, 2000) whereas VPA had no such effect (Crawford, 2002; Sonnen, 1983). Among the new AEDs introduced since the 1990s GBP (Eldon et al., 1998), LTG (Holdich et al., 1991), LEV (Ragueneau-Majlessi et al., 2002), TGB (Mengel et al., 1994) and VGB (Bartoli et al., 1997) have been studied and found to have no significant effect on clearance of the OCs. In addition progesterone levels did not rise during the luteal phase in the studies of LTG, LEV or TGB, a finding that confirmed the prevention of ovulation. FBM administration had modest effect on clearance of ethinylestradiol but lowered the area under the curve (AUC) of gestodene, a newer synthetic progestin, by 42%. However, progesterone levels did not rise during the luteal phase suggesting ovulation had been blocked (Saano et al., 1995). Somewhat surprisingly OXC, a relatively non-CYP-inducing newer AED, had clear effect on clearance of OCs. Even in doses as low as 600 mg/day the AUC of both ethinylestradiol and levonorgestrol were reduced by 47% (Fattore et al., 1999). The risk of contraceptive failure must be considered in view of the interaction.

The interaction between TPM and OCs is more complex. In an initial study Rosenfeld et al. (1997) studied the effect of TPM 200, 400 or 800 on the metabolism of OCs containing 35 μg of ethinylestradiol and 1 mg of norethindrone. Although norethindrone was not affected, ethinylestradiol clearance increased 15–33%. A follow up study was done using lower doses that are now more commonly used. Administration of 50, 100 or 200 mg of TPM in women using the same OC did not significantly reduce concentrations of ethinylestradiol in the blood. In contrast a control group given 600 mg of CBZ exhibited an increase of oral clearance of norethindrone by 69% and ethinylestradiol by 127%. It was concluded a clinically
significant interaction of TPM with a ‘standard’ OC did not occur at doses of 200 mg/day or less (Table 18.1).

**Table 18.1  Effect of AEDs on OC clearance and effectiveness**

<table>
<thead>
<tr>
<th>Increased</th>
<th>Equivocal</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>FLB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GBP</td>
</tr>
<tr>
<td>PB</td>
<td>TPM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>LTG</td>
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<tr>
<td>PHT</td>
<td>TGB</td>
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<tr>
<td>PRM</td>
<td>ZNS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>VPA</td>
</tr>
<tr>
<td>OXC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>OC clearance increased but ovulation blocked.

<sup>b</sup>OC clearance not significantly increased at doses of 200 mg or less.

<sup>c</sup>Unpublished data from Elan (Eisai).

**Specific AED interactions with parenteral sex steroid administration**

Parenteral administration of synthetic progestins and in particular, medroxyprogesterone (Depo-Provera-Ortho), has been available for decades. The route of administration has the advantage of steady release of hormone and minimizes the risk of non-compliance. We conducted studies giving medroxyprogesterone 10 mg three times daily in an effort to achieve amenorrhea to adequately assess any antiepileptic effect (Mattson et al., 1984). Blood mycophenolic acid (MPA) levels (determined by Upjohn Co.) were only about one-half (3–15 ng/ml) compared to normal controls (5–30 ng/ml). To assure compliance and avoid first-pass effect six patients were given 120 mg or 150 mg i.m. medroxyprogesterone (Depo-Provera, Upjohn Co.). Again concentrations in the blood ranged from 1–9 ng/ml (mean 2.6 μg/ml) compared to 5–10 μg/ml for controls. This suggested increased clearance secondary to use of enzyme-inducing AEDs. Although these lower MPA blood levels were found, the dose still sufficed to produce amenorrhea and inhibition of a rise in either estrogen or progesterone. A combination of medroxyprogesterone combined with a pro-drug of estradiol cypionate (Lunelle, Upjohn) has recently become available for contraceptive use. A dermal patch containing norelgestromin and ethinylestradiol (Ortho-Evra) has also become available. Although specific reports are not available, it can be inferred that increased clearance will occur with concomitant use of enzyme-inducing AEDs with an increased risk of contraceptive failure. A subcutaneous implant slow-release formulation of levonorgesterol (Norplant) has been used with excellent contraceptive effects but numerous failures have been reported in women on enzyme-inducing AEDs (Haukkamaa, 1986; Krauss et al., 1996; Odlind and Olsson, 1986). Wyeth no longer manufactures this
product. It can be predicted that increased clearance of all these parenteral products can be expected along with decreased efficacy despite avoiding first-pass effect.

**Testosterone**

Testosterone is produced in the Leydig cells of the testis. Testosterone is highly bound to proteins in the circulation primarily to SHBG. Testosterone is metabolized to dihydroxytestosterone that is physiologically active. Conversion to estrogen occurs in tissues in the body by an aromatase. Many investigators have reported that total and free testosterone levels are below normal in men with epilepsy (Bauer et al., 2004; Isojarvi et al., 1990; 1995; 2004; Macphee, 1988; Mattson and Cramer, 1985). The enzyme-inducing AEDs can not only increase clearance of testosterone, but increase SHBG resulting in lower free testosterone levels (Isojarvi et al., 1990; 1995; 2004). The effect of AED use on testosterone is more difficult to characterize clinically. Testosterone affects libido, potency and spermatogenesis and can lead to disturbances in these functions if amounts are deficient. However, determinants of libido and potency are multi-factorial so attributing dysfunction to low testosterone associated with AED use is more difficult to establish. This is in contrast to the obvious endpoint of unplanned pregnancy with use of OCs. However, Fenwick et al. (1986) were able to correlate erectile dysfunction with low testosterone levels using penile tumescence measurements.

**OC effect on LTG**

In a study of LTG levels during delivery, in the neonate and during lactation, Ohman et al. (2000) found that LTG levels at delivery were markedly lower than pre-pregnancy and 2–3 weeks post partum. Although many reasons can be found for a reduction in AED levels during pregnancy, such changes were not seen in patients also taking CBZ or PHT. They concluded that, glucuronidation was induced by the elevated sex steroid hormones present during pregnancy. This finding was confirmed by Tran et al. (2002), who did LTG clearance studies before, during and after delivery. They found a 65% increase in clearance during the first trimester of pregnancy. Sabers et al. (2001, 2003) reported a marked decrease (mean 49%) in LTG levels after initiating OC treatment in seven epilepsy patients and return after discontinuing the OCs. They concluded that the OCs act on the glucosonyltransferases which catalyzed the conjugation of LTG with glucuronic acid. This initial observation was confirmed in a larger series of 56 women receiving OCs and LTG. A two- to three-fold change in levels, was associated with adding or discontinuing OCs. In these two reports the changes resulting in a drop in LTG levels were sometimes associated with an increase or breakthrough in seizures or adverse effects when LTG levels rose with OC discontinuation.
Management of women on OC

The safest way of dealing with the problem of unwanted loss of OC effectiveness is to avoid AEDs that affect the clearance of sex steroids. Before the introduction of the newer AEDs, VPA was the obvious choice. Unfortunately, if a woman elected to become or accidentally became pregnant, the concern about possible teratogenicity was of critical importance. Knowing the effect of an AED on sex hormone clearance allows some ability to predict the likelihood of success or failure of a contraceptive therapy. A second, but undependable, indicator of inadequate hormone effect is breakthrough bleeding. Sonnen (1983) observed 60–90% of 133 women taking OCs containing 30 or 50 μg of ethinylestradiol had breakthrough bleeding, whereas this bleeding occurred in only 6% of those taking VPA. A better measure of contraceptive effect is the absence of a rise in progesterone above 5 ng/ml during the luteal phase of the menstrual cycle. The limitation to this method of detection of a contraceptive steroid effect is timing of the day of the blood sample for analysis, unless samples are drawn every few days.

A change in the strength of the OC pill may compensate for increased clearance by the enzyme-inducing AEDs and provide a sufficient amount in the blood to allow adequate protection (American Academy of Neurology, 1998).

It is possible that increasing the quantity of ethinylestradiol from 20 or 30 μg to 50 μg (and the combined progestin) is insufficient. Krauss et al. (1996) pointed out that two of five unplanned pregnancies they observed were taking an OC containing 50 μg of ethinylestradiol. Sonnen (1983) observed that increasing the dose to 75 μg corrected breakthrough bleeding in his patients on enzyme-inducing AEDs. Since the bioavailability of the OCs is so variable, it may be difficult to predict the dose needed to provide protection and patients need to be advised of this uncertainty.

Summary

Interactions occur between enzyme-inducing AEDs and synthetic sex hormones used for contraception whether given orally or parenterally. The decrease in available hormones is sufficient to lead to contraceptive failure. AEDs also lower free testosterone levels in men and may contribute to problems with libido, potency and fertility. These effects are not seen with use of VPA and the newer AEDs, GBP, LEV, TGB and VGB. Increased clearance and possible loss of contraceptive effect is found with FBM and OXC. No effect is seen with use of TPM at or below 200 mg/day. A reverse interaction is found with use of OCs. These hormones cause increased clearance and loss of effect of LTG. Surveys indicate that a widespread lack of awareness of these issues persists despite original observations made more than three decades ago.


Classification of psychotropic drugs

Antidepressant drugs

Everybody is familiar with the tricyclic antidepressant drugs (TCAs). However, in recent years a number of newer antidepressant drugs have been introduced into clinical practice (Table 19.1). Essentially these are mainly non-tricyclic, earlier variants included mianserin, maprotiline and viloxazine.

The selective serotonin re-uptake inhibitors (SSRIs) are represented by citalopram, fluoxetine, fluvoxamine, sertraline and paroxetine. Of these, citalopram is the most selective on serotonergic uptake, inhibiting serotonin uptake 3000 times more than noradrenaline uptake, and 22 000 times more than that of dopamine. In general, the SSRIs are better tolerated and safer in overdose when compared with tricyclic drugs.

The latest generation of antidepressants has been developed to derive therapeutic benefits from tailor-made actions at specific monoamine receptor and re-uptake sites, in theory providing better efficacy and tolerability.

Reboxetine is a selective noradrenergic re-uptake inhibitor (NARI) with low affinity for histaminergic, cholinergic, dopaminergic and alpha-1 adrenergic receptors. It appears to be equally as effective as the tricyclics in treating depression, and there is a suggestion that it may be more effective than fluoxetine (Montgomery, 1997). Venlafaxine is a serotonin-noradrenergic re-uptake inhibitor (NSRI), which is similar to the earlier generation of antidepressants, but it does not interact with histaminergic or cholinergic receptors, thus diminishing side effects due to those receptor systems. Several studies have indicated equipotentiality or superior effectiveness with this compound compared with tricyclics (Burnett and Dinan, 1994).

Nefadazone is a noradrenaline serotonin re-uptake inhibitor whose most potent action is blockade of 5HT2 post-synaptic receptors, leading to a dual mechanism
Noradrenaline re-uptake inhibition is only minimal, and there is no interaction with histamine or cholinergic receptors.

Mirtazapine, or noradrenaline-specific serotonergic antidepressant has a selective action at alpha-2 adrenoreceptors, and only at some serotonin receptor subtypes. Its actions increase noradrenergic and serotoninergic transmission by blocking the alpha-2 autoreceptors. However, because it also blocks 5HT2 and 5HT3 receptors, the increased serotonin turnover only stimulates 5HT1 receptors. Thus it enhances noradrenergic and 5HT1A mediated serotoninergic neurotransmission. It is free of muscarinic, alpha-1 adrenergic and 5HT2- and 5HT3-related side effects, but its effects on histamine receptors can cause sedation and increased appetite. Several studies have shown equal or superior efficacy of this compound compared with other antidepressants (Bremner, 1995).

Table 19.1 Classification of the psychotropic drugs currently in use

<table>
<thead>
<tr>
<th>Antidepressants</th>
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<tbody>
<tr>
<td>Mono-amino-oxidase inhibitors (IMAOs) – moclobemide</td>
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<tr>
<td>Tricyclic antidepressant drugs (TCAs) – amitryptiline, nortriptyline, clomipramine, imipramine, desipramine</td>
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<tr>
<td>SSRIs – fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram</td>
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<tr>
<td>NARIs – reboxetine</td>
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<tr>
<td>NSRIs – venlafaxine, nefazodone</td>
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<tr>
<td>Typical</td>
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<tr>
<td>Phenothiazines – thioridazine, mesoridazine, chlorpromazine, prochlorperazine</td>
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<tr>
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<tr>
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<tr>
<td>Atypical</td>
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Antipsychotic drugs

As with the antidepressant drugs, in recent years there have been several newer agents introduced into clinical practice. These essentially, with some exceptions, fall into the class of atypical antipsychotics.

The classical neuroleptic drugs, such as chlorpromazine and haloperidol, antagonize dopamine D2 receptors. Their clinical efficacy has been shown to correlate with inhibitory activity at these receptor subtypes. However, these drugs block dopamine receptors in the striatum leading to catalepsy in animal models, and unwanted extrapyramidal side effects in patients.

The new generation of antipsychotic drugs essentially fall into two categories; those that are clozapine related, which included olanzapine and quetiapine, and others such as risperidone.

Although clozapine has been available for many years, it was initially not available for clinical use on account of its potential to produce agranulocytosis. However it has been reintroduced into clinical practice as a model of an atypical antipsychotic. The term essentially relates to the low potential of these compounds to cause extrapyramidal problems, and to have minimum effects on serum prolactin levels. The mechanism of atypicality seems to relate to activity at different receptor subtypes.

In general, the atypical antipsychotics occupy lower levels of D2 receptors than the classical antipsychotics, but one reason for their differing profile may be due to the rapid displacement of these agents from receptors by endogenous dopamine, then thus being more loosely bound to the receptor. The newer antipsychotic agents also have lower relative affinity for striatal D2 receptors as opposed to limbic D2 receptors (dorsal vs. ventral striatum).

Others

The minor tranquilizers mainly in use are the benzodiazepines, but their use in epilepsy is limited. Problems with dependency have led to caution with the use of these drugs, and in epilepsy withdrawal seizures can be a problem. Clobazam, a 1,5-benzodiazepine is used in the management of intractable seizures, and has effective anxiolytic properties.

The mood stabilizers include lithium, which is proconvulsant, and several antiepileptic drugs (AEDs). Of the older generation, carbamazepine (CBZ) and valproic acid have been shown to have antimanic properties and they help in the prophylaxis of mood disorders. Topiramate and lamotrigine are under investigation at the present time for their mood regulating properties. The mode of action on mood is unclear, and it may not be directly related to their antiepileptic properties.

Stimulants include amphetamine and methylphenidate. These are used mainly to control attention-deficit-hyperactivity disorders, which are not uncommon in the learning disabled, many of which patients also have epilepsy.
On the use of psychotropic drugs in epilepsy

It seems accepted that many patients with epilepsy have psychiatric syndromes, and recent epidemiologic evidence from selective clinics suggests that over 50% of patients may have a recognizable psychiatric disorder. It is also known that many patients with epilepsy receive psychotropic drugs, sometimes but not always on account of psychiatric symptoms. However, the effect of these drugs on the seizure threshold is variable, some, such as the benzodiazepines, being anticonvulsant, others, including many antidepressant and antipsychotic drugs, in contrast, are pro-convulsant.

It has been known ever since their introduction that tricyclic drugs are proconvulsant, and lead to seizures, which, for example in overdose, is one method of fatality.

Of the non-tricyclic drugs, both maprotiline and mianserin seem to be at the more proconvulsant end of the spectrum. Of the newer generation of drugs, the SSRIs are considered to provoke less in the way of seizures than tricyclics, and there is a possibility that the even newer, more selective drugs provoke even less in the way of seizures than the SSRIs, but more data on these compounds are needed. The reporting of seizures with all of the new drugs in clinical trials is at very low levels, either similar to, or lower than the less convulsant tricyclics (Hensiek and Trimble, 2001).

As with the newer antidepressants, there is little information about the effect of atypical neuroleptic drugs on the seizure threshold with the singular exception of clozapine. The latter was known to be proconvulsant from early studies, the seizures seemed to be a dose-related effect. The incidence of seizures rises to about 5% at doses of 600 mg, although electroencephalograph (EEG) changes may be recorded at lower doses, these results emerging from patients with schizophrenia, and not epilepsy. The seizures are often myoclonic, but can be generalized tonic/clonic, or partial depending on the individual patient.

It is perhaps of no coincidence, and of considerable interest that clozapine is probably the most effective antipsychotic drug available, reinforcing again a link between seizures and psychosis, and an integral part of neuropsychiatric practice.

Pharmacokinetic interactions between psychotropic drugs and anticonvulsants

The role of CYP450 system on metabolism of psychotropic drugs

The role of the CYP450 enzyme system and glucuronosyltransferases (UGTs) in clinical psychopharmacology is being increasingly recognized (Mula and Monaco, 2002b; Green and Tephly, 1998). Among antidepressants, TCAs, such as amitriptyline, clomipramine and imipramine, are extensively metabolized by CYP1A2, 2D6 and 3A4 (Table 19.2). Nortriptyline and desipramine are, respectively, the active metabolites
Michael R. Trimble and Marco Mula

of amitriptyline and imipramine and are metabolized mainly by CYP2D6. Moclobemide is primarily metabolized by CYP2C subfamily, of which it is probably an inhibitor, while the atypical antidepressants mianserin and trazodone are metabolized by CYP2D6.

The SSRIs, fluoxetine and paroxetine are metabolized by CYP2D6, while sertraline, fluvoxamine and citalopram are respectively metabolized by CYP3A4, 1A2 and 2C. Paroxetine and fluvoxamine are, respectively, inhibitors of CYP2D6 and 1A2 (Table 19.3). In vitro and in vivo data demonstrated a moderate inhibition activity of fluoxetine on CYP2D6 and 3A4, probably mediated by its metabolites. No clinically significant induction–inhibition properties have been demonstrated for sertraline and citalopram.

Among the new generation of antidepressant drugs, venlafaxine is primarily metabolized by CYP2D6, while CYP3A4 metabolizes nefazodone and reboxetine. Nefazodone is a potent inhibitor of this enzymatic pathway.

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Table 19.2 CYP enzymes involved in psychotropic drug metabolism

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP3A4</th>
<th>CYP2C9/10</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td><strong>Antidepressants</strong></td>
<td><strong>Anticonvulsants</strong></td>
<td><strong>Antidepressants</strong></td>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Amitriptyline</td>
<td>Phenytoin</td>
<td>Amitriptyline</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Clomipramine</td>
<td>Imipramine</td>
<td>Clomipramine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Desipramine</td>
<td>Moclobemide</td>
<td>Imipramine</td>
<td>Mianserin</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Imipramine</td>
<td>Venlafaxine</td>
<td>Venlafaxine</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Norclomipramine</td>
<td>Venlafaxine</td>
<td>Norclomipramine</td>
<td>Nefazodone</td>
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<tr>
<td><strong>Antipsychotics</strong></td>
<td><strong>Antipsychotics</strong></td>
<td><strong>Anticonvulsants</strong></td>
<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Chlorpromazine</td>
<td>Haloperidol</td>
<td>Mephenytoin</td>
<td>Chlorpromazine</td>
<td>Iloperidone</td>
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<tr>
<td>Haloperidol</td>
<td>Clozapine</td>
<td>Esobarbital</td>
<td>Thioridazine</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Risperidone</td>
<td>Mepobarbital</td>
<td>Clozapine</td>
<td>Olanzapine</td>
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<tr>
<td>Olanzapine</td>
<td>Ziprasidone</td>
<td>Venlafaxine</td>
<td>Trimipramine</td>
<td>Iloperidone</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Antipsychotics</td>
<td>Venlafaxine</td>
<td>Iloperidone</td>
<td>Quetiapine</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<td>Antipsychotics</td>
<td>Anticonvulsants</td>
<td>Anticonvulsants</td>
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<tr>
<td>Carbamazepine</td>
<td>Antipsychotics</td>
<td>Venlafaxine</td>
<td>Carbamazepine</td>
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Neuroleptics, such as phenothiazines, are metabolized by intestinal sulfoxidases, although CYP2D6 plays an important role in chlorpromazine and thioridazine metabolism. They are also partially metabolized by CYP1A2 and CYP2C, respectively, and partially inhibit CYP3A4. Haloperidol’s metabolism has been studied for more than 30 years. It is metabolized by CYP3A4 and 1A2 and only partially by 2D6.

Among the atypical antipsychotics, clozapine undergoes extensive hepatic metabolism and multiple CYP enzymes are involved, however the two prominent ones are CYP1A2 and CYP3A4.

New antipsychotic drugs usually have better pharmacokinetic profiles. Risperidone is primarily metabolized by CYP2D6, although a correlation study using a panel of human microsomes suggest that CYP3A4 may also be involved. Olanzapine undergoes extensive hepatic metabolism and shares some of its metabolic routes with the structurally and pharmacologically related clozapine, but UGTs appear to be major metabolic pathways. Quetiapine shares some pharmacologic and structural characteristics with clozapine and olanzapine. In vitro studies using human microsomes showed that CYP3A4 is the main isoenzyme involved in quetiapine metabolism.

### Interactions between anticonvulsants and antidepressants

**SSRI–NSRI**

Data about fluoxetine–CBZ interactions are contradictory. Spina et al. (1993) found no modification in CBZ plasma levels before and after fluoxetine administration,
although in a small group of patients. Grimsley et al. (1991) observed a slight increase in CBZ area under curve (AUC) levels and a decrease in 10,11-CBZ-epoxide AUC.

Nelson et al. (2001) studied the inhibition properties of several SSRIs on phenytoin (PHT) metabolism in an in vitro study with human liver microsomes. They suggested that the risk for a PHT–SSRI interaction is highest with fluoxetine and less likely with the others (paroxetine and sertraline).

Andersen et al. (1991) investigated possible kinetic interaction between paroxetine and CBZ, VPA and PHT in a single-blind, placebo-controlled, crossover trial. Paroxetine caused no change in plasma concentrations and protein binding of the anticonvulsants. Studies of paroxetine plasma concentrations are lacking, but the major enzymatic pathway is a non-inducible enzyme (CYP2D6), therefore modifications in plasma levels are unlikely, when co-administrated with AEDs with inducer properties.

Leinonen et al. (1996) observed an increase in citalopram levels when CBZ was substituted with oxcarbazepine in two patients, demonstrating a significant induction effect of CBZ on citalopram metabolism.

Spina et al. (1993) studied the potential interaction between CBZ and fluvoxamine in eight epileptic patients in steady state for CBZ. No significant changes in CBZ and CBZ-10,11-epoxide occurred.

Mamiya et al. (2001) described a single case of PHT intoxication (from 16.6 to 49.1 μg/ml) after fluvoxamine administration. There are no studies of VPA–fluvoxamine interactions.

Not clear is the possibility of an interaction between sertraline and PHT. Haselberger et al. (1997) described an elevation in PHT plasma levels in two elderly patients, but without any symptoms of toxicity, while Rapeport et al. (1996a) demonstrated the absence of any pharmacokinetic interaction in a double-blind, randomized, placebo-controlled study with 30 healthy volunteers.

Kaufman and Gerner (1998) reported two cases of lamotrigine–sertraline interaction, leading to high lamotrigine plasma levels (doubled in the first case and 33% increase in the second one). Rapeport et al. (1996b), in a double-blind, randomized, placebo-controlled study on 14 healthy volunteers, observed no significant effects of sertraline on CBZ pharmacokinetics. Bonate et al. (2000) demonstrated the absence of drug interaction between clonazepam and sertraline in a randomized, double-blind, placebo-controlled, crossover study with 13 subjects.

No clinical studies are available about potential interactions between venlafaxine and AEDs. Toy et al. (1995) demonstrated no pharmacokinetic interactions between venlafaxine and diazepam in a randomized, crossover study with 18 male subjects.

Roth and Bertschy (2001) reported three cases of increased CBZ plasma levels (from 20% to 100%) after nefazodone introduction. Laroudie et al. (2000) investigated
kinetic interactions between nefazodone and CBZ in 12 healthy subjects. They observed a significant decrease in nefazodone AUC and an increase in CBZ AUC, demonstrating a potential inhibition property of nefazodone on CBZ metabolism.

**TCA**

Generally, phenobarbital (PB), CBZ and PHT stimulate the metabolism of TCAs, while VPA can increase their plasma levels (Monaco and Cicolin, 1999). Wong et al. (1996) investigated the effect of VPA on amitriptyline and its active metabolite (nortriptyline) in an open-label study. The mean AUC and the peak plasma concentration, for the sum of nortriptyline and amitriptyline, were 42% and 19% higher. Fehr et al. (2000) reported the increase in serum clomipramine levels when coprescribed with VPA.

Szymura et al. (2001) investigated the effect of CBZ on imipramine and desipramine serum concentrations in 13 patients with major depression. They demonstrated that CBZ affects not only the metabolism of both TCAs but also their protein binding, leading to a significant increase in the free fraction. Because of this phenomenon, a modification in imipramine dosage regimen does not seem to be necessary in practice. Conversely, Van Belle et al. (1995) demonstrated a significant inhibition in CBZ metabolism by clomipramine in rats.

**Others**

Ketter et al. (1995) investigated the safety and efficacy of CBZ-moclobemide cotreatment in a double-blind study. The combination was well tolerated with no modifications in CBZ kinetics, but they did not assess moclobemide plasma concentrations.

Nawishy et al. (1981) investigated the presence of kinetic interactions between mianserin and three commonly prescribed anticonvulsants (PHT, CBZ and PB). All of them are inducers of the CYP450 enzyme system. They observed a significant reduction in mianserin plasma concentrations.

The use of bupropion is limited by the high seizure risk. CBZ is a potent inducer of its metabolism, taking the antidepressant plasma concentrations to undetectable levels. On the other hand, bupropion has shown marked inhibition properties, increasing VPA levels when prescribed in cotherapy (Popli et al., 1995), and Tekle and al-Kamis (1990) suggested a potential inhibition property of bupropion on PHT metabolism. Odishaw and Chen (2000) investigated the effect of steady state slow release bupropion on the pharmacokinetics of lamotrigine in a randomized, open-label, crossover study with 12 healthy subjects. The kinetic parameters of a single 100-mg lamotrigine dose were not modified significantly.
Interactions between anticonvulsants and antipsychotic drugs

Phenothiazines–butyrophenones

Thioridazine is metabolized by intestinal sulfoxidases that are induced only partially by AED inducers such as CBZ, PHT and PB but some authors have reported an increased clearance of thioridazine and a relevant decrease of mesoridazine (the active metabolite of thioridazine) in patients taking CBZ and/or PHT (Ellenor et al., 1978; Linnoila et al., 1980). On the other hand, thioridazine, as chlorpromazine and prochlorperazine, inhibits PHT (Vincent, 1980; Kutt, 1984), PB (Gay and Madsen, 1983) and VPA (Guengerich, 1997) metabolism.

Several studies have shown that haloperidol plasma levels decrease by 50–60% after CBZ co-administration, with concomitant worsening of the psychiatric clinical features (Kidron et al., 1985; Jann et al., 1985; Arana et al., 1986). Hirokane et al. (1999) evaluated haloperidol levels in patients comedicated with CBZ or PB. In the first group plasma levels were 37% lower; in patients treated with PB they were 22% lower. Interestingly, Iwahashi et al. (1995) observed that serum CBZ concentrations in patients treated without haloperidol were significantly decreased (on average 40%), compared to those treated with both CBZ and haloperidol. Hesslinger et al. (1999) compared the effects of CBZ and VPA cotreatment on the plasma levels of haloperidol and on the psychopathologic outcome in schizophrenic patients. VPA had no significant effects on haloperidol plasma levels and it was associated with a better psychopathologic outcome. Doose et al. (1999) investigated the effect of topiramate on haloperidol pharmacokinetics in healthy volunteers, observing no clinically significant interactions.

Benzisoxazoles and benzisothiazoles

Preliminary evidence from drug monitoring studies and case reports (Bork et al., 1999; Spina et al., 2000) demonstrated that CBZ might cause a prominent decrease in plasma concentrations of risperidone. Spina et al. (2000) compared the risperidone total active moiety (risperidone plus its active metabolite – TAM) steady state plasma concentrations in patients treated with risperidone alone and in patients comedicated with CBZ or VPA. Unlike CBZ, VPA (at dosages up to 1200–1500 mg/day) had minimal and clinically insignificant effects on plasma levels of risperidone TAM, suggesting that VPA could be added safely to an existing treatment with risperidone. Ono et al. (2002) evaluated the relationship between CYP2D6 genotype and the pharmacokinetic interaction with CBZ, suggesting that the decrease in risperidone concentration is dependent on the CYP2D6 activity. Recently, an open study described a mild increase in CBZ plasma levels in eight patients with epilepsy after addition of risperidone 1 mg, suggesting that the antipsychotic, or more likely its metabolites, could modulate CYP3A4 activity.
Interestingly, Furukory et al. (2001) demonstrated a different enantioselective 9-hydroxylation of risperidone by CYP2D6 and CYP3A4. In the literature, there is no information about differences in pharmacologic activity of these two enantiomers.

Ziprasidone and perospirone are newly available antipsychotic drugs and there are few clinical studies about their interactions. Miceli et al. (2000) studied the effect of CBZ on steady-state ziprasidone in healthy volunteers in an open, randomized, parallel-group study. They observed a clinically insignificant reduction (<36%) in steady-state ziprasidone levels.

**Thienobenzodiazepine, dibenzothiazepine and dibenzothiazepine derivatives**

Generally, PHT, PB and CBZ (Facciola et al., 1998; Prior et al., 1999) cause a decrease in clozapine plasma concentrations. However, CBZ is rarely used in combination with clozapine because of the high risk of hematologic side effects. Existing data on the effect of VPA co-administration are contradictory (Centorrino et al., 1994; Costello and Suppes, 1995; Longo and Salzman, 1995; Facciola et al., 1999). According to some authors, VPA has a moderate inhibiting effect on the demethylation of clozapine (catalysed by CYP1A2 and 3A4) but, in two small studies (Finley and Warner, 1994; Longo and Salzman, 1995) serum concentrations of clozapine and norclozapine (one of clozapine’s metabolites) were found to decrease respectively by 15% and 65%, suggesting induction of clozapine metabolism. Moreover, clozapine disposition is characterized by large individual variability, being affected by age, gender, body weight, dose per kg, smoking habits and ethnicity (Chong and Remington, 1998).

Olanzapine plasma concentrations are decreased by CBZ (Lucas et al., 1998), but the authors did not consider this interaction clinically relevant because of the wide therapeutic index of the antipsychotic. In the literature, there are no controlled studies assessing drug interactions between olanzapine and new AEDs in humans.

Quetiapine is a newly introduced atypical antipsychotic, and clinical data about pharmacokinetic interactions are lacking. Wong et al. (2001) demonstrated that PHT has a marked effect on the metabolism of quetiapine, suggesting that dosage adjustment of quetiapine may be necessary when quetiapine is coprescribed with other AED inducers such as CBZ or PB.

**Interactions between anticonvulsants and anxiolytics**

Generally, anxiolytics have a wide therapeutic index; therefore the clinical relevance of pharmacokinetic interactions is very limited. AEDs with enzyme-inducing properties may stimulate the biotransformation of many benzodiazepines. CBZ has been reported to induce clobazam and diazepam metabolism (Dhillon and Richens, 1981; Levy et al., 1983). CBZ has also been demonstrated to enhance
the clearance of clonazepam and alprazolam (Lai et al., 1978; Furukori et al., 1998). A clinically relevant interaction occurs between AED inducers and midazolam (Backman et al., 1996) that is extensively metabolized by CYP3A4.

**Pharmacodynamic interactions between antiepileptic and psychotropic agents**

**Anticonvulsants and antidepressants**

Antidepressants have been extensively evaluated in relation to the general problem of their proconvulsant activity. But the definition of pharmacodynamic interaction implies that the typical pharmacologic properties of a drug are modified by another drug, without any change in the drug concentration. This definition comprises also side effects such as sedation, confusion, psychomotor impairment and others.

The risk of antidepressant-induced seizures is well known, particularly in people with epilepsy. Most of the data arise from studies using in vitro technique, animal studies and clinical observations (Torta and Monaco, 2002). Among SSRIs, fluoxetine is the most studied drug. It is interesting to note that several studies emphasized the role of serotoninergic transmission in enhancing the anticonvulsant effects of AEDs (Trimble et al., 1977; Yan et al., 1994). Leander (1992) demonstrated, in an animal model of epilepsy, that the selective inhibition of serotonin uptake by fluoxetine can enhance the anticonvulsant potency of PHT and CBZ. Therefore, a favourable pharmacodynamic interaction may be suggested (Table 19.4).

As far as other interactions are concerned, Dursun et al. (1993) reported a single severe case of the serotonin syndrome after fluoxetine was added to carbamazepine. The occurrence of an extrapyramidal syndrome within fluoxetine and AED cotreatment (Gernaat et al., 1991) are described, but clinical studies are lacking.

Two different studies of Rapeport et al. (1996a, b) investigated pharmacodynamic interactions between sertraline and PHT or CBZ. Both of them showed no clinically significant interactions.

**Anticonvulsants and antipsychotic drugs**

Historically, antipsychotic drugs have been considered proconvulsants possibly because of their D2-receptor blocking activity. One of the most important issues in prescribing these two types of drug at the same time is about the effect of antipsychotics on the anticonvulsant effect of AEDs.

To determine the risk for drug-induced seizures we can use different approaches: observational studies (case-control studies and case reports), drug-induced EEG changes, animal models and in vitro techniques in isolated tissue samples. One of the problems of the recent literature is that most of the studies have been
performed on psychiatric patients and, although theoretically correct, it is not known if drug-related seizures in non-epileptic patients predict risk in patients with epilepsy, and if different syndromes of epilepsy have different risks for psychotropic-induced seizures.

Generally chlorpromazine and clozapine are considered proconvulsant in epileptic patients. The former only at high doses (1000 mg/day) and the latter at medium and high doses (>600 mg/day) (Allredge, 1999). Clozapine frequently causes epileptiform EEG changes and seizures in 3–5% of patients treated, even at therapeutic doses. Devinsky et al. (1991) observed a mean prevalence of seizures of 2.9% with clozapine, and considering different doses, the prevalence is respectively 1, 2.7 and 4.4% for doses <300 mg, 300–600 mg or 600–900 mg/daily. Pacia and

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>VPA</th>
<th>PHT</th>
<th>LTG</th>
<th>TPM</th>
<th>PB</th>
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Symbols on the left are referred to antidepressant drug and within brackets to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑, Increased plasma concentration; ↓, decreased plasma concentration; =, unchanged plasma concentration.

*Dosage adjustments are not necessary.

LTG, lamotrigine; TPM, topiramate.

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>VPA</th>
<th>PHT</th>
<th>LTG</th>
<th>TPM</th>
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<td>Fluoxetine</td>
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Symbols on the left are referred to antidepressant drug and within brackets to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑, Increased plasma concentration; ↓, decreased plasma concentration; =, unchanged plasma concentration.

*Dosage adjustments are not necessary.

LTG, lamotrigine; TPM, topiramate.
Devinsky (1994) analysed only patients without a previous history of seizures and the prevalence of seizures was respectively 0.9, 0.8 and 1.5% for the same range of doses of the previous study. Thus, with clozapine this seems to be a dose-related phenomenon but probably the role of the titration time and increase of dose is more important (Langosch and Trimble, 2002).

Olanzapine, quetiapine and risperidone demonstrated an extremely low risk of seizures when compared with haloperidol and can be considered safer (Tables 19.5 and 19.6).

---

### Table 19.5 Risk for seizures exhibited by some antidepressant and antipsychotic drugs

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressant drugs</strong></td>
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<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Amitriptyline</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Imipramine</td>
<td>Trazodone</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Venlafaxine</td>
<td>IMAO</td>
</tr>
</tbody>
</table>

| **Antipsychotic drugs** | | |
| Chlorpromazine (dose related) | Olanzapine | Fluphenazine |
| Clozapine (titration and dose related) | Quetiapine | Pimozide |
| | Haloperidol | Trifluoperazine |
| | | Risperidone |

### Table 19.6 Pharmacokinetic interactions between antiepileptic and antipsychotic drugs

<table>
<thead>
<tr>
<th>CBZ</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
<th>LTG</th>
<th>TPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>↓</td>
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<td>(†)</td>
</tr>
<tr>
<td>Thioridazine</td>
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<td>↓</td>
<td>(†)</td>
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<td>(†)</td>
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<tr>
<td>Mesoridazine</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>=*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↓</td>
<td>(†)</td>
<td>↓</td>
<td>↓</td>
<td>=*</td>
</tr>
<tr>
<td>Clozapine</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>=*</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>↓</td>
<td>↓*</td>
<td>↓*</td>
<td>↑</td>
<td>=*</td>
</tr>
<tr>
<td>Risperidone</td>
<td>↓</td>
<td>(†)</td>
<td>↓*</td>
<td>↓*</td>
<td>=*</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>↓</td>
<td>↓*</td>
<td>↓*</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>↓+</td>
<td>(†)</td>
<td>↓*</td>
<td>↓*</td>
<td>=*</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>↓</td>
<td>↓*</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbols on the left are referred to antipsychotic drug and within brackets to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

†, Increased plasma concentration; ↓, Decreased plasma concentration; =, Unchanged plasma concentration; *Theoretical data, no clinical studies available.
Anticonvulsants and lithium

Lithium carbonate is frequently used for manic episodes in bipolar disorder, in association with valproate and carbamazepine. Carbamazepine also demonstrates antimanic properties, and a possible favourable pharmacodynamic interaction could be suggested, but carbamazepine can increase lithium toxicity as well. Shukla et al. (1984) suggested that CBZ enhanced the development of a lithium neurotoxic syndrome in patients with underlying central nervous system (CNS) disease or metabolic disease. This syndrome is characterized by symptoms such as confusion, drowsiness, lethargy, tremor and cerebellar signs that are typical of both lithium and CBZ toxicity. Therefore, a pharmacodynamic synergic interaction is probable. Kramlinger and Post (1990) studied the effects of this combination in 23 patients with affective disorders. They observed a significant increase in many haematologic parameters (mainly the mean white blood cell count, probably lithium counteracts the neutropenic properties of carbamazepine) and a significant modification in thyroid function with decrease in T4 and freeT4. Another well-known issue is the opposing effects of CBZ and lithium on electrolyte regulation, with the occurrence of severe hyponatremia when lithium alone is stopped (Vieweg et al., 1991).

The combination of lithium and VPA is widely used in rapid cycling, manic, depressive and mixed episodes in bipolar disorder. This combination has a higher tolerability than the co-administered CBZ and a pharmacodynamic synergistic interaction has been suggested (Freeman and Stoll, 1998).

Chen et al. (2000) investigated lithium pharmacokinetics when co-prescribed with lamotrigine in 20 healthy subjects. There were no significant differences in lithium pharmacokinetic parameters.

Conclusions

Several factors must be considered when predicting the outcome of a potential interaction: patient-related (sex, age, ethnicity) and drug-related (the presence of active metabolites, the activity and potency at the enzyme site, the therapeutic window). Clinicians should be aware of these potential interactions especially if the patient shows no response to a psychotropic drug therapy or signs and symptoms of intoxication.

As far as antidepressant drugs are concerned, fluoxetine and nefazodone interactions are probably the most relevant in epilepsy from a clinical point of view. The former for its long half-life and the presence of different enantiomers with different kinetic properties, and the latter for its inhibitory properties on CYP3A4. AED inducers increase the clearance of all the antipsychotic drugs; therefore dosage adjustments are quite often required for antipsychotics.
Careful clinical monitoring and personalized dosages and titration time can usually lower the risk threshold of side effects due to pharmacologic interactions, which is one of the major factors for good clinical practice and patient compliance.

REFERENCES


Antiepileptic drugs in non-epileptic health conditions: possible interactions

Jerzy Majkowski
Center for Epilepsy Diagnosis and Treatment Foundation of Epileptology, Warsaw, Poland

Introduction: AEDs in non-epileptic conditions

Ever since they first appeared, antiepileptic drugs (AEDs) have not infrequently been used to treat patients with conditions other than epilepsy. Some AEDs, e.g. phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA), have for long been indicated in a number of neurological and psychiatric disorders. The same is true for some of the new generation AEDs, such as gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (O-CBZ), tiagabine (TGB), topiramate (TPM) and pregabalin (PGB). It seems that newer AEDs – compared with the older ones – may be at least equally effective in non-epileptic disorders, but with fewer adverse events, and with minimal or no drug interactions. However, it should be stressed that evidence-based medicine varies broadly as far as the efficacy of particular drugs in given disorders or health conditions is concerned. Moreover, the number of reports and trials, and the extent of usage of these drugs vary greatly.

Epilepsy with its prevalence of about 1% is one of the most common neurological conditions. However, because AEDs have been used in several other neurological and psychiatric conditions with a higher prevalence than epilepsy, altogether they present a large market for AED usage. For example, in the United States LTG, TPM and GBP use – in terms of pharmaceutical market (IMS, 2000, 2001, 2002) – is greater for non-epileptic disorders than for epilepsy; moreover, there is an increasing trend for use of TPM and LTG from 2000 to 2002 (Table 20.1). In European countries (e.g. France, Germany, Italy, Spain and UK) GBP use is also greater in other fields than epilepsy, and as in the USA this trend is increasing. Two other AEDs (TPM and LTG) have been, also, showing an increasing use in non-epileptic disorders in Germany and Spain (IMS, 2000, 2001, 2002).

A national survey in the USA showed that approximately 10% of nursing home residents were taking AEDs, usually with other drugs (Cloyd et al., 1994; Lackner et al., 1998). In 18% of the residents receiving AEDs, indications were other than epilepsy. In Poland in 2002, the number of VPA prescriptions for non-epileptic
disorders was about 21% (IMS, Health Poland, 2002). Thus, the term antiepileptic
does not reflect the whole spectrum of these drugs’ potential therapeutic effects.

It is estimated that combination therapy occurs in about 10% of the general
population, and in the elderly and in women the percentage is even higher (Nobili
et al., 1997). Patients over 65 years use 2–6 prescribed medications, and 1–3.4
over-the-counter drugs (Stewart and Cooper, 1994). Therefore, knowledge of possible
drug interactions in non-epileptic patients taking AEDs is just as important as it is
in epileptic patients. Rules for combination therapy and information concerning
possible interactions between AEDs and non-epileptic drugs (non-AEDs) are the
same as those discussed in Chapters 8, 16, 18 and 19.

The purpose of this chapter is to emphasize the spectrum and scale of AED usage
in medical disciplines other than epilepsy, and to increase awareness of unpredicted
drug interactions when combination therapy with two or three drugs is used. As in
the treatment of epilepsy, awareness of possible drug interactions with AEDs is an
important part of the treatment strategy.

**Rationale for using AEDs in disorders other than epilepsy**

There are a number of pharmacological reasons why AEDs have therapeutic effects
in non-epileptic neurological and psychiatric conditions. With the exception of two
AEDs (TGB and vigabatrine (VGB)) that are thought to have a single mechanism
of pharmacological action, all other AEDs have multiple neurophysiological and
neurochemical actions (Macdonald, 1997; Moshè, 2000). Even when various mech-
anisms are involved, the primary mechanism of reducing high frequency firing in
neurones is by enhancing sodium channel inactivation. Indeed, this mechanism

---

**Table 20.1  AEDs used in non-epileptic disorders in 2002 (first 9 months of the year)**

<table>
<thead>
<tr>
<th>AED</th>
<th>Country</th>
<th>Pharmaceutical market</th>
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<tbody>
<tr>
<td>LTG</td>
<td>USA</td>
<td>61%</td>
</tr>
<tr>
<td>TPM</td>
<td>USA</td>
<td>71%</td>
</tr>
<tr>
<td>GBP</td>
<td>USA</td>
<td>85%</td>
</tr>
<tr>
<td>GBP</td>
<td>France</td>
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</tr>
<tr>
<td>GBP</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>Italy</td>
<td>56–89%</td>
</tr>
<tr>
<td>GBP</td>
<td>Spain</td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>UK</td>
<td></td>
</tr>
</tbody>
</table>

*Increasing from 2000 to 2002 (percentages calculated for year 2000–2002, refer to the first 9 months of each year).
may be one of the main reasons for the antineuralgic effects of AEDs in various pain syndromes (Brau et al., 2001; Carter and Galer, 2001). However, AEDs have several other ways of modifying abnormal neuronal activity, presumably involved in a number of neurological and psychiatric disorders, which at first glance are very different from those found in epilepsy. These mechanisms involve: inhibition of the sodium, L-, N-, T-calcium and chloride channels; blockage of the N-methyl-D-aspartic acid (NMDA) receptor, decrease of glutamate release, antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and adenosine receptors, increase in 5-HT release, increase in different modes of operation of gamma-amino butyric acid (GABA) – one of the principal inhibitory neurotransmitters. AEDs have been shown to potentiate GABAergic synaptic transmission either by increasing GABA concentrations through the inhibition of GABA-transaminase (VGB) or GABA up-take (TGB). Other drugs act directly at the synaptic GABA receptor complex (benzodiazepines, PB) or increase GABA concentration in several specific brain regions (VPA) (Löscher, 1999; Macdonald and McLean, 1986). The parallels of the neurochemistry and pathophysiology of epilepsy and chronic pain provide the basis for re-evaluating the use of AEDs in various pain syndromes (Ross, 2000).

Recently, research into the mechanisms of migraine and the progressive recognition that cortical hyperexcitability and an imbalance between neuronal inhibition and excitation (mediated by GABA and amino acids, respectively) may play an important role in migraine pathophysiology, provided rationale for using AEDs in prophylaxis and treatment of migraine and other headaches (Krychmantowski et al., 2002). Quality of evidence-based reviews and guidelines for the efficacy of various AEDs in migraine prophylaxis and in migraine aura therapy have been provided by the American Academy of Neurology (2000) and D’Andrea et al. (2003).

There are also physiological reasons for using AEDs in bipolar psychosis or other recurrent disorders. Ever since Kraepelin (1921), it has been postulated that bipolar affective disorders are of a progressive nature, just like seizures, and a kindling mechanism has been proposed (Post and Weiss, 1989).

**Drug interactions in various health conditions**

In pregnant women serum propranolol concentrations are increased by 50%. However, in hypertensive pregnant women treated with 90 mg of PB, a significant decrease in serum propranolol concentration has been observed, thus suggesting that pregnancy alters the half-life of propranolol therapy associated with PB (Hoffmann-Traeger et al., 1987).

It has also been reported that clearance of LTG in pregnancy may be increased (Tomson et al., 1997). Moreover, in one study LTG plasma concentrations were
slightly lower in females (13.7%) than in males (May et al., 1996). However, in another study this difference was not confirmed (Chen, 2000).

Combination of PB and theophylline results in increased theophylline clearance in children and adults but not in premature neonates (Kandrotas et al., 1990).

Serum concentration of tirilazad mesylate (a membrane lipid peroxidation inhibitor), when given with PB in subarachnoid hemorrhage, may increase by 69% (Fleishaker et al., 1996).

Drugs which compete for albumin bindings may increase the risk of kernicterus, e.g. combination of PB with aminophyline, cefotaxime and vancomycin shows that the bilirubin-displacing effect in the drug combinations cannot be predicted from each drug’s individual effect in premature infants (Robertson and Brodersen, 1991).

Primidone (PRM) withdrawal in a 14-year-old girl with congenital adrenal dysplasia and epilepsy resulted in a three-fold increase of hypercorticolism and a reduction of plasma testosterone and 17 OH progesterone concentrations (Young and Hughes, 1991), thus showing the need to adjust the dose.

In patients with liver cirrhosis grade A, B and C (Child-Hugh classification), the median oral clearance was 0.31, 0.24 and 0.10 ml/min/kg, respectively, in comparison with 0.34 ml/min/kg in normal healthy subjects. Correspondingly, median $T_{1/2}$ of LTG was 36, 60 and 110 h, whereas for patients with normal liver function it was 32 h (Glaxo Wellcome Inc., 1999). LTG dosage must be downwardly adjusted in patients with liver dysfunction.

LTG clearance in patients with hyperbilirubinemia (Gilbert’s syndrome) was 32% lower, and $T_{1/2}$ was 37% longer than in the healthy controls (Posner et al., 1989). Close clinical monitoring of such patients is needed when LTG is administered; possible downward dosage adjustment should be considered.

Clearance of LTG in Asians and non-Whites is lower than in Whites. This difference may have significant clinical relevance for non-Whites if LTG is administered, particularly when it is combined with non-AEDs, which are hepatic enzyme inhibitors.

Renal failure slows down the urinary excretion of prednisone and its metabolites, making dose reduction of corticosteroids necessary. However, combination of prednisone and PB increases excretion of prednisone without any clear change in 17 OH steroids and prednisolone urinary excretion (Perignon et al., 1985). This drug interaction is associated with a decrease of graft tolerance in renal transplant patients.

It is interesting to note that serum VPA concentrations are higher in uremic serum than in normal serum, but there is no further displacement of VPA in the presence of mefenamic acid or fenoprofen. However, when uremic serum is treated with charcoal at pH 3.0, it removes the protecting effect of uremic serum, and VPA displacement from protein binding is higher (Dasgupta and Emerson, 1996).

VPA displacement from albumin binding may depend on concentrations of non-AED, e.g. ketoconazole is an antifungal agent widely used in the management
of patients with fungal infections, especially patients with acute acquired immunodeficiency syndrome (AIDS). Ketoconazole is 99% bound to serum albumin and readily interacts with VPA. Statistically significant displacement of VPA has been observed at normal albumin level but only when ketoconazole concentrations were high (10–20 µg/ml). However, in patients with hypoalbuminemia, significant displacement of VPA was observed with lower ketoconazole concentrations (Dasgupta and Luke, 1997). It is interesting that there is no displacement of VPA by ketoconazole in uremic serum. On the contrary, the free fraction of VPA decreases in the presence of ketoconazole in uremic serum.

Salicylate displaces CBZ from protein binding in normal sera but this effect is significantly reduced in uremic sera (Dasgupta and Thompson, 1995). On the other hand, significant displacement of CBZ from protein binding by tolmetin, ibuprofen and naproxen (non-steroidal inflammatory drugs) has been observed in uremic serum whereas in normal serum significant displacement has been found only with higher concentrations of naproxen (Dasgupta and Volk, 1996).

Renal elimination plays only a minor role in overall elimination of LTG. Thus, even in patients with moderate renal dysfunction and much lower clearance than in healthy people, the difference is not clinically relevant (Wootton et al., 1997). However, in patients with more severe renal failure and particularly if hemodialysis is required, the daily dose of LTG should be downwardly adjusted to the overall renal clearance (Fillastre et al., 1993).

Seizures are a relatively common occurrence in patients with human immuno virus (HIV) infection. Seropositive patients are usually treated with AEDs. In such patients AEDs should be carefully chosen. The ideal AED:

1. should not stimulate viral replication,
2. has limited protein bindings,
3. has no effect on the cytochrome P450 system.

GBP, TPM, TGB and PRG meet these criteria. VPA stimulates HIV replication. Thus combination of AED with antiretrovirals should be carefully considered (Romanelli and Ryan, 2002). Combination of CBZ and ritonavir in patients with HIV infection may result in CBZ intoxication (Mateu-de Antonio et al., 2001) and antiretroviral therapy failure (Hugen et al., 2000).

**Unpredicted interactions when more than two drugs are used**

Pindolol (beta-adrenergic blocking agent) does not increase serum PHT concentrations when PHT is administered in monotherapy. However, it does increase PHT concentrations when PHT is combined with other AEDs (Greendyke and Gulya,
GBP does not seem to have any pharmacokinetic interaction with PHT; however, co-administration with VGB and PHT results in marked reduction in clearance of PHT (Matar et al., 2000).

It has been found that AEDs increase fentanyl requirement during anesthesia for craniostomy (Tempelhoff et al., 1990). However, this is a dose-effect relationship between the number of AEDs received and the maintenance dose of fentanyl required for balanced anesthesia. AEDs have a similar dose-effect relationship with pipercuronium neuromuscular blockade (myorelaxants), also resulting in induction of a significant effect of AEDs (Jellish et al., 1993).

A case of retroperitoneal hematoma due to interaction between PHT and acenocoumarol, possibly potentiated by concomitant administration of paroxetine, has been reported (Abad-Santos et al., 1995).

The fact that over-the-counter drugs and nutritional supplements are increasingly being self-administered by patients creates the risk of drug interactions. Internet self-diagnosed and self-treated cases can also contribute to drug–drug interactions.

**Interactions with folk medicine**

In many countries folk medicine is frequently used for various reasons. Knowledge of active ingredients and possible interactions with AEDs is usually poor. Widely used ginkgo preparations are a good example. Co-medication of ginkgo and AEDs may result in decreased effectiveness of AEDs due to the presence of seizure provoking contaminants in some ginkgo preparations. Ginkgo products may contain neurotoxin 4′-O-methylpyridoxine, which is a B₆ antivitamin (Wada et al., 1985). When seizures occur in patients for the first time, particularly in children, it is recommended that subjects be asked whether they have been taking ginkgo seeds or leaf extracts (Arenz et al., 1996; Yagi et al., 1993). In the probable mechanism of seizures, 4′-O-methylpyridoxine appears to inhibit pyridoxal kinase and when taken in a sufficient amount may result in convulsions. The amount of this neurotoxin in gingko leaves or seeds depends on the growing seasons during which the product was harvested (Arenz et al., 1996).

Another example is primrose oil. Concurrent use of evening primrose oil and AEDs may result in seizures (Holman and Bell, 1983). Combination of phenothiazines (for presumed schizophrenia) and evening primrose oil resulted in epileptic seizures. Withdrawal of primrose oil and CBZ administration resulted in seizure control. Evening primrose oil activated temporal lobe epilepsy in two patients with schizophrenia (Vaddadi, 1981). For the same reason, evening primrose oil is contraindicated in patients with mania and epilepsy (Barber, 1998; Newall et al., 1996).
AEDs in non-epileptic disorders

Carbamazepine

CBZ is one of the most commonly used AEDs in epilepsy and other neurological and psychiatric disorders. CBZ mechanisms involve inhibitory action on sodium and on calcium (L- and N-type) channels, inhibitory effect on the release of somatostatin, increase of 5-HT release, effect on synaptic transmission and receptors, purine, monoamine, acetylcholine, adenosine and NMDA receptors (Crowder and Bradford, 1987; Lampe and Bigalke, 1990; Worley and Baraban, 1987). Its broad spectrum of pharmacological actions may explain the potent effect of CBZ in disorders other than epilepsy.

The analgesic effect is most comprehensively documented in neuralgias (Cambell et al., 1966; Nicol, 1969; Rockliff and Davis, 1966). However, it is also used in diabetic polyneuropathy (Rull et al., 1969), phantom limb pain syndrome, thalamic pain, cerebellar tremors and migraine (Leijon and Boivie, 1989; McQuay et al., 1995; Rompel and Bauermeister, 1970; Sechi et al., 1989).

There are reports that CBZ is also effective in hemifacial spasm, myotonia, restless legs syndrome (Montagna, 1992; Telstad et al., 1984) and hyperactivity disorders in children (Silva et al., 1996). In patients with dementia, CBZ is given to alleviate agitation, aggressiveness or other behavioral abnormalities. There are many reports and a long history of CBZ use in alcoholism, psychiatric disorders such as acute mania, bipolar disorders and mood stabilizing in affective and aggressive disorders (Dunn et al., 1998; Kishimoto et al., 1983; Mayo-Smith, 1997; Post et al., 1997; Post, 1988).

Gabapentin

GBP is widely and more frequently used in fields other than epilepsy. This may be due to its multiple mechanisms of action and to the fact that it is not associated with any significant pharmacokinetic interaction with other drugs. Most frequently, GBP is indicated for various pain syndromes and bipolar disorders. In these health conditions GBP efficacy is well documented in clinical controlled trials.

In pain-resistant conditions, combination of GBP with other analgesics is frequently used. In these cases GBP is the optional drug in elderly patients because in this population polytherapy is frequently used and GBP, usually, does not interact with other drugs. However, antacids (Maalox (R)) given concurrently with GBP reduced GBP bioavailability by 20% and when given 2 h after GBP, reduction was by 5% only (Product Information: Neurontin (R), Pfizer, New York, 2002).

GBP in combination with antiretroviral medication showed some effects in neuropathic pain due to immunodeficiency syndrome (Nevill, 2000). Amitriptyline or GBP are alternatives for postherpetic neuralgia, and other AEDs (GBP, LTG, TGB and TPM) are alternatives for seizures since indinavir interaction with CBZ
causes antiretroviral therapy failure (Hugen et al., 2000). Adding GBP to stable opioid medication in neuropathic cancer pain resulted in significant pain reduction without new adverse events (Caraceni et al., 1999). However, concurrent use of GBP and morphine may result in an increase of GBP plasma concentration (Product Information: Neurontin (R), Pfizer, New York, NY, 2002), requiring GBP dosage reduction in the elderly.

GBP administration resulted in significant reduction of spontaneous or evoked pain (brush-induced allodynia, cold-induced alldynia and hyperalgesia) (Attal et al., 1998). Good effects of GBP were reported in newly diagnosed trigeminal neuralgia (Magnus, 1999), in diabetic neuropathy in randomized studies (Backonja et al., 1998) and in postherpetic neuropathy (Rowbotham et al., 1998).

GBP (1800–2400 mg/day) administered in patients with migraine resulted in significant prophylactic migraine attack reduction: in 36% of the patients, 50% reduction of migraine attacks was observed (in comparison with 14% in the placebo group) (Mathew et al., 1999).

In patients with bipolar or monopolar disorders and mild depression, moderate to marked response was reported using GBP (Ghaemi et al., 1998; Harden et al., 1999; Ryback et al., 1997). Good effect was also observed in the treatment of acute mania using GBP alone or in combination with other antimanic drugs (Grunze et al., 1999; Hatzimanolis et al., 1999). These positive effects were observed in open-label study, on rather small number of patients and short-treatment duration. However, placebo-controlled studies showed that GBP does not have such beneficial effects in bipolar psychosis (Frye et al., 2000).

Other neurological disorders: GBP administration resulted in significant beneficial effects in spasticity and paroxysmal symptoms associated with multiple sclerosis (Cutter et al., 2000). In Parkinson's disease GBP in addition to dopaminergics showed a significant improvement in favour of GBP over a short period of co-medication (Olson et al., 1997). In amyotrophic lateral sclerosis controversial results were reported during GBP administration (Miller et al., 1996; Mazzini et al., 1998).

GBP was administered in Huntington’s disease and other movement paroxysmal disorders (Cosentino et al., 1996; Hardoy et al., 1999; Kothare et al., 2000). In open studies, long-term GBP administration of 900 mg showed moderate to good beneficial effects, without adverse events in tardive diskinesia, facial diskinesia, blepharospasm, hemichorea or hemibalismus. On the other hand, various movement disorders appeared when GBP was initiated; these disappeared when GBP was withdrawn. In 48% of the patients with restless legs syndrome clinical improvement was observed during GBP administration (Alder, 1997).

Paroxysmal dystonic movement, in both hands, occurred during combination of 900 mg GBP with propranolol in the elderly. After reduction of propranolol to
40 mg/day the paroxysmal dystonia subsided immediately. A pharmacodynamic interaction effect was suggested (Palomeras et al., 2000).

Combination of GBP with propranolol led to significant tremor improvement (Gironell et al., 1999). Orthostatic tremor was reduced in the majority of patients with GBP treatment (Onofrj et al., 1998). In another study, however, GBP 1800 mg/day was added for 2 weeks to baseline anti-tremor treatment without any significant tremor reduction compared to the placebo (Pahwa et al., 1998). No drug interactions were reported.

**Various rare neurological conditions:** GBP was administered in reflex sympathetic dystrophy, central pain, myokymia, cramp syndrome, idiopathic chronic hiccup and usually with clinical improvement (Merren, 1998).

Since GBP is eliminated predominantly by renal excretion, it may be influenced or may affect pharmacokinetics of other drugs showing the same pattern of elimination at the renal site (McLean, 1994). In patients with renal dysfunction or in the elderly, the daily dose of GBP should be downwardly adjusted according to creatinine clearance decrease.

**Lamotrigine**

LTG has multiple mechanisms of action including decrease of glutamate release in addition to inhibition of sodium and calcium (L- and N-type) currents, and increase of GABA.

It has been suggested that LTG possesses distinct psychotropic effects in addition to its antiepileptic action (Brodie, 1992; Uvebrant and Bauziene, 1994). Placebo-controlled trials in epilepsy treatment show some mood improvement (greater well-being) (Jawad et al., 1989; Smith et al., 1993) and there are theoretical reasons to suggest that LTG, like other AEDs, may possess mood-stabilizing properties. Polytherapy is usually used in bipolar psychoses, since there is no single mood stabilizer (Frye et al., 2000; Shelton and Calabrese, 2000). LTG monotherapy administered in two groups of patients with bipolar-I depression showed that 250 mg of LTG was significantly better than the placebo. LTG was effective in patients with rapid-cycling bipolar disorder and was useful in the treatment of bipolar-II disorder. LTG has not been shown to have clear efficacy in the treatment of mania or unipolar depression (Calabrese et al., 1999, 2000). Based on efficacy, adverse events and costs, it has been suggested that the use of LTG in mood disorders should probably be on the basis of a second-line agent for bipolar depression (Hurley, 2002).

**Levetiracetam**

LEV is an AED with unique profile of activity with potent broad-spectrum efficacy including effect on the high voltage N-type calcium channel, and at GABA and glycine-gated channels.
Information concerning LEV usage in non-epileptic disorders is too limited to allow any firm conclusions to be made. However, a number of preliminary reports show that LEV is well tolerated and effective in a wide variety of pain states (cervical and lumbar radiculopathy, traumatic peripheral nerve injury, neuropathic component in neoplastic pain, postherpetic neuralgia, allodynia, myelopathic pain and paresthesia in multiple sclerosis). LEV is presently undergoing extensive evaluation for the treatment of various neuropathic pains and migraines; however, it is only registered for the treatment of epilepsy (Mealy et al., 2002; Pakalnis, 2002).

Migraine and various headaches are other disorders in which LEV has been used with positive effects in reducing severity and frequency with modest side effects (Drake et al., 2001; Krusz, 2001). In refractory migraines LEV was given intravenously (i.v.) with good effect and was well tolerated (Krusz and Daniel, 2002).

There is also a suggestion that LEV may by used as a mood stabilizer (Bowden, 2001).

LEV is not associated with any pharmacokinetic interactions.

Oxcarbazepine

There are few publications concerning the use of O-CBZ in non-epilepsy conditions, although it has been used to treat acute mania (Emrich, 1990). However, since O-CBZ is better-tolerated than CBZ (with the exception of more common hyponatremia), and has similar mechanisms of action, it may be used in indications similar to those for CBZ (Asconape, 2002). O-CBZ is associated with far fewer pharmacokinetic interactions than CBZ.

Phenobarbital

Phenobarbital is the oldest AED in use and is still extensively used in developing countries. The mechanism of action of PB involves antagonism of AMPA receptor subtype and includes enhancement of GABAergic inhibition, enhancement of ionic currents by interactions with GABA_A receptor, decrease of excitatory amino acid release and post-synaptic response due to blocking of the excitatory glutamate response (Smith and Riskin, 1991). A broad spectrum of pharmacological actions may contribute to potential therapeutic activity in neurological conditions other than epilepsy. However, cognitive impairment, morning sedation, potential for abuse, severe toxicity and withdrawal syndrome are contraindications for routine use of PB (strong inducer) in such disorders.

In the past, i.v. injections of PB were frequently used to prevent cerebral hemorrhage in preterm neonates. However, a critical review of the literature suggests that PB has no beneficial effect (Crowther and Henderson-Smart, 2000) and in fact increased the incidence of intraventricular hemorrhage in infants with respiratory disease (Porter et al., 1985).
PB has also been used in increased intracranial pressure to reduce the effect of cerebral blood flow and metabolism (Trauner, 1986). However, it may impair cerebral perfusion pressure by inducing hypotension (Roberts, 2000) and therefore the benefit to risk ratio is low.

Neonatal hyperbilirubinemia can be controlled with a high single dose of PB (12 mg/kg) after birth (Wallin and Boreus, 1984). However, such a dose results in a prolonged sleep-state. In this condition, infants spend more time sleeping than they do with smaller doses.

Combination of chenodeoxycholic acid (750 mg/day) with PB (90–180 mg/day) was effective on the rate-limiting enzymes of liver cholesterol and bile acid synthesis. In patients with gallstones this effect was more pronounced than when each drug was used alone. Thus, an advantageous interaction was observed (Coyne et al., 1975; 1976).

When asthmatic children were treated with PB, theophylline clearance increased by 42%, resulting in a 30% decrease in steady-state serum theophylline concentration (Saccar et al., 1985). This drug combination requires theophylline dosage upward adjustment.

Reversible toxic encephalopathy was reported in a girl, possibly due to the toxic effect of ifosamide (cytostaticum) in combination with PB (Ghosn et al., 1988).

The rapidly fatal outcome of fulminant hepatitis caused by nilutamide, a non-steroidal antiandrogen derivative, was enhanced by co-administration with PB (Pescatore et al., 1993).

**Phenytoin**

PHT seems to be used much more frequently in the USA and the UK than in other European countries. In Poland, PHT constitutes 6.7% of the pharmaceutical market. PHT is a strong inducer of hepatic enzymes and is involved in numerous drug interactions with AEDs and non-AEDs. Moreover, due to non-linear pharmacokinetics and side effects, PHT is less frequently used today in non-epileptic disorders than it was before the introduction of the new generation of AEDs.

PHT has a broad spectrum of pharmacological action on neurotransmitter receptors and ion channels and this may explain why PHT is so effective in conditions other than epilepsy, such as: neuropathic pain, various pain syndromes, spasticity, myotonia and other disorders. However, evidence on the efficacy of PHT from randomized clinical trials in these and other non-epileptic conditions is rather scant.

**Neuropathic pain**: It has been reported that PHT may have a beneficial effect in trigeminal neuralgia, glossopharyngeal and superior laryngeal neuralgias, postherpetic and diabetic neuropathy, thalamic syndrome, phantom limb pain, diabetic pain and cancer pain. The efficacy of PHT in other pain syndromes is at best modest.
(Chadda and Mathur, 1978; Saudek et al., 1977). Unlike CBZ, evidence for efficacy of PHT in trigeminal neuralgia and similar conditions is based on an uncontrolled study only. However, PHT was more effective than aspirin in reducing pain in glycolipid lipidosis (Fabry disease) (Lockman et al., 1973).

In myotonic treatment, PHT and CBZ were used interchangeably and their efficacy was comparable to the efficacy of procainamide (Munsat, 1967; Sechi et al., 1983). However, adverse events may be more pronounced. In a double-blind placebo-controlled study PHT had a positive effect on motion sickness (Stern et al., 1994).

**Pregabalin**

PGB ((S)−(+)(−)−3 isobutylgaba) is a GABA derivative, but does not interact with GABA_A or GABA_B receptors and does not influence GABA concentrations (Whitworth and Quick, 2001). Instead, PGB binds to sub-units β_2, α_1, α_2–δ of the Ca^{2+} channel and this reduces the release of glutamate, noradrenaline and substance P (Dooley et al., 2000; Errante and Petroff, 2003). These mechanisms of action seem to be important in the treatment of epileptic seizures, pain and anxiety (Field et al., 2001). PGB is not associated with any pharmacokinetic interactions with CBZ, LTG, PB, PHT, TGB, TPM or VPA.

**Primidone**

PRM has been used in prospective, randomized clinical trials in essential tremor (Findley et al., 1985; Gorman et al., 1986) and is as effective as propranolol (Gorman et al., 1986; Sasso et al., 1990) and more effective than PB (Baruzzi et al., 1983).

Possible adverse events associated with PRM are similar to those with PB, which limits their use.

**Tiagabine**

TGB is an inhibitor of GABA uptake. The drug was developed specifically for use as an AED based on the concept of the GABAergic mechanism of epileptic seizures. Since reduction in GABAergic neuronal activity has been proposed not only in epilepsy but also in various neuropsychological disorders, anxiety and pain (Krogsgaard-Larsen, 1988; Meldrum, 1982), TGB may have a beneficial effect in these health conditions.

TGB has been evaluated in various GABAergic mechanism-related disorders e.g. sleep disorders (Meldrum and Chapman, 1999), pain (postherpetic and diabetic neuropathy), movement disorders (related to basal ganglia disorders, e.g. tardive diskinesia) (Gao et al., 1994; Thaker et al., 1987), spasticity (Holden and Titus, 1999), bipolar disorders (Kaufman, 1998), anxiety (Neilson, 1988) and neuroprotection
against ischemia-induced cell loss (Johansen and Diemer, 1991). A moderate effect of TGB in migraine has been observed (Drake et al., 1999; Freitag et al., 2000).

In casuistic observation TGB was administered in psychiatric patients (bipolar disorders) as add-on therapy to venlafaxine, lithium, flurazepam, bupropion, methylphenidate and paroxetine (Kaufman, 1998; Schaffer and Schaffer, 1999).

Dosages of TGB should be adjusted in patients with liver dysfunction (Beydoun and Passaro, 2002).

In general, preliminary reports suggest that TGB use in non-epileptic conditions requires longer-term studies based on larger numbers of patients and on evidence-based medical principle. The few reports relating drug interactions between TGB and non-AEDs are discussed in Chapter 8.

Topiramate

The mechanisms of action of TPM involve: sodium channel blockade, inhibition of AMPA glutamate receptors, potentiation of GABA-related neuroinhibition at GABA_A receptors (White, 1999); blocking of excitatory neurotransmission mediated by non-NMDA receptors. TPM is also a weak carbonic anhydrase inhibitor (Dodgson et al., 2000) and may have an inhibitory effect on calcium channels (Zhang et al., 2000).

Preliminary data suggest that TPM, with multiple pharmacological properties, may have therapeutic effects in various chronic pain syndromes, migraine and cluster headache prophylaxis, tremor and certain psychiatric disorders.

Analgesic effect of TPM combination with opioids was reported in neuropathic pain; and these effects were not the result of any drug interaction.

TPM was prophylactically effective in migraine and other headaches (Potter et al., 2000; Wheeler and Carrazana, 1999). TPM and propranolol combination resulted in control of essential tremor, particularly in the hands compared to the head or voice (Connor, 2000; Galvez-Jimenez and Hargreave, 2000). No drug interaction was reported.

In psychiatric disorders TPM was combined with tricyclic antidepressants (Ortho McNeil Pharmacological) or with serotonin reuptake (Edwards et al., 2000). TPM has been used as an alternative treatment for bipolar disorder (Doose et al., 1999a), and was effective in 55% of initially manic patients after a mean of 312 days of treatment. There was no clinically significant effect of TPM on haloperidol serum concentrations (Doose et al., 1999b) but a modest decrease in lithium serum concentration was observed though the interaction was without clinical relevance.

Nightmares and binge-eating responded well to TPM in an open-label trial (Shapira et al., 2000). Two patients with Tourette’s syndrome were successfully treated with TPM while previous medications were discontinued (Abuzzahab, 2001). No interaction was reported.
In general, the reports on TPM administration in non-epileptic disorders are based on short preliminary studies and/or small numbers of patients.

**Valproic acid**

VPA is an AED with broad-spectrum efficacy against various forms of epileptic seizure. This is due to the combination of several neurochemical and neurophysiologic mechanisms (Lösch, 1999; Zeise *et al.*, 1991), which may explain its effects in various neuronal dysfunctions. The mechanisms of VPA action include

1. increase of GABA turnover potentiating GABAergic functions in various specific brain regions,
2. inhibitory effect on voltage-sensitive sodium channels (Lösch, 1999),
3. inhibitory effect on neuronal excitation mediated by the NMDA (Zeise *et al.*, 1991).

Several double-blind controlled trials have demonstrated the efficacy of VPA in migraine treatment and prophylaxis (Hering and Kuritzky, 1992; Jensen *et al.*, 1994; Klapper, 1997). Migraines with paroxysmal discharges in the electroencephalograph (EEG), mainly of the dysrhythmic type, were successfully treated with VPA (Viswanathan *et al.*, 1995). VPA is also effective in chronic headaches, (Mathew and Ali, 1991), and in cluster-form headaches (Hering and Kuritzky, 1989). VPA can occasionally be combined with other groups of medication for migraine treatment, including β-adrenergic channel blockers or anti-inflammatory drugs. In such cases potential drug interaction with VPA may occur (see Chapter 8).

In addition to its analgesic effect (DeFeudis, 1984), VPA also shows efficacy in various psychiatric and neurotic disorders. It was reported that VPA is effective in patients with acute mania and its subtypes (Emrich and Wolf, 1992; Pope *et al.*, 1991), depression (Brown, 1989; Young *et al.*, 2000) and bipolar disorders (Goldberg *et al.*, 1998; Hirschfeld *et al.*, 1999; Schaff *et al.*, 1993). Moreover, VPA has been used in anxiety disorders, stress condition, aggressive behavior and tardive diskinesia.

Evidence-based medicine varies greatly but even so, VPA is widely used in fields other than epilepsy in the majority of countries.

**Summary**

Many drug interactions can be demonstrated but only a few of them are so clinically significant that they require adjustment of drug dosages. However, some drug combinations may produce unexpected changes of various extents and directions in different subjects and in different health conditions. The reasons for this variability include genetic control of the rate of drug metabolism as well as internal factors, such as serum changes, renal or hepatic disorders, gender and ageing. In this
chapter, clinically and/or potentially significant drug interactions between AEDs and non-AEDs in health conditions other than epilepsy are discussed. Case reports of toxic effects due to drug interactions are presented as a warning signal calling for attention when polytherapy has to be used. In such cases, careful drug selection and dosage adjustment based on serum drug monitoring and clinical observation are the main rules for risk minimization. Awareness and knowledge of possible drug interactions is a good starting point before making treatment decisions.

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Drug monitoring in combination therapy

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Introduction

In 1978 Penry remarked ‘The clinical management of epilepsy has improved dramatically in the past decade through the determination of serum antiepileptic drug (AED) concentrations’ (Penry, 1978). The recommendations for undertaking therapeutic drug monitoring of AEDs in serum are based on clinical experience and on a number of studies demonstrating a correlation between serum concentrations of AEDs on the one hand, and seizure frequency and dose-dependent adverse effects on the other hand. Such a correlation, which is more significant for some AEDs than for others, has been found for the majority of the established AEDs. As for new AEDs, with the exception of vigabatrin, analogous data are increasingly becoming available (Johannessen et al., 2003).

The relationship between serum concentration, seizure frequency and side effects gives the therapeutic range or target range (Table 21.1). In this range, an AED can be considered to be associated with no dose-dependent side effects in the majority of the patients in whom it is effective. Thus the range provides guide values which give a more rapid identification of a patient’s individual therapeutic range, which reflects the patient’s clinical susceptibility to seizures, seizure type, etc. However, despite a good deal of anecdotal testimony, surprisingly little has been published demonstrating the benefits of anticonvulsant therapeutic drug monitoring in epileptic populations (Eadie, 1995). In two randomized controlled trials on the clinical impact of therapeutic drug monitoring in patients with epilepsy, the implementation of serum AED level monitoring did not improve overall therapeutic outcome, and the majority of patients could be satisfactorily treated by adjusting dose on clinical grounds (Fröscher et al., 1981; Jannuzzi et al., 2000). In the study by Camfield et al. (1985), 82 newly diagnosed children were started on AED therapy and followed prospectively for 12–36 months. Serum concentrations were not observed to be different between children who had a relapse and children who continued to have seizure control; concentrations were within the therapeutic range in both groups. In a study of AED side effects in 197 patients, Laplane and Carydakis...
Drug monitoring in combination therapy

(1985) concluded that the recording of side effects from a case history and a physical examination is far more useful than the determination of the serum concentration. By these results, on the one hand the value of a routine serum concentration determination is doubtful, on the other hand most epileptologists are convinced that monitoring improves the pharmacotherapy of the epilepsies even if there is a lack of statistically significant results. At present, the determination of AEDs is considered to be indicated in the situations which are listed in Table 21.2. These indications are valid not only for the established drugs but also for the new AEDs, with the exception of vigabatrin, which is associated with a somewhat unusual mechanism of action whereby its pharmacological effect long outlasts its serum concentration.

### Table 21.1 AED therapeutic ranges

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic range (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>3–12</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40–100</td>
</tr>
<tr>
<td>Felbamate</td>
<td>20–110</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2–60</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0.5–15</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3–60</td>
</tr>
<tr>
<td>Oxcarbazepine/MHD(^a)</td>
<td>10–50</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10–40</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>3–20</td>
</tr>
<tr>
<td>Primidone(^b)</td>
<td>5–15</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>5–70</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2–25</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>40–100</td>
</tr>
</tbody>
</table>

\(^a\)During oxcarbazepine treatment it is only necessary to determine the pharmacologically active monohydroxy derivative (MHD) metabolite.  
\(^b\)During primidone treatment it is only necessary to determine the phenobarbital concentration.


(1985) concluded that the recording of side effects from a case history and a physical examination is far more useful than the determination of the serum concentration. By these results, on the one hand the value of a routine serum concentration determination is doubtful, on the other hand most epileptologists are convinced that monitoring improves the pharmacotherapy of the epilepsies even if there is a lack of statistically significant results. At present, the determination of AEDs is considered to be indicated in the situations which are listed in Table 21.2. These indications are valid not only for the established drugs but also for the new AEDs, with the exception of vigabatrin, which is associated with a somewhat unusual mechanism of action whereby its pharmacological effect long outlasts its serum concentration.

### Indications for drug monitoring in antiepileptic combination therapy

The applicability of therapeutic drug monitoring during combination therapy with different AEDs or during combination of an AED and drugs used for the
treatment of non-epilepsy-related conditions relates to three main considerations, which are discussed below.

**Avoidance of underdosage**

One of the most frequent prescription errors relates to treatment with two drugs that are below the effective dose. If it is not possible to tell from the case history as to which drug is effective, the determination of the serum concentration can provide invaluable information as to which of the two drugs should be adjusted in relation to its dosage. Thus if a patient continues to have seizures on drug A and a drug B, one will determine the serum concentration of both drugs. If the serum concentration of A is within the target range and the serum concentration of B is below, then a first therapeutic step would be to increase the dosage of drug B. In contrast, in a seizure-free patient with the same treatment regimen described above, one would reduce the dosage of drug B and keep the dosage of drug A the same. Undertaking such a step-wise approach also serves to take into account the possibility of pharmacokinetic interactions. Owing to the possibility of drug interactions, the addition or withdrawal of a drug to or from a drug combination may result in a considerable shift in serum concentration. The immediate detection and correction of such a shift may help to prevent underdosage with recurrences of seizures or intoxication. If a patient is seizure free with a combination of lamotrigine with a medium serum concentration and a low serum concentration of valproic acid, the withdrawal of valproic acid may induce seizures, not because of the high efficiency of the low dose of valproic acid but because of the drop of the lamotrigine serum concentration (valproic acid is an enzyme inhibitor, capable of reducing the rate of metabolism of the co-administered lamotrigine; Patsalos et al., 2002). Although valproic acid withdrawal
may be undertaken without knowledge of lamotrigine serum concentrations, their knowledge would allow for a more gradual and predictive therapeutic response.

Another setting whereby underdosage can occur is when an AED, whose metabolism is susceptible to enzyme induction, is co-prescribed with an enzyme-inducing AED. If, for example, in a patient with focal epilepsy the occurrence of tonic–clonic seizures has been stopped by valproic acid monotherapy but complex focal seizures persist, one could add the enzyme-inducing drug carbamazepine. This might induce an increase of seizure frequency by an acceleration of the elimination of valproic acid (Patsalos et al., 2002). The cause of the deterioration of the seizure frequency will be explained quickly by measuring the serum concentration of valproic acid. In another patient, the same combination might not increase the seizure frequency but induce toxicity by an increase of the serum concentration of the carbamazepine-epoxide metabolite. The clinical significance of this interaction is particularly important in children, where high concentrations of carbamazepine-epoxide have been observed, along with severe side effects such as vomiting and tiredness. This example also demonstrates the value of monitoring a pharmacologically active metabolite such as carbamazepine-epoxide in special situations.

When an enzyme-inducing AED such as phenytoin is withdrawn from a treatment regimen, one needs to take into account the consequent de-induction. If phenytoin is discontinued abruptly rather than gradually, the valproic acid concentration will increase to its new steady-state level at about 1 week later. In contrast, a drug with a longer half-life (e.g. phenobarbital) would take longer to reach its new steady-state concentration (Mattson, 1995). In these complex situations, monitoring of serum concentration provides invaluable information for the optimal management of patients.

AED underdosage may also be induced by the addition of a drug which has been indicated for a non-epilepsy-related condition. If, for example, gabapentin is co-ingested with hydroxides of aluminium or magnesium (antacids), the absorption of gabapentin will be reduced (Patsalos et al., 2002). The extent of the reduced absorption is best ascertained by measuring the serum concentration.

**Avoidance of intoxication and identification of suspected side effects**

Clinically relevant examples of interactions between AEDs with the consequence of an increase of the serum concentration of one of the drugs (or both drugs, e.g. when phenytoin and phenobarbital are co-prescribed) are the combination of the enzyme-inhibiting valproic acid and phenobarbital (increase of phenobarbital), valproic acid and lamotrigine (increase of lamotrigine), topiramate and phenytoin (increase of phenytoin), sulthiame and phenytoin (increase of phenytoin), and the aforementioned combination of valproic acid and carbamazepine (increase of carbamazepine-epoxide; Patsalos et al., 2002; Rambeck et al., 1987).
When combination therapy is associated with symptoms of intoxication, the clinical features and the electroencephalogram (EEG) are often not the right tools to ascertain which AED is responsible. When non-specific neurological symptoms such as tremor and ataxia appear, it is not always clear whether the symptoms are due to intoxication or to the underlying disease, particularly if the disease is progressive. The same is true for psychic symptoms. The difficulty of distinguishing between the symptoms of an underlying disease and intoxication is illustrated by the following case history of a patient on phenytoin monotherapy. We observed a 55-year old epileptic patient with a psychosyndrome, which had been interpreted as postcontusional by the doctor in attendance. The patient was disoriented and decelerated. He was treated with 300 mg phenytoin per day. The neurological examination was hindered because the patient did not cooperate. AED side effects were not expected by the doctor in attendance. The phenytoin level was 53 μg/ml. In reality the psychosyndrome thought to be postcontusional was a pharmacogenetically associated psychosis which disappeared after the withdrawal of phenytoin (Fröscher, 1992).

In ambiguous cases of intoxication in which the concentration of the administered drug is ‘normal’ and the drug has a pharmacologically active metabolite, the measurement of the metabolite, for example phenylethylmalonamide (PEMA) during primidone therapy or carbamazepine-epoxide during carbamazepine therapy, may be diagnostically helpful. Indeed it should not be forgotten that with AEDs such as carbamazepine and primidone the alleged monotherapy in fact comprises of two or three components (carbamazepine, carbamazepine-epoxide; phenobarbital, PEMA, primidone). Another consideration in doubtful cases of intoxication is the possibility of the intake of drugs which have not been prescribed including over the counter supplements and herbal remedies. Such drugs can only be detected and quantitated by methodologies that are based on basic analytical principles such as high performance liquid chromatography. The use of reagent-based commercial analysis such as enzyme immunoassay may not be sufficient to identify the drug that is responsible for the clinical presentation as the following case history demonstrates. A 28-year old female patient with focal epilepsy was admitted to the hospital because of gait ataxia. The only prescribed drug was carbamazepine. Therefore, at admittance, only the serum concentration of this drug was determined. The carbamazepine value was in the lower part of the target range. With some delay we detected that the patient had continued to take phenytoin which she should have stopped 18 months before. The subsequently measured phenytoin concentration was 60 μg/ml, which was far above the target range.

When AEDs are co-prescribed with drugs for other indications, intoxication can similarly occur. For example, when carbamazepine and erythromycin are
co-prescribed, the measurement of carbamazepine serum concentration is indicated because this combination can be associated with a significant increase in carbamazepine concentrations; the extent of which cannot be predicted reliably (Patsalos et al., 2002; Patsalos and Duncan, 1993).

**Monitoring of concomitant medication**

Another consideration arising from the combination of AEDs and drugs used for other indications may be an underdosage of the latter drugs. If one combines, for example, cyclosporine with an enzyme-inducing drug such as carbamazepine, phenobarbital, phenytoin or oxcarbazepine (Rösche et al., 2001), careful monitoring of cyclosporine is necessary because serum cyclosporine concentrations can be expected to decrease. Thus in patients that have undergone an organ transplantation, this interaction would quickly result in a rejection of the transplanted organ.

**Prerequisites of the determination of AEDs in serum**

The essential prerequisite for monitoring serum concentrations, both in monotherapy and in combination therapy, is the reliability (accuracy and precision) of the assay methodology (Wilson et al., 1989; Williams et al., 2003). Another important factor is the consideration of the time interval between drug intake and the collection of blood. Thus if a drug has a short half-life value, the blood sampling of a patient in an outpatients setting often does not result in the determination of a trough concentration. In combination with an enzyme-inducing AED, the half-life value of tiagabine, for example, is reduced from 5–8 h (monotherapy) to 2–5 h. When phenobarbital and valproic acid are administered in combination, the half-life value of valproic acid is reduced while the half-life of phenobarbital is increased and its peak concentration is delayed (Patsalos et al., 2002).

Also, as in the case of monotherapy, one has to take into consideration whether or not the measured serum concentration is reflective of steady state. When the dosage is changed, the new serum concentration should not be determined until steady state has been achieved (typically this can be expected to occur after five half-life values of the affected drug).

**Measurement of the free (non-protein bound) concentration of AEDs**

Some AEDs are highly protein bound in blood to albumin. These include carbamazepine (80%), phenytoin (90%), tiagabine (96%) and valproic acid (95%). Some AEDs may interact at the albumin protein-binding site and free concentration may
increase; for example free carbamazepine-epoxide concentrations are significantly increased in patients taking carbamazepine plus valproic acid (Liu et al., 1995). Since only the free concentration can penetrate the blood–brain barrier, several attempts have been made to improve treatment by using free drug concentration measurements; for example by determining AEDs in saliva or by measuring the free concentration in blood by ultrafiltration (Liu and Delgado, 1999). The clinical relevance of the determination of the free AED concentrations is somewhat controversial, even for highly protein bound drugs (Fröscher et al., 1985). Nevertheless, overall there are clinical settings where patient management would best benefit from measurement of free serum concentrations. Indeed, when phenytoin and valproic acid are co-prescribed, measurement of total phenytoin concentrations would be misleading because of the protein-binding displacement interaction that occurs between these AEDs (Patsalos and Perucca, 2003).

Limits and dangers of the determination of serum concentrations of AEDs

The effectiveness of serum concentration determination depends on the accuracy of the therapeutic ranges of the individual AEDs. Therefore, for phenytoin with its narrow therapeutic range the indication for serum concentration monitoring is much clearer than, for example, phenobarbital, for which the upper limit of the therapeutic range is very blurred.

As for the new AEDs, the clinical relevance of drug monitoring is limited by the fact that the target ranges are derived from the clinical trial data collected during their evaluation as add-on therapy (Johannessen et al., 2003). These studies enrol patients that are highly selected and as such are not reflective of patients seen in general clinical practice. Nevertheless, these ranges are valuable as they provide reference values, which can aid patient management. Serum monitoring of new AEDs is particularly useful when interacting AED combinations are co-prescribed.

The appropriate procedure for adjusting the dosage is essentially the same irrespective of whether or not the serum concentration is determined. In both cases the dose is increased slowly until seizures cease or, if seizures persist, until the intoxication limit is reached. The upper limit of the serum concentration is merely a warning signal, not a barrier. The procedure must be similar because the individual therapeutic ranges are different. The lower limit of the target range or therapeutic range is even more indistinct than the upper limit.

It is imperative that therapeutic ranges are appreciated for what they are, that is statistical ranges whereby if a patient achieves a serum concentration within that range, the probability of achieving a desirable therapeutic response (with minimal side effects) is high. A serum concentration should be used in conjunction with the
knowledge of the patient, the clinical information and also the pharmacokinetic characteristics of the drug. The therapeutic range should be used as a guide.

**Special laboratory tests**

Sometimes when there is an interaction associated with AED treatment, a surrogate physiological marker may be necessary other than the measurement of a serum drug concentration, so as to ascertain the interaction. An example of this is the combination of phenprocoumon or warfarin and an enzyme-inducing AED, whereby the serum concentration of phenprocoumone/warfarin will decrease. In this setting the careful monitoring of the prothrombin time (or international normalized ratio, INR) is indicated. Another example is that of valproic acid-induced encephalopathy. Valproic acid occasionally induces stuporous or comatose states. This encephalopathy is frequently accompanied by hyperammonemia without signs of hepatic failure. Valproic acid encephalopathy may occur after initiation of valproic acid as monotherapy or, more often, in combination with other AEDs (e.g. phenobarbital, phenytoin, topiramate). In this setting monitoring of plasma ammonia concentrations would be a valuable diagnostic tool (Hamer et al., 2000).

**Future of monitoring**

Therapeutic drug monitoring has greatly enhanced the treatment of epilepsy in that it has allowed the individualization of treatment and thus maximized the desirable anticonvulsant effects of AEDs while keeping to a very minimum the undesirable side effects that are associated with AEDs. Monitoring is essential for drugs with a narrow therapeutic index and for those drugs with unacceptable incidence of toxicity. This is particularly exemplified by phenytoin (Gentry and Rodvold, 1995). With regards to the new AEDs, target ranges are at their infancy and will inevitably require fine tuning as our clinical experience with these drugs increases. The usefulness of drug monitoring during combination polytherapy is dependent on the propensity of the combination to interact and the extent and mechanism of the interaction. For pharmacodynamic interactions, drug monitoring is only of value in that it is used to exclude the possibility that an interaction is pharmacokinetic in nature. For many pharmacokinetic interactions, the direction and extent of the associated change in serum drug concentration cannot be reliably predicted. Furthermore, some interactions may be associated with either an increase or a reduction in serum concentration. The likelihood of an unpredictable interaction is much lower with some of the new AEDs compared with the established drugs. Indeed gabapentin and levetiracetam have a particularly low propensity to interact...
Therefore, the role of drug monitoring will not be important during combination therapy with these AEDs.

Summary

Combination therapy is an important indication for AED therapeutic drug monitoring as it is an invaluable aid in avoiding underdosage and intoxication and also to confirm drug-related side effects.

If it is not possible to conclude from the case history which component of a combination is probably effective, the determination of the serum concentration helps identify which drug dosage should be increased or lowered. In this setting one has to take into account the possibility of drug interactions. In particular, consequent to a pharmacokinetic interaction, the addition or withdrawal of a drug to or from a combination may result in a considerable shift in serum concentration. The early detection and correction of such a shift may help to prevent, for example, underdosage with recurrences of seizures. With the combination of a medium dose of lamotrigine and a low dose of valproic acid, the withdrawal of valproic acid may induce seizures not because of the low dose of valproic acid but as a consequence of the decrease of the lamotrigine serum concentration. When combination therapy has led to intoxication symptoms the clinical picture and the EEG are often not helpful in recognizing the responsible drug. In sedated patients taking a combination of valproic acid and phenobarbital, drug monitoring can help to differentiate between valproic acid encephalopathy with a ‘normal’ serum concentration and phenobarbital intoxication as the consequence of an inhibitory interaction between phenobarbital and valproic acid with a consequent elevation of phenobarbital serum concentrations.

REFERENCES


Cognitive side-effects due to antiepileptic drug combinations and interactions

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Introduction

The possibility that cognitive impairment may develop as a consequence or aftermath of epilepsy was raised as early as 1885 when Gowers described 'epileptic dementia' as an effect of the pathological sequela of seizures. Nonetheless, the topic was not coupled to antiepileptic drug (AED) treatment until the 1970s.

It has now been established that AED treatment may be associated with a variety of side-effects (Aldenkamp, 1995, 1998; Vermeulen and Aldenkamp, 1995, 2001). Some effects appear immediately after the start of drug exposure, such as nystagmus, but are relatively benign because they show habituation (Kulig and Meinardi, 1977), or are reversible when they are dose dependent. Others may be of insidious onset, emerging only after extended periods of treatment (i.e. chronic side-effects). A multitude of such chronic side-effects have been documented (Reynolds, 1975), but the most frequently reported effects concern central nervous system (CNS) effects. This chapter reviews some of our knowledge about a specific subgroup of such CNS-related chronic side-effects of AED treatment, that is, cognitive side effects: the adverse effects of drug treatment on information-processing systems.

Such effects are considered to be much more moderate than for example, some of the idiosyncratic reactions to drugs and normally do not lead to discontinuation of drug treatment. Nonetheless, a number of studies have claimed that the drug-induced cognitive impairments may have a much greater impact on daily life function than had hitherto been suspected (Trimble, 1983, 1987a, b), for example through the impact on critical functions, that is, learning in children (Aldenkamp, 1995) or driving capacities in adults (often requiring milliseconds precision), or on vulnerable functions such as memory function in elderly. Moreover, as the cognitive side-effects represent the long-term outcome of AEDs, the effects may increase...
with prolonged therapy, which may contribute to the impact on daily life functioning in patients with refractory epilepsies (Committee on Drugs, 1985).

**Review of psychometric studies**

The interest in the cognitive side-effects of AED treatment is of relatively recent origin and the first studies are from the 1970s (Ideström et al., 1972; Dodrill and Troupin, 1977), probably stimulated by the widening range of possibilities for drug treatment during that period; valproate (VPA) and carbamazepine (CBZ) were clinically introduced in this same period and many studies compare these drugs with phenytoin (PHT). A first paragraph of this chapter reviews the literature in lines of evidence-based medicine, that is, reviewing the empirical data that were published in peer-reviewed journals. Potentially relevant studies were identified through computerized and manual searches of the English-language literature published from January 1970 through December 1994. A computerized search of the DIMDI database was conducted. In addition, the bibliographies of several reviews on the same topic were examined (Trimble and Thompson, 1981, 1983; Trimble, 1983, 1987a; Evans and Gualtieri, 1985; Novelly et al., 1986; Smith, 1991; Dodrill, 1992). Criteria for selection of the papers were:

1. English-language report of original research, published in peer-reviewed journals in the period 1970–1994; studies after 1970 were all done at a time when most of the current AEDs had become available and modern cognitive tests had come into widespread use.

2. Studies that report psychometrically assessed cognitive functions (excluding for example clinical observations).

3. Only current AEDs (excluding experimental drugs that have been removed from study programmes, such as zonisamide (ZNS), felbamate or flunarizine).

4. Only studies on patients with epilepsy (excluding AED studies in for example psychiatric patients). The resulting meta-analysis has been published on the data concerning monotherapy (Vermeulen and Aldenkamp, 1995). Here we focus on the results for combination therapy or polytherapy.

In the meta-analysis, studies were classified into the polytherapy category if subjects were treated with more than one drug at a time and no comparisons between individual drugs, or single drug vs. no AED, were possible. Studies that were identified through the aforementioned procedure and involving polytherapy are listed in Table 22.1 (Reynolds and Travers, 1974; Debakan and Lehman, 1975; Matthews and Harley, 1975; Sommerbeck et al., 1977; Wilensky et al., 1981; Thompson and Trimble, 1980, 1982, 1983; Corbett et al., 1985; Ludgate et al., 1985; Berent et al., 1987; Durwen et al., 1989; Prevey et al., 1989; Duncan et al., 1990; Van
Rijckevorsel–Harmant, 1990; Dodrill and Wilensky, 1992; Durwen et al., 1992; May et al., 1992; McGuire et al., 1992; McKee et al., 1992; Pieters et al., 1992; Chataway et al., 1993; Dodrill et al., 1993; Durwen and Elger, 1993; Gilham et al., 1993; Mitchell et al., 1993; Smith et al., 1993; McKee et al., 1994).

From Table 22.1, the following points can be noted:

1 *Treatments.* This section shows the treatment conditions associated with assessment points. The nomenclature and abbreviations for individual AEDs comply with the recommendations in *Epilepsia,* 1993, 34, 1151. In addition: P, polytherapy; SAD, single additional dose; Mono, monotherapy; plac, placebo; none, no AEDs. Subscripts: AEDcr, controlled release formulation; AEDDhi/Dme/Dlo, high, medium, low dosage; AEDShi/Slo, high vs. low serum (or saliva) levels; P_red, mod, P reduction [c.q.], other modification; P_AED+/, P with vs. without a particular AED; P_tox+/, P with toxic vs. non-toxic serum levels. Slashes (/) indicate contrasts under study in a parallel group or post-test-only design. Crosses (×) indicate crossover elements. Arrows (→) indicate change of one treatment to another. Plus signs (+) indicate that medication is added to an existing regimen.

2 *Number of subjects.* The numbers are shown separately for each treatment condition and untreated controls; they indicate the number of subjects who completed the trial and for who test data were available. A range is given for n when not all subjects completed all tests. Occasionally, we were unable to determine these numbers for the separate treatments (e.g. when only an overall n was provided), or for one or more outcome measures. This is indicated by a question mark.

3 *Drop-out rate.* This gives a rough indication as to whether a selection artefact might have developed during the trial. An overall rate is given separately for subjects on AEDs and untreated controls. About half the studies reviewed mentioned dropout losses and present sufficient data to compute a drop-out rate for each outcome measure. A range may be given here as well as due to incompletion in various degrees. A few studies explicitly state that no dropout losses occurred (–). In others, dropout losses are mentioned but insufficient data is provided to compute a loss rate (?). Often, dropout losses or their absence are not mentioned (n.m.), which may or may not mean that no such losses occurred. Sometimes a minimum rate is quoted (≥), more subjects may have been lost, but the data are unclear or ambiguous in this regard.

4 *Design.* (Table 22.2 gives an overview of the general design types encountered.) The term design as used here refers to the scheduling of treatments (i.e. AEDs, placebo, no treatment) and outcome measurement sessions, and to the way subjects were assigned to treatment groups (i.e. on a random basis or not). Occasionally, we were unable to discover a consistent principle underlying
Table 22.1 Review summary of polytherapy polytherapy studies (1970–1994)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments</th>
<th>Subjects (N)</th>
<th>Untreated controls</th>
<th>Drop-out rate</th>
<th>Design</th>
<th>Cognitive variables (N)</th>
<th>Time on AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds and Travers (1974)</td>
<td>P</td>
<td>57</td>
<td>–</td>
<td>n.m.</td>
<td>Post-test</td>
<td>3</td>
<td>?</td>
</tr>
<tr>
<td>Dekaban and Lehman (1975)</td>
<td>(P_Dhi → P_Dme → P_Dlo)/none</td>
<td>8–12</td>
<td>6_Ne</td>
<td>n.m.</td>
<td>Parallel</td>
<td>6</td>
<td>14–20 days</td>
</tr>
<tr>
<td>Matthews and Harley (1975)</td>
<td>P tox+ /P tox−</td>
<td>35/28</td>
<td>–</td>
<td>n.m.</td>
<td>Post-test</td>
<td>33</td>
<td>?</td>
</tr>
<tr>
<td>Sommerbeck et al. (1977)</td>
<td>P + (VPA × plac)</td>
<td>8–20</td>
<td>33–73%</td>
<td>X-over (R)</td>
<td>30</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Thompson and Trimble (1980, 1982)</td>
<td>P(P → (P_red/P_red + CBZ))</td>
<td>10/20/15</td>
<td>–</td>
<td>n.m.</td>
<td>Parallel</td>
<td>6</td>
<td>6 months</td>
</tr>
<tr>
<td>Wilensky et al. (1981)</td>
<td>PHT + (CLZ × PB)</td>
<td>43</td>
<td>–</td>
<td>22%</td>
<td>X-over (R)</td>
<td>?</td>
<td>4 months</td>
</tr>
<tr>
<td>Thompson and Trimble (1983)</td>
<td>Pshi × P slo</td>
<td>28</td>
<td>–</td>
<td>n.m.</td>
<td>X-over</td>
<td>20</td>
<td>3 months</td>
</tr>
<tr>
<td>Corbett et al. (1985)</td>
<td>P</td>
<td>312</td>
<td>–</td>
<td>n.m.</td>
<td>?</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Ludgate et al. (1985)</td>
<td>P → Mono</td>
<td>12</td>
<td>–</td>
<td>33%</td>
<td>Single</td>
<td>17</td>
<td>1 year</td>
</tr>
<tr>
<td>Berent et al. (1987)</td>
<td>P → (P_red + ZNS)</td>
<td>9</td>
<td>–</td>
<td>18%</td>
<td>Single</td>
<td>16</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Brodie et al. (1987)</td>
<td>P/CBZ/VPA/PHT</td>
<td>66</td>
<td>25</td>
<td>n.m.</td>
<td>Single</td>
<td>20</td>
<td>?</td>
</tr>
<tr>
<td>Durwen et al. (1989)</td>
<td>P → P_mod</td>
<td>13</td>
<td>–</td>
<td>n.m.</td>
<td>Single</td>
<td>18</td>
<td>?</td>
</tr>
<tr>
<td>Prevey et al. (1989)</td>
<td>P → VPA</td>
<td>8</td>
<td>–</td>
<td>n.m.</td>
<td>Single</td>
<td>17</td>
<td>5 months</td>
</tr>
<tr>
<td>Duncan et al. (1990)</td>
<td>P/(P → (P_HPT−/P_CBZ−/P_VPA−))</td>
<td>25/20–21/14</td>
<td>–</td>
<td>16–17%</td>
<td>Parallel</td>
<td>8</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Van Rijckevorsel et al. (1990)</td>
<td>P → P_mod</td>
<td>26</td>
<td>–</td>
<td>28%</td>
<td>?</td>
<td>5</td>
<td>3 months</td>
</tr>
<tr>
<td>Durwen et al. (1992)</td>
<td>P → P_mod</td>
<td>13</td>
<td>–</td>
<td>n.m.</td>
<td>Single</td>
<td>18</td>
<td>5 days</td>
</tr>
<tr>
<td>Dodrill and Wilensky (1992)</td>
<td>PHT/P_HPT+/P_HPT−</td>
<td>11/11/11</td>
<td>–</td>
<td>83%</td>
<td>Parallel</td>
<td>20</td>
<td>5 years</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Description</td>
<td>Dropout</td>
<td>Response</td>
<td>Design</td>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>McGuire et al. (1992)</td>
<td>P/(P + VGB)</td>
<td>15/15</td>
<td>n.m.</td>
<td>Parallel</td>
<td>7</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>McKee et al. (1992)</td>
<td>CBZ → (CBZ + VPA)</td>
<td>16</td>
<td>n.m.</td>
<td>Single</td>
<td>7</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>May et al. (1992)</td>
<td>P_{PH+}/(P_{PH+} → P_{PH-})</td>
<td>12/17</td>
<td>n.m.</td>
<td>Parallel</td>
<td>15</td>
<td>10 weeks</td>
<td></td>
</tr>
<tr>
<td>Pieters et al. (1992)</td>
<td>P_{CBZ} → P_{CBZG}/none</td>
<td>15</td>
<td>15NE</td>
<td>Parallel</td>
<td>22</td>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>Bittencourt et al. (1993)</td>
<td>PB + (PHT/CBZ)</td>
<td>50</td>
<td>15%</td>
<td>Parallel</td>
<td>?</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Gilham et al. (1993)</td>
<td>P + (VGB × plac)</td>
<td>24</td>
<td>13%</td>
<td>X-over (R)</td>
<td>10</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Smith et al. (1993)</td>
<td>P + (LTG × plac)</td>
<td>40-44</td>
<td>46–51%</td>
<td>X-over (R)</td>
<td>9</td>
<td>18 weeks</td>
<td></td>
</tr>
<tr>
<td>Dodrill et al. (1993)</td>
<td>P → (P + (VGB/plac))</td>
<td>83/85</td>
<td>8%</td>
<td>Parallel (R)</td>
<td>19</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Chataway et al. (1993)</td>
<td>P/(P_{CZP} → P_{CZP-})</td>
<td>11/11</td>
<td>52%</td>
<td>Parallel</td>
<td>4</td>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>Durwen and Elger (1993)</td>
<td>P → P_{mod}</td>
<td>27</td>
<td>n.m.</td>
<td>Single</td>
<td>19</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>Mitchell et al. (1993)</td>
<td>P_{mod}</td>
<td>?</td>
<td>n.m.</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>McKee et al. (1994)</td>
<td>CBZ + (OCBZ × plac)/VPA + PHT + (OCBZ × plac)/OCBZ</td>
<td>9/9/10/7</td>
<td>19%</td>
<td>X-over (R)</td>
<td>8</td>
<td>3 weeks</td>
<td></td>
</tr>
</tbody>
</table>

VGB, vigabatrin; LTG, lamotrigine; OCBZ, oxcarbazepine; CLZ, clorazepate.
Randomized treatment allocation, or treatment sequencing in a crossover and parallel design, is indicated by the suffix (R).
the scheduling of treatments and assessment points, or different schedules were employed for different subjects. In such cases the design was classified as unclear (?).

5 **Number of cognitive variables.** This gives an indication of the possible scope of the study with respect to cognitive functioning; also, this is a statistically relevant characteristic. Uncertainty as to the number of variables actually employed (?) in analysing the data may occur even if the tests used are mentioned; often multiple outcome variables may be derived from a single test (e.g. response speed, accuracy, subscales in intelligence tests).

6 **Time on AED.** This characteristic is important in judging the relevance of the results to chronic AED use. Its meaning depends on the particular design employed. In a post-test-only design the figures quoted relate to the duration of treatment prior to the assessment point. In repeated measurement designs with one or more groups (i.e. single and parallel) this refers to the duration of the experimentally changed AED-treatment or the continuous medication interval studied. With multiple assessment points during the trial, the maximum interval studied is given. In a crossover design where multiple AEDs or dosages are given, this refers to the time on each AED [c.q.] dosage.

**Methodological considerations**

Closer inspection of the studies that we identified shows many methodological problems, most of which are inherent to polytherapy as such. These methodological

<table>
<thead>
<tr>
<th>Abbreviated designation</th>
<th>Design name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-test</td>
<td>Post-test-only</td>
<td>One or more groups of subjects are tested after (but not before) receiving treatment</td>
</tr>
<tr>
<td>Single</td>
<td>Single group pre-test–post-test</td>
<td>A single group is tested both before and after the treatment period</td>
</tr>
<tr>
<td>Parallel</td>
<td>Parallel groups</td>
<td>Two or more groups are assigned to different treatment conditions and tested both before and after the treatment period</td>
</tr>
<tr>
<td>X-over</td>
<td>Crossover</td>
<td>The same subjects are tested under different treatment conditions, counterbalancing the order of treatments</td>
</tr>
</tbody>
</table>

Randomized treatment allocation, or treatment sequencing in a crossover design, is indicated by the suffix (R).
problems must be taken into consideration carefully because they restrict the validity of the information from these studies.

Treatment reproducibility

Polytherapy is by nature a heterogeneous treatment category; thus, one finds treatment descriptions such as ‘various combinations of the three major AEDs’ (Reynolds and Travers, 1974) or ‘PHT and one or more other AEDs’ [c.q.], ‘drug regimens exclusive of PHT’ (Dodrill and Wilensky, 1992), or even ‘no attempt was made to standardize drug therapy as part of the study’ (Mitchell et al., 1993). Obviously, widely different drug regimes would fit such descriptions, and results established with one regimen may not apply to another. Also, the polytherapy manipulations used in many studies are actually quite complex, making replication problematical. For example, all polytherapy reduction studies are done as part of individualized programs of therapy rationalization. That is, patients did not have their medications changed for research purposes, and different types of medication change were not subjected to randomization. Rather, changes were typically made ‘according to the individual needs of each patient’ (Durwen et al., 1992). The clinical considerations underlying the medication changes are a major ingredient of the treatment package, albeit one that may not be easily reproduced.

Drug interactions

Combinations of AEDs may alter metabolism to produce changes in the level of active and/or toxic metabolites. Examples include the decrease in CBZ levels due to the increased elimination of the drug when given together with PHT and/or phenobarbital (PB). Such interactions can alter seizure control efficacy and may be relevant to cognitive functioning. With multiple drugs, identifying the components of a treatment most responsible for any observed effects presents a difficult problem.

Serum concentration-effect relationships

Cognitive AED effects may be examined through an analysis of the relationship between test scores of subjects and their individual serum drug levels, and this approach seems to offer a way out of the problem mentioned above. In fact, a number of studies report such relationships suggesting that, generally, higher serum levels are associated with lower cognitive scores. However, in patients with epilepsy, higher serum concentrations may be the reflection of higher AED doses prescribed for more severe epilepsy (Reynolds, 1989), perhaps with seizures not fully controlled (Butlin et al., 1984). Also, AEDs may interact on receptor sites (pharmacodynamics), which would not necessarily be reflected in the pharmacokinetics expressed in serum concentrations. Such factors greatly reduce the interpretability of relationships between serum concentrations and cognitive performance.
Seizure confound

Polytherapy is typically given to patients with refractory epilepsy, and separating seizure effects from AED effects may thus be very difficult, particularly in add-on studies, where the cognitive evaluation is usually made in connection with an efficacy trial. That is, adverse cognitive AED effects may be masked by beneficial effects of better seizure control. Also, patients with refractory seizures may not be representative of the general population with epilepsy.

Discussion of cognitive effects

Due to the validity threats described above, acting singly or simultaneously, drawing conclusions about the cognitive effects of polytherapy studies is not without complications. Table 22.1 shows a heterogeneous number of treatments and designs. Moreover, the anecdotal-type of information is best illustrated by the large number of question marks both in the column expressing numbers of patients, for the dropout rates and even for design, number of cognitive variables, and time on AEDs. Starting from the principles of evidence-based medicine we can therefore only proceed carefully. Conclusions will be drawn on a general level.

Reviewing the literature, five types of studies can be distinguished:

- The first type of study is the single measurement polytherapy study. Corbett et al. (1985) is an example of studies that analyze polytherapy in a single measurement design. Patients who received polytherapy are analysed for cognitive impairments. Although, without exception all these studies report severe cognitive impairment the design does not allow the isolation of drug effects from the effects of the epilepsy.
- The second type consists of studies comparing monotherapy with polytherapy. Brodie et al. (1987) showed no difference between monotherapy CBZ, VPA, PHT and polytherapy at a single assessment study. Other studies did, however, show serious impairments for polytherapy. Bittencourt et al. (1993) used a complex add-on with a polytherapy at baseline (with either PHT or CBZ added to an existing low-dose PB regime) and monotherapy (PHT or CBZ) at endpoint. The study shows statistically significant improvements on measures of memory and attention after withdrawal from polytherapy. As for the former type of study, it is extremely difficult to avoid the seizure confound here as polytherapy is mostly given to different patients.
- A convincing group of studies showed the effect of reduction of polytherapy. Durwen et al. (1989) showed that reduction of polytherapy resulted in improvements of verbal memory. Duncan et al. (1990) used a rather interesting design in which separate drugs (PHT, CBZ, VPA) were removed from polytherapy regimes showing consistent improvements in cognitive function, irrespective of the type of drug that was discontinued. Thompson and Trimble (1980, 1982) Ludgate et al.
(1985) and Van Rijckervorsel et al. (1990) are other examples of studies that showed marked improvement after reduction of polytherapy.

- In contrast, the fourth type of study does not show convincing effects of polytherapy. In these add-on studies a new drug is added to either monotherapy or to an existing polytherapy. Berents et al. (1987) showed impaired verbal learning when a new drug was added to an already existing polytherapy. Most other studies (Dodrill and Wilensky, 1992; McGuire et al., 1992; Pieters et al., 1992; Dodrill et al., 1993; Gilham et al., 1993), however, showed no effects of newer drugs to an existing polytherapy. These are, however, all studies within the context of drug trials in refractory epilepsy, where the added effects of a new drug are difficult to entangle from the beneficial effects of improved seizure control.

- Finally, the last type of study that we could distinguish analyzed the relationship between cognitive impairment in polytherapy with serum level. Dekaban and Lehman (1975) claim a relationship but the study does not control interfering factors such as dose and seizure confound and, hence, does not guarantee valid interpretation. The same situation occurs for other studies such as Reynolds and Travers (1974), Matthews and Harley (1975) and Thompson and Trimble (1983).

The existing evidence from especially the reduction studies, therefore suggests the possibility of potentiation of tolerability problems in polytherapy and specifically an increase of cognitive problems. It may therefore be hypothesized that drug interactions may be responsible for this potentiation. This seems to be a general effect as it occurs in many combinations of drugs and so far not a specific combination has been identified.

### Clinical effects

Although the psychometric studies generally show a tendency of cognitive impairments in polytherapy compared to monotherapy, this merely suggests a drug interaction effect. As previously mentioned evidence-based confirmation will be extremely difficult due to the methodological problems that occur when studying polytherapy and especially in the light of the many interfering factors, especially the seizure confound. Any study will have difficulties entangling the interfering factors of seizure effects and the effects of polytherapy, when typically polytherapy is used in the more refractory epilepsies.

Nonetheless, we may look at more anecdotal clinical information. In many drug trials a similar effect has been found as suggested by the psychometric studies: a higher incidence of side-effects in combination therapy when compared to the same drug in monotherapy. This is often observed in post-marketing studies. Many of the new drugs are first tested in add-on designs and monotherapy is only used later. A recent example is topiramate showing not only a higher incidence of
side-effects in combination therapy but also different types of dominant complaints when compared to monotherapy (Aldenkamp, 2000; Aldenkamp et al., 2000). Table 22.3 illustrates this.

When inspecting this example we see cognitive impairments are reduced in monotherapy, but other impairments, especially paresthesia, are increased. This may lead to the hypothesis of potentiation of some tolerability problems and especially cognitive side-effects.

Of course, it is imperative to emphasize that the monotherapy studies typically include patients with other epilepsies compared to the initial add-on studies, which are done in refractory partial epilepsies with an associated risk of epilepsy-induced cognitive impairments. Moreover, in contrast with the former paragraph of this chapter, these side effects have not been established with formal psychometric or other objective measurements, but are based on clinician ratings of subjective patient complaints.

### Table 22.3 Percentage of side-effects for topiramate (TPM) in polytherapy vs. monotherapy; potentiation of side-effects due to polytherapy?

<table>
<thead>
<tr>
<th>Subjective patient complaints</th>
<th>Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common AEDs with TPM</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>29</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25</td>
</tr>
<tr>
<td>Ataxia</td>
<td>16</td>
</tr>
<tr>
<td>Nervousness</td>
<td>16</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>13</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>13</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>13</td>
</tr>
<tr>
<td>Memory difficulty</td>
<td>12</td>
</tr>
<tr>
<td>Confusion</td>
<td>11</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>11</td>
</tr>
<tr>
<td>Diplopia</td>
<td>10</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
</tr>
</tbody>
</table>

* *Incidence ≥10% and ≥5% difference in incidence vs. placebo.*
### Subjective reported side effects in 346 patients in a community-based study

<table>
<thead>
<tr>
<th>Area and type of side effect</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General CNS</strong></td>
<td>68.2 (overall CNS complaints)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20.3</td>
</tr>
<tr>
<td>Tiredness</td>
<td>18.8</td>
</tr>
<tr>
<td>General slowing</td>
<td>12.1</td>
</tr>
<tr>
<td>Headache</td>
<td>8.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.1</td>
</tr>
<tr>
<td><strong>Motor problems</strong></td>
<td>31.5 (overall motor complaints)</td>
</tr>
<tr>
<td>Tremor</td>
<td>13.3</td>
</tr>
<tr>
<td>Ataxia</td>
<td>13.0</td>
</tr>
<tr>
<td>Falling</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Gastrointestinal complaints</strong></td>
<td>33.2 (overall gastrointestinal complaints)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12.4</td>
</tr>
<tr>
<td>Micturition problems</td>
<td>8.4</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>5.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>61.8 (overall cognitive complaints)</td>
</tr>
<tr>
<td>Memory problems</td>
<td>21.4</td>
</tr>
<tr>
<td>Concentration difficulties</td>
<td>16.1</td>
</tr>
<tr>
<td>Speech problems</td>
<td>8.7</td>
</tr>
<tr>
<td>Language difficulties</td>
<td>7.8</td>
</tr>
<tr>
<td><strong>Visual</strong></td>
<td>7.5 (overall visual complaints)</td>
</tr>
<tr>
<td>Double vision</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Mood and behavior</strong></td>
<td>22.3 (overall mood/behavior complaints)</td>
</tr>
<tr>
<td>Agitation/irritability</td>
<td>14.8</td>
</tr>
<tr>
<td>Depression</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Cosmetic</strong></td>
<td>20.4 (overall cosmetic complaints)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>7.2</td>
</tr>
<tr>
<td>Gum problems</td>
<td>7.8</td>
</tr>
<tr>
<td>Skin complaints</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>Sleep problems</strong></td>
<td>8.7 (overall complaints about sleep)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.7</td>
</tr>
</tbody>
</table>

*One patient may be reporting several side effects.*

*Summary of both moderate and severe complaints.*
finished a community-based study, using subjective patient complaints about side effects of their treatment as primary outcome measure (Carpay et al., 2002).

Taking advantage of the reliable databases of AED use in the pharmacies in the Netherlands we were able to establish a non-selected unbiased community-based study group of adult patients with epilepsy from a suburban area (100,000 inhabitants) with a prevalence equivalent of 0.4% (i.e. 346 patients). All patients finished a rating scale on side-effects of their treatment. Almost half the patients reached a 2-year seizure remission; about one-third considers the seizures unacceptable. About 80% of the patients are on monotherapy. Nonetheless, almost 60% of the patients report side-effects in at least three areas.

Table 22.4 shows that the two areas with clearly most reports are: (a) general CNS-related complaints (such as fatigue and dizziness) with 68% complaints; and (b) cognitive complaints (61.8%). If we combine cognitive and mood areas, then behavioural complaints are, with 84.1% complaints, the dominant complaint in our study group. Within the areas, two types of complaint have been reported by >20% of the patients: memory problems (21.4%) and fatigue (20.3%). Two other complaints are reported by between 15% and 20% of the patients: tiredness (18.8%) and concentration difficulties (16.1%). It is thus clear that cognitive complaints are a dominant complaint even in a group of patients with a well-controlled epilepsy, mainly using monotherapy.

Subsequently, differences in side-effect profile were tested per AED. This was only possible for four groups with >50 patients, that is, patients on monotherapy of VPA, CBZ or PHT and patients on polytherapy (28.7%, 24.7%, 15.7% and 19.1% of the study group respectively). All remaining groups were too small to achieve sufficient statistical power. Table 22.5 shows exclusively the 7 areas with statistical differences between the four groups. On all areas the differences were caused by the higher percentage of complaints in patients using polytherapy. The remaining differences show more concentration difficulties for PHT compared to VPA, more weight gain for both VPA and PHT compared to CBZ.

**Conclusion**

Systematic analysis of subjective patients complaints about side-effects of AEDs show that the impact of side-effects may be larger than hitherto suspected both in number of patients involved (our community-based sample suggests that almost 60% of the patients with AED have complaints) and the frequency of the complaints. Especially the behavioral (and within this class the cognitive) side-effects occur frequently and require careful monitoring and possible interventions.

Still using subjective patient complaints it is clear that a switch from monotherapy to polytherapy entails a serious risk of increasing side-effects. This has been
reported from clinical groups, in patients with refractory epilepsy and within the context of many drug trials (most recently for topiramate: Tatum et al., 2001), but is now also confirmed in a community-based sample (Carpay et al., 2005). On the other hand, Bourgeois reports reduction of side effects when reducing polytherapy; this is considered proof for a partially cumulative toxic effect (Bourgeois, 1988). When in clinical decision-making the option of polytherapy arises, the serious risk of an increase in side-effects should be taken into consideration carefully. This is especially important in the light of recent revivals of polytherapy, for example, within the context of rational polytherapy.

A similar effect is often observed when new drugs proceed from initial add-on studies to studies in monotherapy. Although the efficacy profile often remains unchanged, the tolerability profiles often have to be adjusted with much more moderate profiles in monotherapy.

Formal psychometric studies are much more difficult to interpret, especially when formal scientific standards in line with evidence-based medicine are applied.

Table 22.5 Differences per area of complaint between the four groups: VPA, CBZ, PHT and polytherapy. Results from a community-based study in 346 patients

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Overall difference: Chi Square based on the Kruskall–Wallis test</th>
<th>Differences between the four groups based on the Mann–Whitney U-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness</td>
<td>9.276; df 3; ( P = 0.03 )</td>
<td>Polytherapy &gt; CBZ (( U = 1834; P = 0.02 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; PHT (( U = 1041; P = 0.005 ))</td>
</tr>
<tr>
<td>Ataxia</td>
<td>11.073; df 3; ( P = 0.01 )</td>
<td>Polytherapy &gt; VPA (( U = 2226.5; P = 0.007 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; CBZ (( U = 1952.5; P = 0.02 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; PHT (( U = 1170; P = 0.03 ))</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.389; df 3; ( P = 0.04 )</td>
<td>Polytherapy &gt; VPA (( U = 2334; P = 0.03 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; PHT (( U = 1184; P = 0.02 ))</td>
</tr>
<tr>
<td>Tiredness</td>
<td>10.047; df 3; ( P = 0.02 )</td>
<td>Polytherapy &gt; VPA (( U = 2089; P = 0.02 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; CBZ (( U = 1724.5; P = 0.003 ))</td>
</tr>
<tr>
<td>General slowing</td>
<td>9.830; df 3; ( P = 0.02 )</td>
<td>Polytherapy &gt; VPA (( U = 1995.5; P = 0.005 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; CBZ (( U = 1789; P = 0.009 ))</td>
</tr>
<tr>
<td>Concentration</td>
<td>8.253; df 3; ( P = 0.04 )</td>
<td>PHT &gt; VPA (( U = 1799; P &lt; 0.05 ))</td>
</tr>
<tr>
<td>difficulties</td>
<td></td>
<td>Polytherapy &gt; VPA (( U = 2084.5; P = 0.01 ))</td>
</tr>
<tr>
<td>Weight gain</td>
<td>8.040; df 3; ( P &lt; 0.05 )</td>
<td>VPA &gt; CBZ (( U = 3234; P = 0.05 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PHT &gt; CBZ (( U = 1617; P = 0.004 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polytherapy &gt; CBZ (( U = 2117.5; P = 0.02 ))</td>
</tr>
</tbody>
</table>

The sign > indicates a high percentage of patients reporting problem for that specific area.
Nonetheless, we may claim that a systematic review supports these conclusions. It may be considered conceivable that polytherapy increases the risk of behavioral and specifically cognitive impairments. We may therefore hypothesize a potentiation of tolerability problems leading to cognitive impairments due to interactions between AEDs. This seems to be a general effect as it occurs in many combinations of drugs and so far no specific combination has been identified.

REFERENCES


Cognitive side-effects due to AED combinations and interactions


Part V

Conclusions and future perspectives
Selection of drug combinations in clinical practice: current and future perspectives

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Introduction

Polytherapy has flourished in the long history of epilepsy. In recent decades, it has waxed and waned depending on our current knowledge and availability of antiepileptic drugs (AEDs). Introduction of effective AEDs in the first half of the twentieth century shifted treatment strategy towards monotherapy in the 1950s and 1960s. However, in the 1960s and 1970s, when carbamazepine (CBZ), valproic acid (VPA), benzodiazepines and other AEDs made their appearance, treatment reverted towards polytherapy once again. The concept of treatment was based on the erroneous assumption that polypragmasy improves the effectiveness of AEDs without increasing their toxicity. Besides, clinical trials of AEDs were biased and methodologically dubious (Coatsworth, 1971).

Introduction of double-blind trials and other rules for drug evaluation protocols was an important step in comparative and more objective AED clinical evaluation (Delgado-Escueta et al., 1983; Mattson et al., 1983). Moreover, when the negative aspects of polytherapy were reported in the 1970s and 1980s (Shorvon and Reynolds, 1979; Reynolds and Shorvon, 1981), there was a return to monotherapy in the majority of patients. Tests of AED concentration in the blood serum and credibility of the measurements substantially contributed to this shift in treatment strategy (Pippenger et al., 1976; Richens, 1980).

In the late 1980s and in the 1990s several new AEDs were introduced to the pharmacutic market and used as add-on therapies. This led to yet another shift towards polytherapy in difficult-to-treat patients. At this time the concept of ‘evidence-based medicine’ provided more objective quantified drug effect evaluation and the principle of ‘good clinical practice’ was coined to emphasize the need to individualize the choice of drug(s) and dose.

Rational AED selection and combination is a relatively recent event in the history of treatment of epilepsy based on animal models (Masuda et al., 1981; Löscher and Ebert, 1996; Czuczwar, 1998). However, clinical trials of phenobarbital (PB)
and phenytoin (PHT) monotherapies vs. combination of both drugs were performed many years ago, emphasizing the beneficial effect of this combination (Yahr et al., 1952). Consequently, there is not much clinical experience in this field and there is very little knowledge of how to combine drugs most efficiently. The concept has been developed over the last 10–15 years and a number of new AEDs have been approved for epilepsy treatment in the majority of countries. At present, 15 AEDs are available in all. They have different mechanisms of action, tolerability, pharmacokinetic and pharmacodynamic profiles and possible interactions. The availability of such a variety of AEDs has widened the choice of combinations and made the choice much more complex for clinicians than 15 years ago. But on the other hand, it provides better opportunity for the treatment of patients with fewer adverse events.

Selection of the best AED combination for a given patient is no easy task since there is no simple rule. Moreover, it is good to remember that populations of patients with epilepsy are heterogeneous and therefore it is hard to compare the efficacy of drug combinations in such populations. However, a broad knowledge of the characteristics of old and new AEDs and consideration for the distinctive profile of the patient make it easier to make the most reasonable and knowledgeable decision, and to select the best and optimal patient care for those who are resistant to pharmacotherapy. These patients present the greatest problem and are the biggest challenge for epileptology today. For clinicians, the challenge is to identify patients early and to select the most appropriate AED combinations. For researchers, the challenge is to discover the cause of drug resistance and to synthesize new and more efficient AEDs.

In this chapter, polytherapy with old and new AEDs, current clinical experience with drug combinations and future treatment strategies in pharmacoresistant epilepsies will be discussed.

**Pharmacotherapy-resistant seizures**

The majority of patients (60–70%) with newly diagnosed epilepsy can apparently be controlled with a single AED. The remaining group with recurrent seizures – so-called refractory epilepsy – requires two or (in a small percentage of patients) even three AEDs to improve seizure control – providing that AED selection is based on currently available knowledge of their pharmacologic profile and drugs are appropriately matched to the unique characteristics of the epileptic patient (type(s) and severity of seizure, age, sex, health condition, medical history, concomitant medications, profession, level of acceptance of seizures and/or adverse events, etc.).

The concept of pharmacotherapy resistance is justified and useful (Table 23.1), even if there is no generally accepted definition (Ohtsuka et al., 1988; Lüders, 1990;
The need to use more than one drug for seizure control may be called drug resistance. For combination therapy this definition is useful enough for the time being. But when should combination therapy be started? How many monotherapies should be tried when about 15 AEDs are available? Different neurologists answer this question differently. In 14 Mediterranean countries, 23–67% of neurologists chose combination therapy when monotherapy with one drug failed to control seizures, rather than trying a second, alternative monotherapy (Baldy-Moulinier et al., 1998). It seems that in newly diagnosed patients at least two (or even three) drugs with different mechanisms of action should be used in monotherapy before combination therapy is started.

Patients with refractory epilepsy have always been in polytherapy with more or less effective drugs. At present, selection of AED combinations is mainly based on personal experience and on a few clinically documented studies. On the other hand, there are a number of promising studies based on animal seizure and epilepsy models showing that certain combinations of two AEDs are more or less effective than others and have better or worse tolerability (Bourgeois, 1986, 1988; Czuczwar, 1998; Deckers et al., 2000). These results require critical clinical verification, however, for example the beneficial effect of CBZ with calcium channel blockers combination, reported in many experimental animal studies (Czuczwar et al., 1992), has not been confirmed at the clinical level (Chaisewikul et al., 2001a). The authors, in an overview of corresponding literature, do not recommend this comedication because of significant withdrawal rate probably due to side-effects (flunarizine) or not convincing evidence of effectiveness (nifedipine or nimodipine). There is also the question not only of drug combinations but also of dose and side-effect differences in animal models and human beings. It was also shown in experimental studies that synergism of two drugs may be evident at only some drug ratios (Czuczwar and Borowicz, 2002).

**Scale of the problem**

Mattson (1992) estimates that success of a monotherapy in newly diagnosed partial epilepsies may be observed in 65% of patients. In the remaining 35%, less than
one-third (10%) may be markedly improved by two-drug combinations and a further 5% by more than two AEDs. Thus, about 35% of newly diagnosed patients are left with partially controlled or uncontrolled seizures and are subject to various drug combinations of two or more AEDs. Taking into consideration incidence, high prevalence, chronic characteristics of epilepsy and possible remissions, it seems that the ratio of patients with chronic epilepsy to newly diagnosed and controlled patients is rather increasing, even if newly diagnosed patients are being successfully treated at the expected level. Thus, the number of patients requiring long-term combination therapy is at least 30–40% of the general epileptic patient population.

This figure is also derived from successive monotherapies with three different AEDs in previously untreated patients (Kwan and Brodie, 2000). Out of 470 previously untreated patients, seizures were successfully controlled by monotherapy in 61% of patients. In our multicentre studies performed on 6204 patients in 13 epilepsy-oriented centres in Poland in 2001, the use of monotherapy and polytherapy was compared (Table 23.2) (Majkowski et al., 2005). The study shows that 42.2% of patients (n = 2588) are on polytherapy. The five most frequent combinations of two AEDs, i.e. CBZ + valproate (VPA), VPA + lamotrigine (LTG), CBZ + LTG, CBZ + vigabatrin (VGB), and CBZ + topiramate (TPM), were used in 47% of the patients, 22 combinations were used in 43% and 10% of combinations in the remaining 203 patients with localization-related seizures, thus showing great variability of AED combinations. Deckers et al. (2000) reviewed 33 animal and human studies on AED combinations and found that several combinations offered improved effectiveness, but no uniform approach was used in the studies.

### Rational polytherapy

The concept of so-called rational polytherapy – broadly discussed in previous chapters – was introduced in the 1990s. This concept is based on a better understanding of pharmacokinetic and pharmacodynamic drug interactions and allows, to some extent, the prediction of their clinical effects. A review of the literature on the possible

#### Table 23.2 Mono- and polytherapy in 6117 patients with chronic epilepsy

<table>
<thead>
<tr>
<th>Number of AEDs</th>
<th>% and (number) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>57.7 (3530)</td>
</tr>
<tr>
<td>Duotherapy</td>
<td>31.7 (1940)</td>
</tr>
<tr>
<td>Three drugs</td>
<td>8.8 (541)</td>
</tr>
<tr>
<td>More than three</td>
<td>1.7 (106)</td>
</tr>
</tbody>
</table>
impact of AED interactions on therapeutic outcome when bitherapy had to be used has recently been published (Patsalos et al., 2002; Patsalos and Perucca, 2003).

The aim of rational polytherapy is to improve the effectiveness to toxicity ratio: effectiveness should be supra-additive or at least additive and toxicity should be lower than additive. Effectiveness of drug combination is measured by frequency and/or severity reduction of seizures. It may also have some economic benefits if combination therapy is cheaper than therapy with either of the drugs or when seizure and/or toxic effects are more successfully controlled, just decreasing indirect costs. Improved well-being of the patients is difficult to calculate.

A good understanding of AED pharmacologic mechanisms of action should help the therapist to choose the best two-AED combination (Czuczwar, 1998; Deckers et al., 2000). It has been proposed that combination of AEDs with different mechanisms of action may have a better clinical effect than drugs with the same mechanisms. It seems logical, for the majority of patients, that combination of drugs with different mechanisms of action is more effective than two drugs with a similar mode of action. Combining a drug facilitating gamma amino butyric acid (GABA)-ergic transmission with a drug reducing the excitatory effects of aminoacids (LTG) or a Na\(^+\) channel blocker (CBZ) with a drug increasing GABA levels (VGB) is probably more advisable than combining two Na\(^+\) channel blockers (e.g. CBZ + PHT). This idea is based on experimental data and theoretical speculations. However, knowledge about various and usually complex or unknown mechanisms of action of the majority of AEDs is incomplete. Tiagabine (TGB) and VGB are the only two drugs which have been developed on the basis of the seizure mechanism concept and both have a single mechanism of action, i.e. both increase GABA-mediated inhibition, but their modes of operation are different. Ethosuximide (ESM) is the third drug with a single mechanism of action (calcium channel blocker). The remaining AEDs have multiple mechanisms of action and therefore act like combination therapy.

Moreover, at the clinical casuistic and experimental level, there are exceptions to this idea, e.g. treatment with two GABA-ergic agents (VGB and TGB) resulted in substantial improvement of seizure control in two patients with refractory epilepsy (Leach and Brodie, 1994). At the experimental level, combination of TGB and gabapentin (GBP) – two drugs affecting the GABA-ergic system – has shown supra-additive interaction without adverse events in mice models of seizures (Luszczki et al., 2003). The authors suggest that this very promising experimental result should be verified clinically.

### Combination therapy with old AEDs

The general principles of AED combination are shown in Table 23.3. Additive or supra-additive efficacy was claimed in a number of reports when two drugs were
combined and compared to monotherapy. Many studies, however, are based on small numbers of patients, with possibly some essential methodological pitfalls which are discussed in Chapters 10 and 12. There are also casuistic reports showing exceptions from the rules.

One of the earliest beneficial effects of combination therapy of CBZ with PHT was observed in 15% of patients (5 of 33) in comparison with successful cross-over monotherapy with either drug in 67 of 100 patients (Hakkarainen, 1980). An additive or even supra-additive effect was observed in refractory absence seizures in five patients following combination of VPA and ESM (Rowan et al., 1983); neither of the drugs used in monotherapy was effective. A pharmacodynamic interaction was suggested. In one study of VPA and ESM comedication, serum levels of VPA were significantly \( P < 0.01 \) lower in this combination than in VPA monotherapy (Sälke-Kellermann, 1997). The mechanism of this interaction is unknown.

Good efficacy with minor side-effects was obtained with CBZ and VPA comedication (Fröscher et al., 1984). At least 50% seizure reduction was reported in 50% of patients. The best results were observed in patients with generalized seizures as opposed to partial complex ones. In such comedication, the additive anticonvulsant effect seemed to be more significant than the additive effect of neurotoxicity (Bourgeois, 1988). However, it was also reported that combination of CBZ with VPA may result in additive effectiveness and in supra-additive neurotoxicity due to increased CBZ-epoxide levels resulting from inhibition of expoxide hydrolase by VPA (Warner et al., 1992).

Deckers et al. (2001) used a different methodological approach to evaluate drug combination. In newly diagnosed patients, CBZ and VPA monotherapy were compared to a half drug load of both. The authors did not find any difference in neurotoxicity or efficacy.

### Table 23.3 General principles of AED combination

1. Failure of monotherapy with two (or even three) successive drugs.
2. Knowledge of pharmacokinetic and pharmacodynamic profiles of the AED.
3. To select drugs considering their interactions.
4. To select drugs which have low probability of adverse events and high therapeutic index.
5. Combining AEDs which have different mechanism of action seems to be more beneficial than using two drugs with similar mechanism.
6. Combination therapy is more effective in two or more different seizure types.
7. Adding or withdrawing AEDs should be carefully monitored clinically (and blood level concentration if appropriate) during first days or weeks of modified treatment because of possible drug interactions.
Combination of CBZ with VPA or with PHT resulted in a decrease of generalized tonic–clonic seizures in half of the patients (Mattson and Cramer, 1988). A similar effect of at least 50% seizure frequency reduction and complete seizure control was obtained in one-half of 100 patients with uncontrolled partial and secondarily generalized seizures by switching from CBZ monotherapy to bitherapy combining VPA with CBZ (Dean and Penry, 1988).

Beneficial effects of combination of CBZ and VPA in patients with complex partial seizures and secondarily generalized seizures were observed in 14 of 17 patients who failed to respond to VPA or CBZ monotherapy (Walker and Koon, 1988).

In a double-blind prospective study of patients with complex partial seizures receiving CBZ or PHT in monotherapy, divalproex sodium (an oligomeric complex composed of sodium valproate and VPA in a 1:1 molar ratio) or placebo was randomly added (Willmore et al., 1996). Significant seizure frequency reduction (by 43%) was obtained in patients on drug combination with divalproex compared with the placebo group.

Thus, in localization-related seizures, combination of CBZ with VPA seems to be more effective than monotherapy with CBZ or VPA in some patients resistant to these drugs. The same is true for combination therapy of VPA with ESM in absence seizures.

These favorable effects in various two-drug combination therapies (PHT, PB, CBZ and VPA) were not confirmed by other authors (Schmidt, 1982; Schmidt and Gram, 1995).

Negative drug combinations have also been reported. In clinical practice, combination of benzodiazepines with PB, resulting in additive efficacy and adverse events at the pharmacodynamic level, is not recommended in long-term therapy (Leppik and Wolff, 1993).

**Combinations with new AEDs**

**Lamotrigine plus**

Combination of LTG with VPA in refractory localization seizures has been reported in a number of publications (Panayiotopoulos et al., 1993; Pisani et al., 1993, 1999a; Brodie et al., 1997). In a European multicentre study (Brodie et al., 1997), adding LTG to VPA, CBZ or PHT monotherapies produced significantly better efficacy ($P < 0.001$) than combination of CBZ or PHT with LTG. The proportion of responders were 64%, 41% and 38%, respectively. The authors suggest that the lower efficacy of the last two combinations compared with LTG alone may be due to the induction effect of PHT and CBZ on LTG and lower serum concentration.

A pharmacodynamic supra-additive effect of efficacy and infra-additive toxicity of LTG with VPA combination was suggested (Brodie et al., 1997; Frey and Kanner,
1999; Pisani et al., 1999a). However, the contribution of pharmacokinetic interaction cannot be excluded. Serum level of LTG was measured in add-on therapy with VPA or CBZ in 60 patients with resistant partial seizures (Benetello et al., 2002). In 70% of the patients there was complete seizure control or at least 50% seizure reduction. Mean LTG serum level was significantly higher in responders than in non-responders. The best results were in VPA-cotreated patients with the highest LTG serum level. Central nervous system (CNS) toxicity developed in patients with the highest LTG concentrations, whereas CNS toxicity seemed to be unrelated to CBZ or CBZ-epoxide serum concentrations.

In casuistic reports seizure control was achieved with LTG plus VPA combination in unusual refractory myoclonic epilepsy (Ferrie and Panayiotopoulos, 1999) and in very resistant absence seizures (Besag et al., 1995).

The beneficial effect of combination of LTG with CBZ seems to be controversial due to the marked increase in serum CBZ-epoxide concentration: the toxic effect is supra-additive whereas the antiepileptic affect is additive, possibly at the pharmacodynamic level (Warner et al., 1992; Besag et al., 1998; De Romanis and Sopranzi, 1999).

In randomly double-blind add-on therapy, LTG or placebo was added to previous AED medications in 30 therapy-resistant children with generalized epilepsy and Lennox–Gastaut syndrome (Eriksson et al., 1998). There was a statistically significant reduction (>50%) in seizure frequency in the LTG group compared with the placebo group.

In an open-label prospective study LTG was added to previous AED medications in partial epilepsy with drop attacks and secondary bilateral synchrony on electrocardiogram (EEG) (Bisulli et al., 2001). Good efficacy (seizure reduction >50%) was observed, including EEG improvement in all types of seizures in 12 of 14 patients.

**Gabapentin plus**

In a casuistic report, five patients with a long history of resistant partial complex seizures and unsuccessful treatment, with various new and conventional drug combinations, became seizure-free when GBP was added to LTG (two patients), to LTG and VPA (two patients) or to LTG and CBZ (one patient) (Pisani et al., 1999). Any attempt to discontinue LTG or GBP resulted in loss of seizure control.

**Topiramate plus**

In a double-blind, placebo-controlled study, combination of TPM (200 mg/day) added to CBZ in 263 patients with partial-onset seizures was studied (Guberman et al., 2002). Median seizure frequency reduction was 44% in the TPM group and 20% in the placebo group \( (P < 0.001) \).

It has been reported that the combination of TPM with LTG significantly reduces the frequency of tonic and myoclonic seizures in children (mainly in Lennox–Gastaut
Vigabatrin plus

The combination of VGB with GBP, VGB with LTG or VGB and TGB does not show pharmacokinetic interactions and may be particularly useful in pharmacotherapy-resistant partial complex seizures (Leach and Brodie, 1994; Ferrendelli, 1995). Indeed, a number of authors reported good efficacy of VGB with LTG combination in localization-related seizures compared with monotherapy with one of the drugs (Fröscher et al., 1992; Stewart et al., 1992; Arzimanoglou et al., 1993; Robinson et al., 1993; Stolarek et al., 1993; Schapel et al., 1996). However, the studies are based on rather small numbers of patients with localization-related seizures, and on casuistic reports. In another study the synergistic effect of LTG and VGB was not confirmed (Sills et al., 1993).

In 215 CBZ-resistant patients with partial seizures, VGB or VPA were randomly added to CBZ treatment (Brodie and Mumford, 1999). Combination therapy of VGB with CBZ or CBZ with VPA had similar effects: 50% of seizure frequency reduction was observed in 53% and 51% of patients, respectively. The authors conclude that VGB and VPA which increase neuronal inhibition mediated by GABA, can be added to or substituted for CBZ when it fails to control seizures.

In newly diagnosed epilepsy, combination therapy of VGB with CBZ was compared to VGB or CBZ monotherapy in 51 of 58 patients. Among 14 patients who had seizures on VGB or CBZ cross-over monotherapy, combination of both drug resulted in seizure control in five patients (Tanganelli and Regesta, 1996). Good efficacy of this combination was also obtained by adding VGB to CBZ in therapy-resistant patients (Muri and Judice, 1995). In both studies VGB with CBZ combination resulted also in toxic side-effects. These effects, which were also observed in our study in localization-related seizures, may be partly due to a pharmacokinetic interaction resulting in an increase of CBZ serum level concentration when VGB is added (Jędrzejczak et al., 2000).

Tiagabine plus

Combination of CBZ + TGB or PHT + TGB did not result in better seizure control than treatment with TGB alone. However, adverse events were the reason for withdrawal of CBZ or PHT (Biton et al., 1998). This may be an example of pharmacodynamic antagonism of drug combination.

Combination therapy of three or more AEDs

There is no convincing evidence that three or more AEDs are better than a combination of two at the maximally tolerated dose. However, everyday clinical practice
suggests that in some pharmacotherapy-resistant patients, combination of three AEDs has a better effect than two drugs. Duncan (1996) noted that refractory patients occasionally achieve better seizure control with three drugs than with two. Cereghino et al. (1975) observed that in patients with poorly controlled seizures (generalized and/or partial) the combination of CBZ plus PB plus PHT was more effective than each drug alone or combination of two drugs. A similar casuistic observation has also been reported (Fröscher, 2000).

Favorable combination of three drugs (GBP + LTG + VPA and GBP + LTG + CBZ) resulting in complete seizure control in three patients was already mentioned (Pisani et al., 1999b).

Clinical controlled trials of new AEDs show beneficial effects when a third new AED is added to two previous drugs. As a matter of fact, it is not the study design which is the target for evaluation of combination therapy. The emphasis of the study is put on efficacy of a new AED, regardless of its combination with other drugs. Moreover, the studies are based on a very heterogeneous group with a high proportion of patients with poor prognosis. Despite these limitations, meta-analysis of the controlled clinical trials of oxcarbazepine (O-CBZ) (Castillo et al., 2000), LTG (Ramaratnam et al., 2003), TPM (Jette et al., 2002; Ribacoba Montero and Salas Puig, 2002), TGB (Pereira et al., 2002), levetiracetam (LEV) (Marson et al., 2001; Chaisewikul et al., 2001b), zonisamide (ZNS) (Chadwick and Marson, 2003) in combination with other AEDs showed that 50% of the reduction of localization-related seizure frequency varies between 20% and 50% with about 10% of seizure-free patients.

In our studies, already quoted (Table 23.2), three AEDs were used in 9% (541 patients) and more than three AEDs in 1.7% (106 patients). In 541 patients about 250 different AED combinations were used; the most frequent combinations were: CBZ + VPA + LTG, CBZ + VPA + CZP (clonazepam), CBZ + VPA + VGB, CBZ + VPA + TGB, VPA + LTG + TPM, CBZ + VPA + TPM. These six combinations encompassed 28% of the patients; 25 different three-drug combinations were used in 20% of the patients; in the remaining 52% AED combinations were not repeatable. This reflects dramatic trial and error, and helplessness to improve seizure control rather than knowledge of AEDs – in otherwise therapy-resistant patients with mixed types of seizures and a long history of various drug administrations with unknown sequence of effects of preceding drug on the successive one.

A strategy for temporary administration of three AEDs is proposed by Elger and Fernandez (1999) and in Chapter 10.

Combination of four AEDs which is used in clinical practice, in a rather small percentage of patients, is unlikely to be beneficial – even if concepts of subtherapeutic doses of polytherapy are used.
Combination therapy of AED and non-AED

Such combinations have been used in a more or less controlled way for many years but have not often been subject to systematic study. In catamenial seizures, an intermittent combination of acetazolamide is rather widely used in those phases of the menstrual cycle when the risk of seizures is higher. A beneficial effect was reported for uncontrolled seizures in catamenial epilepsy by adding medroxyprogesterone (Mattson et al., 1982). Clobazam administered paramenstrually had similar effects (Feely and Gibson, 1984). Diazepam given per rectum in cluster seizures or prophylactically in children with febrile convulsions diminished AED requirement (Majkowski et al., 1995).

Combination of 25 mg of PB with 10 mg of procyclidine (anticholinergic agent), known as Didepil, was introduced by Doychinov in the 1960s. This combination in adults (in doses of 75–150 mg of PB + 30–60 mg of procyclidine per day) showed a better effect than monotherapy with PB, PRM, VPA or CBZ (Doychinov, 1980; Lysakowska et al., 1980). Anticholinergic adverse events were observed in a majority of patients, in 23% of them the dose of this combination was decreased. It was suggested that the effect of this combination is synergistic (Doychinov, 1980) but we found increased serum blood level of PB due to procyclidine interaction.

Drug interactions may produce increases in desired metabolites or decreases in the formation of undesired metabolites. For example, danazol inhibits the metabolic epoxide-trans-diol pathway of CBZ, resulting in doubled half-life (Krämer et al., 1986). The relatively low CBZ-epoxide level is possibly responsible for the good tolerability of high CBZ levels, exceeding 20 µg/ml (Fröscher, 1998). Propranolol has been used to control tremor induced by VPA; propranolol is just as effective as PRM (Gorman et al., 1986).

New perspectives on resistance to pharmacotherapy

Resistance to pharmacotherapy occurs in a significant number of patients with chronic epilepsy; its pathogenesis and mechanism(s) of development are not fully understood. It is not clear whether the drug resistance already existed before AED therapy began or whether it developed in relation to the number of seizures, AED administration, underlying brain pathology of epilepsy or genetic factors. It is also possible that a combination of various factors contributes to its occurrence (Sisodiya, 2003). Drug resistance seems to be associated with the progressive course of epilepsy. The progressive nature of epilepsy has been observed in the majority of untreated patients with generalized tonic–clonic seizures (Elwes et al., 1988) and with partial seizures (Majkowski, 1998, 2000; Jędrejczak et al., 2002); it has also been observed in treated patients despite treatment (Arroyo et al., 2002; Elices and Arroyo, 2002). The
currently available AEDs prevent neither primary epileptogenesis nor, in some patients, secondary brain epileptization with its biologic and psycho-social consequences which may be irreversible, particularly, in the developing brain.

The fact that some patients with chronic epilepsy do not respond to various AED therapies may not necessary be due to pharmacologic properties of AEDs but to an intrinsic drug resistance. Three main, and not necessarily mutually exclusive, mechanisms may play a role in drug resistance:

1. loss of pharmacologic target, e.g. GABA receptor;
2. cellular mechanism of drug pharmacologic action is blocked;
3. poor penetration of drug into the CNS (Marroni et al., 2003), which may depend on a number of impaired mechanisms of blood–brain barrier (BBB) drug-crossing or drug transporters.

In experimental models of epilepsy, as in epileptic patients, there are good and bad responders to different AEDs. In recent years a number of studies have shown some reasons for such differences.

Using patch-clamp recordings from resected hippocampal tissue from patients with temporal lobe epilepsy, the mechanism of CBZ action was studied in responders and non-responders to CBZ (Remy et al., 2003). It was found that the mechanism of CBZ action – blocking of voltage-dependent Na$^+$ channels – was completely lost in CBZ-resistant patients: seizure activity, elicited in human hippocampal slices, was insensitive to CBZ. In contrast, CBZ was effective in blocking Na$^+$ channels and seizure activity, in vitro, in patients who were responsive to CBZ. Using the same method, the authors demonstrated the ineffectiveness of CBZ on the Na$^+$ channel in chronic experimental epilepsy. The study suggests that loss of Na$^+$ channel drug resistance may constitute a novel mechanism underlying the development of drug resistance in epilepsy.

Along this line of experimental research it has been suggested that the PHT effect on after-discharges in the kindling model in rats may be different (Ebert et al., 1999). The authors suggest that the difference between PHT responders and non-responders may be genetically determined rather than due to experimental factors.

In another line of recent studies the role of drug transporters has been emphasized in the disposition of some drugs – not only in epilepsy. Immunohistochemical and molecular genetic data have shown an over-expression of a number of genes and proteins that may be responsible for pharmacoresistance (Seegers et al., 2002; Sisodiya et al., 2002; Sisodiya, 2003; Marroni et al., 2003; Potschka et al., 2003a). Because the AED(s) is (are) not reaching the epileptic neurons, secondary epileptization with its progressive symptomatology is taking place, as in untreated
patients. In such cases the kindling mechanism is a good candidate for the explanation of the progressive nature of the process in humans (Majkowski, 1999).

One of the mechanisms of resistance which has recently been identified is over-expression of drug-resistance proteins: such as multidrug-resistance gene – 1 P-glycoprotein (MDR 1, ABCB 1) and multidrug-resistance-associated proteins (MRP 1–5). Transporters, particularly MDR 1 and MRP 2, may play an important role in pharmacotherapy-resistant patients with epilepsy. They are crucial in mediating the efflux of some AEDs, such as CBZ, PHT, PB, LTG, and FBM across the BBB (see reviews of the literature by Patsalos and Perucca, 2003; Potschka et al., 2003a). Over-expression of MDR 1 or MRP 2 and possibly other proteins may limit penetration of AEDs to their brain target sites. Over-expression of multidrug-resistance proteins 2 (MRP 2; ABCC 2) was found in the apical membranes of brain capillary endothelial cells of epileptic tissue from drug-resistant patients (Potschka et al., 2003b). A complementary study shows that, in the kindled animal epilepsy model, deficiency of e.g. MRP 2 in mutant rats is associated with increased anticonvulsant response to CBZ (Potschka et al., 2003a).

The role of MRP 2 in drug disposition into the brain is poorly defined. Potschka et al. (2003b) used an interesting strategy to determine the contribution of MRP 2 to BBB function. They showed that MRP inhibitor probenecid increases the extra-cellular brain level of PHT in rats, thus indicating that PHT is a substrate of MRP 2 in the BBB. It has also been demonstrated that in MRP 2-deficient rats extra-cellular PHT brain levels were significantly higher compared with a normal strain. In the kindling model, coadministration of probenecid significantly increased the anticonvulsant effect of PHT. The same effect was observed in kindled MRP 2-deficient rats (Potschka et al., 2003b).

It was shown that the proteins may be over-expressed in the brain tissue (neurons and glia) in patients with refractory epilepsy associated with dysembryoplastic tumors, focal cortical dysplasia and hippocampal sclerosis (HS) (Sisodiya et al., 2002). The authors conclude that the over-expressed resistance proteins lower the interstitial concentration of AED in the area of the epileptogenic pathology, resulting in pharmacotherapy-resistant epilepsy. In normal brain tissue MDR 1 is expressed almost exclusively by endothelial cells whereas in epileptic cortex it is expressed by endothelial cells and perivascular astrocytes. The tissue differences may be caused by genomic factors (e.g. DNA level) (Marroni et al., 2003).

However, there is still limited proof that the candidates for mediators of drug resistance are functionally important in human drug resistance (Sisodiya, 2003). Since amygdala kindling does not induce any lasting over-expression of P-glycoprotein in areas involved in the kindling process, the process underlying epilepsy seems to be responsible for the seizures, not for over-expression of
the protein (Seegers et al., 2002). Since there are many pathophysiologic and pharmacologic similarities between the kindling model and temporal lobe epilepsy, the authors suggest that drug resistance in patients is the result of uncontrolled seizures, not the underlying pathology of epilepsy.

Siddiqui et al. (2003) tested the hypothesis that CC genotype at the ABCB 1 C3435T polymorphism, which is associated with increased protein expression, influences the response to AED. ABCB 1 3435 was genotyped in therapy-resistant and drug-responsive epileptic patients, and in control subjects without epilepsy. These pharmacogenomic results identified a genetic factor (CC genotype at ABCB 1 3435) associated with resistance to AEDs in a majority of epileptic patients.

The role of transporters in the distribution of glutamate may be just as important as AEDs. Increased extra-cellular glutamate levels in the epileptogenic hippocampus have been reported in temporal lobe epilepsy. These increased levels of glutamate transporters may be the result of malfunctioning and/or downregulation of glutamate transporters (Proper et al., 2002). The authors have shown differences in mRNA and protein levels of glutamate transporter subtype in specific hippocampal regions; in the HS subgroup excitatory amino acid transporters were reduced (parallel to severe neuronal cell loss) whereas in epileptic patients without HS there was an increase in number of glutamate transporter subtypes. The functional consequence of these findings is not determined.

These new lines of recent research show, on the one hand, how complex the pathogenesis of drug resistance is, and on the other hand, they show how necessary it is to revise the current preclinical strategy for the development of new AEDs with better penetration across the BBB than presently available drugs. All AEDs have been tested on normal animal models of seizures and epilepsies, assuming that the drugs reach the brain epileptic neurons. However, differences in kindling and AED response in normal animals and animals with developmental brain defects have been found (Majkowski, 1983; Majkowski et al., 1984; Majkowski et al., 1986). Moreover, it has been postulated that animal models of drug-resistant kindled seizures are more promising (Lösch, 2002; Lösch and Leppik, 2002). Current limitations of AED therapy and methodological problems of mono- vs. combination therapy have been recently reviewed by Deckers et al. (2003). Indeed, a new approach is needed to prevent undesirable consequences of uncontrolled seizures.

This type of future research in no way limits the concept of more rational therapy based on knowledge of pharmacokinetic and pharmacodynamic drug interactions. Clinical verification of experimental data on combination therapy, in a more homogeneous subgroup of early identified drug-resistant patients, performed in multicentre studies on a sufficient number of subjects, seems to be the best therapeutic strategy for today.
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Future research: an experimental perspective

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Introduction

The previous chapters have amply demonstrated both the need for effective combinations of antiepileptic drugs (AEDs) and the problems associated with the use of such combinations. The first problem is to choose which drugs should be combined and in which dose ratio. To be superior to monotherapy, the drug combination should either act synergistically with respect to the antiepileptic effect or antagonistically with respect to adverse effects, or both. The second major task is assessment of the efficacy of a combination and the experimental demonstration that the efficacy is significantly better than monotherapy.

It is the challenge for basic research:

1 To provide the theoretical basis to design effective combinations for specific epilepsies.
2 To provide new tools to assess whether the effect of a combination is synergistic, additive or antagonistic.

In this chapter, we will focus only on achieving maximal synergy for the antiepileptic effect. Alternatively, aiming at achieving maximal antagonism could be applied to minimize adverse effects.

Ultimately, the advantage of a combination of drugs over a single drug can be demonstrated only in in vivo experiments. In vitro experiments are highly useful for the analysis of interactions at specific targets, but can never take into account all aspects that contribute to the final efficacy in the intact organism. Therefore, studies on combination therapy should include both approaches. When designing in vivo experiments and choosing an experimental animal model to demonstrate synergy (or antagonism) of drug combinations, a number of points should be taken into consideration. Pharmaco-resistance is associated with a few specific types of epilepsy. Drug combinations should therefore be tested in those types of epilepsy, and appropriate experimental animal models should be selected to investigate the
efficacy and usefulness of such combinations. Furthermore, the mechanism of
epileptogenesis, the possible progressive nature of the epilepsy and the chronic use of
AEDs may all cause modification or functional adaptation of the efficacy of a drug.

In this chapter the factors influencing AED responses will be discussed first. Subsequently, the use of computer simulations based on mechanistic interaction
models for designing efficient study protocols and data interpretation will be
introduced. Finally, the assessment of the efficacy of combinations based on
pharmacokinetic–pharmacodynamic (PK/PD) modeling of concentration–effect
data will be dealt with.

Factors influencing AED response

Mechanisms of epileptogenesis

Development of new effective AEDs and therapeutic approaches ideally implies
elucidation of the basic mechanisms of epileptogenesis and seizure generation and,
thereby, identification of the appropriate targets (Lösch and Ebert, 1996). Different
epilepsies have different mechanisms of epileptogenesis. Therefore, the choice of the
experimental model to study basic mechanisms is critical. Epileptogenesis and
seizure generation seldom depend on a single cause but rather on a combination of
factors. This can be, for example, reduction of GABAergic inhibition, enhancement
of glutamatergic excitation, a change in properties of voltage-regulated Na⁺-chan-
nels, etc.; but it may also depend critically on specific neuronal loss, synaptic reor-
ganization and gliosis. Furthermore, developmental abnormalities and tumor
growth may be associated with generation of ‘epileptogenic networks’ characterized
by enhanced seizure susceptibility. Intuitively, it might be argued that effective phar-
macotherapy will depend on correctly targeting a number of properties of neuronal
systems simultaneously. The fact that a remarkable number of AEDs appear to have
multiple actions indirectly supports this notion. One approach could be to design
drugs that incorporate several specified actions in a single molecule (Lösch and
Ebert, 1996). This may be possible at some time, but for the near future it is more fea-
sible to attempt to combine drugs with highly selective actions on specific targets.
Such combinations would represent truly rational polytherapy. Presently, drug com-
binations consist only of compounds with putative antiepileptic action. However, it
is conceivable that future combinations will also include drugs that are presently not
considered antiepileptic.

Experimental animal models

For studies on drug combinations experimental epilepsy models should be used that
mimic human epilepsies and seizure types exhibiting a high percentage of resistance
to pharmacotherapy Stables et al (2002). The subpopulation of refractory epilepsy is not a well-defined group. About 60% of all refractory patients have temporal lobe epilepsy presenting with complex partial seizures (Reynolds et al., 1983). Refractory epilepsy also occurs very often with severe syndromes such as Lennox–Gastaut (Sillanpää, 1995) and in some forms of primary generalized epilepsy (Reutens and Berkovic, 1995). However, seizures do not persist in all patients with any one of these forms of epilepsy. Regesta and Tanganelli (1999) recently discussed a number of factors that may be useful as predictors of refractoriness. Apart from syndromes and types of epilepsy, this list includes other factors such as frequency of seizures, number of seizures before treatment, status epilepticus, brain lesions, brain tumors and genetic factors.

From the discussion above, it is clear that many factors can contribute to the emergence of pharmaco-resistance. However, at present there are only a few models available that faithfully represent types of epilepsy associated with pharmaco-resistance (Coulter et al., 2002; Löscher, 1997).

Löscher and co-workers developed an interesting model. They observed that a subpopulation of amygdala-kindled animals do not respond to phenytoin (Löscher et al., 1993). In this subpopulation other AEDs are not effective either, with the possible exception of levetiracetam. From their studies, evidence is accumulating that this can be considered as a true model for pharmaco-resistant epilepsy (Cramer et al., 1998; Löscher, 1997; Löscher et al., 1998).

Recently the 6-Hz-psychomotor seizure model of partial epilepsy was evaluated as a potential screening model of therapy-resistant limbic seizures (Barton et al., 2001). Because of the phenytoin insensitivity, this model was originally abandoned, but this very property may indicate its usefulness as a model of pharmaco-resistant epilepsy. In a study on the effect of twelve established and new AEDs in this model, it was found that at low-stimulus intensity, nearly all drugs exhibited full or partial protection. Increasing the stimulus intensity decreased the efficacy of all AEDs and only levetiracetam and valproate remained fully protective, although with a lower potency.

Generalized epilepsies respond well to monotherapy, as do experimental genetic models of absence-like epilepsies such as the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) and the WAG/Rij rats from Nijmegen (The Netherlands). Accordingly, these models appear to be less relevant for sophisticated drug interaction studies. However, recently a model has been described that appears to reflect properties of atypical absences (Cortez et al., 2001), a progressive form of epilepsy that eventually responds poorly to drug treatment. The model is based on inhibition of cholesterol synthesis in a critical postnatal period. Although it has not yet been characterized rigorously (including response to drug treatment), it might prove an interesting model for drug interaction studies. Since the animals exhibit spontaneous seizures, this model more closely resembles true epilepsy.
A number of experimental models have been developed, based on the long-term effects of induction of status epilepticus, which share a number of properties with human temporal lobe epilepsy. Status epilepticus can be induced either by administration of convulsant drugs (Sperk, 1994; Turski et al., 1989) or application of nearly continuous electrical stimulation to selected brain structures (Gorter et al., 2001; Lothman et al., 1989; Nissinen et al., 2000; Shirasaka and Wasterlain, 1994). Although the models differ in details, they have in common that the animals develop spontaneous seizures after a so-called latent period.

Most pharmacologic studies in these models have involved testing efficacy of anticonvulsant drugs in the acute phase or (less frequently) on spontaneous seizures (Glien et al., 2002; Leite and Cavalheiro, 1995; Nissinen et al., 2004). Other studies have focused on mechanisms of epileptogenesis in order to identify new targets and to prevent cell death, development of spontaneous seizures, etc. (Liu et al., 1999; Mazarati et al., 1998b; Pitkänen et al., 1999; Rice and DeLorenzo, 1999). Only few studies have attempted to characterize development of pharmaco-resistance. It has been noted that the efficacy of AEDs rapidly diminishes after induction of status epilepticus (Kapur and Macdonald, 1997; Mazarati et al., 1998a; Morrisett et al., 1987). However, how induction of status epilepticus and the process of epileptogenesis leading to spontaneous seizures affect the time course and nature of reduction in efficacy of AEDs, has not yet been studied systematically and quantitatively.

Studies in the post-status model of spontaneous seizures after hippocampal electrical stimulation have revealed a novel factor that may underlie pharmaco-resistance, namely a change in the molecular structure of the Na\(^+\) channel, characterized by the emergence of the neonatal form, detrimental to the adult form (Aronica et al., 2001). This is associated with a change of the kinetics of Na\(^+\) currents (Ketelaars et al., 2001) and may account for a change in the sensitivity to AEDs such as carbamazepine (Vreugdenhil and Wadman, 1999; Reny et al., 2003). This illustrates the relevance of using proper experimental animal models for the evaluation of AEDs, alone or in combinations.

An unexplored area is the use of animal models developed by controlled mutations. Identification of the genetic mutations in well-defined human epilepsies in principle provides the tools to induce similar syndromes in animals. This provides exciting opportunities that might become available within a few years.

**Disease progression**

Some types of epilepsy are clearly progressive in nature and the same is observed in a number of experimental models, for example kindling and the post-status models. This aspect is a central issue of these models. It is likely that progression of the epileptogenic process will alter the response to AEDs. A good example is the failure of N-methyl-D-aspartate (NMDA) antagonists in clinical studies (Löscher and
Schmidt, 1994), which may be due to profoundly altered properties of NMDA receptors, as has been observed after kindling (Mody, 1999). Few studies on AEDs have been performed from this perspective. Studies by Cleton et al. may serve as an indication of the importance of this aspect and as a proof of concept. The efficacy of midazolam to enhance gamma amino butyric acid alpha (GABA_A)-mediated inhibition was compared in fully kindled animals and unstimulated controls, using the increase in the β-frequency band in the electroencephalogram (EEG) as a marker for enhanced inhibition. Kindling reduced the maximal effect by about 25% and similar reductions were found in the cortical stimulation model and in WAG/Rij rats, which exhibit spontaneous absence seizures (Cleton et al., 1998; 1999b). This indicates that this phenomenon is not restricted to a specific experimental model. Remarkably, kindling did not affect the efficacy of tiagabine, a drug that enhances GABAergic inhibition to a similar degree, but by a different mechanism (Cleton et al., 2000a). On the contrary, the potency of tiagabine was increased. Thus, alterations in efficacy of AEDs may differ for each drug (and drug combination), depending on the mode of action.

Influence of chronic medication
AEDs are always taken chronically. The continuous exposure of a receptor to a drug may cause adaptation of that receptor. This is commonly called tolerance development, of which the benzodiazepines are the classical example. Studies by Cleton et al. on midazolam and tiagabine yielded interesting observations. Chronic treatment with midazolam, either by continuous infusion or by administration via implanted slow-release devices, caused a reduction in efficacy of the order of 50% (Cleton et al., 2000c), similar to the reduction in efficacy in different epilepsy models. Investigation of chloride uptake in synaptoneurosomes from amygdala-kindled animals, and animals chronically treated with midazolam suggested that reduction in efficacy of the administration of midazolam was caused by adaptation of the GABA_A receptor in both cases (Cleton et al., 1999b). Thus, similar adaptive (homeostatic) mechanisms may be present in disease progression and drug tolerance. Nevertheless, chronic administration of tiagabine in amounts that enhanced GABA_A-mediated inhibition to the same extent as midazolam, did not affect the efficacy at all (Cleton et al., 2000b). Whether chronic treatment alters the efficacy or not, these observations emphasize that the effect of chronic treatment needs to be taken into account when studying drug combinations.

Pharmacokinetic factors and interactions
When considering the efficacy of drug treatment or when comparing the efficacy of a specific regimen under different conditions, it is of course necessary to ensure that the level of target exposure is known. In other words, pharmacokinetic
parameters should be determined as well. Chronic medication, the epileptic state of the brain and disease progression may all influence the pharmacokinetics of a drug. In addition, pharmacokinetic interactions often occur when drugs are given in combination. Thus, it is self-evident that determination of pharmacokinetic properties should always be included in studies on drug efficacy, in particular with drug combinations. In the face of these arguments it is surprising that this is the case only in about half of the studies in the literature. The pharmacokinetic processes that may influence the drug effect are absorption, rate of metabolism, formation of active metabolites, distribution (also within the brain), protein binding, passage of the blood–brain barrier and active transport out of the brain.

Development of drug combinations: a modeling approach

The commonly held view is that only combinations of AEDs with different mechanisms will result in a synergistic action. The logic of this is clear, but beyond this statement the development of effective drug combinations largely remains a matter of trial and error. There is no theoretical basis to predict which combinations of mechanisms will yield a synergistic, additive or antagonistic effect, how large a synergistic or antagonistic effect will be, and how this will depend on the efficacy and concentration (or dose) of each drug. Even in oncology, where combination therapy is the rule rather than the exception, design of new combinations is often simply based on overlap of efficacies and lack of overlap of toxicities (Peters et al., 2000). Two scenarios can be envisaged in which combination therapy could be applied. Refractory epilepsy often starts with an initiating event (e.g. head trauma, febrile seizures or stroke), which sets in motion a cascade of irreversible events ultimately leading to pharmacoresistance. Each step in the cascade is a potential target for intervention (Löscher, 2002). A cocktail of drugs aimed at these targets could prevent this domino effect. This requires of course, knowledge of the involved risk factors, mechanisms of epileptogenesis and seizure generation, disease progression, and of the time course of the cascade at a level that is presently not available, but it could become feasible in the future. The alternative scenario is to design drug combinations based on knowledge about the various mechanisms presently known to be involved in pharmaco-resistant epilepsies. Also this approach is hampered by a lack of understanding of all the involved factors, but the prospects in this direction are considerably better.

Knowledge of the mechanisms that operate in an interaction can be used to simulate the response of a combination at all concentration pairs. This approach is based on the operational model of agonism introduced by Black and Leff (1983). The key feature of this model is the separation of the drug–receptor interaction and the subsequent transduction into the response. Thus, the model incorporates both drug-related properties (e.g. receptor affinity) and system-related properties
An important system property is the parameter characterizing the transduction efficiency. For a series of analog compounds this parameter indicates the relative efficacy, that is whether a compound is a full or a partial agonist.

The starting point of the study by Jonker and Visser (2005) was the distinction of three general types of interaction (Figure 24.1). The simplest interaction is the competition of two drugs for the same binding site on a receptor (competitive interaction). The second possibility is the binding of two drugs to separate binding sites on the same receptor. In this case the binding of one drug can modulate the binding of the other and the subsequent receptor activation. This so-called allosteric modulation can be in the positive or negative direction. The third type of interaction is the binding of the two drugs to different receptors. In the first two types of interaction the response after receptor activation is generated through a common transduction pathway. In the last case, however, the final response is generated through different transduction pathways that converge at some point.

To compare the different interaction schemes they developed an elegant method. The classical method used to evaluate drug interactions is the isobolographic analysis (Berenbaum, 1989). In this analysis different concentration pairs of the two drugs needed to elicit an effect of the same magnitude are plotted.
so-called isobole (or iso-effect line) is linear, the interaction is considered to be additive. Significant deviation of linearity indicates synergy or antagonism. However, this method has several disadvantages. First, the method is purely empirical and therefore does not allow conclusions concerning mechanistic aspects. Second, the shape of the iso-effect line depends on the shape of the concentration–effect relation of each drug. For example, if these relationships are described by a sigmoid $E_{\text{max}}$ model with different slope factors for each drug, the iso-effect line will not be linear. Third, if the two drugs differ in maximal response, the isobole is not defined at responses above the lower of the two maxima. Thus, interpretation of such data is not a straightforward matter.

As an alternative, three-dimensional response surfaces were generated to depict the interaction of the drug combinations (Greco et al., 1995; Minto et al., 2000). The response surface predicted by the interaction model is compared to a reference response surface. If an additive interaction is assumed, the reference surface can be constructed according to the concentration–addition method for drug A in the presence of drug B and vice versa (Pöch and Holzmann, 1980). The occurrence of synergy, simple addition or antagonism is then most easily visualized by subtracting the two surfaces. A flat surface of zero effect indicates simple addition, whereas hills and valleys indicate regions of synergy and antagonism, respectively (Figure 24.2). This method is very attractive because it allows recognition of the concentration regions of interest in a single glance and provides insight into the magnitude of the interaction as well. The simulations indicated that the best chances for observing synergism are to be expected with allosteric modulation, and if two different receptors are involved.

Figure 24.2 Visualization of an allosteric interaction. The concentration–effect relationship for agonist A is characterized by a sigmoid function. The concentration $C_a$ is normalized by dividing $C_a$ by the affinity constant $K_a$. Drug B binds to the same receptor complex but does not exert an effect of its own. The left panel shows the predicted response surface for simple addition, the middle panel for the allosteric interaction model. The right panel represents the difference between the reference and the allosteric modulation and clearly shows the concentration region of interactions.
The interaction models incorporated simple sigmoid functions to describe the drug–receptor interaction and the signal transduction. The translation of receptor activation into effect strongly influences the magnitude of the combined effect. Remarkably, stronger synergism was predicted with moderately efficient than with highly efficient signal transduction. In other words, combinations of partial agonists are more likely to yield synergy than combinations of full agonists. Many other system parameters determine whether synergism will occur. For example, a steep relation between receptor activation and effect increases the maximum degree of synergism. On the other hand, baseline receptor activation can reduce the degree of synergism predicted with allosteric interaction. Simulations have also been carried out for situations where the concentration–effect relationship of a drug cannot be described by a sigmoid function. The interaction was modeled successfully for the case where one of the drugs exerts a biphasic effect. Modeling of drug interactions is therefore not restricted to relatively simple situations. This is important because it is likely that with increasing insight into the mechanisms leading to the final response of a drug, more complex interaction models will be needed.

It should be noted that the interaction models did not only predict synergism, but under certain conditions also antagonism. Thus, in certain concentration ratios, drug combinations can be detrimental to the anticonvulsant effect.

In summary, the computer simulation proposed by Jonker and Visser appears to be a promising tool to predict which drug combinations are likely to be synergistic or antagonistic, based on mechanistic considerations. The simulations have also indicated that synergistic or antagonistic interactions do not occur at all concentration pairs. This offers a considerable advantage for designing experiments to confirm predictions, because the concentration ranges at which combinations need to be tested can be restricted and this will considerably reduce the amount of experimental work required to characterize the efficacy of a drug combination. Finally, it may be applied to establish the mechanism of unknown interactions by comparing the experimentally determined surface plot with theoretical models.

**Assessment of efficacy of drug combinations: experimental aspects**

When evaluating the efficacy of drug combinations, the objectives are simple. The anticonvulsant effect should be measured in appropriate experimental models of pharmaco-resistant epilepsy, at specified concentrations of each drug. However, in practice this is a formidable task. If we take the post-status model as an example, spontaneous seizures start to appear after a latent period of about 1 week and it takes 8 weeks to reach a steady state of approximately 10 seizures per day (Gorter et al., 2001). If suppression of spontaneous seizures were taken as pharmacodynamic
endpoint, it would cost many animals, and months if not years, to characterize the response surfaces of drugs A and B and their combination, to decide whether the combination is synergistic. Furthermore, since seizures occur at unpredictable moments, it would be necessary to maintain drug concentrations at specified levels for appreciable periods of time and to monitor plasma concentrations closely. This is obviously not feasible. Preferably the anticonvulsant efficacy of a drug or a combination should be assessed on seizure activity that can be elicited repeatedly and in a controlled manner. This should be done over a wide range of concentrations and in a reasonably short time. Simultaneously, plasma concentrations of each drug should be determined to account for possible pharmacokinetic interactions and to allow estimation of the concentration at the effect site.

**Controlled seizure activity and pharmacologic endpoints**

Seizures can be evoked easily by electrical stimulation of various brain areas. However, post-ictal threshold changes and ethical considerations often prevent repeated measurements in the same animal, certainly at short-time intervals. This virtually excludes methods like the maximal electroshock test, but seizures evoked in the kindling model or in the 6-Hz-psychomotor seizure model are useful endpoints. Suppression of seizures is a meaningful endpoint but it is an all-or-nothing event. More accurate information can be obtained by determining the threshold for convulsions, for example by stepwise increase of the stimulus intensity. However, this is a time-consuming procedure, and post-ictal changes may confound threshold values with repeated determination. These disadvantages have been eliminated by stimulation with ramp-shaped pulse trains, which provides a quick and accurate measure for the seizure threshold (Hoogerkamp et al., 1994; Voskuyl et al., 1989, 1992). Moreover, with some restrictions, it may be repeated at very short intervals (minutes) in the same animal. So far, this method has been explored only in cortical motor areas. Seizures can also be elicited by application of convulsant drugs (e.g. pentylentetrazole) and similarly the threshold can be determined by timed intravenous (i.v.) infusion. The time to the first convulsive event may be used as a measure for the minimal convulsant dose. The plasma concentration of the convulsant at that time point is an even more precise parameter. Unfortunately, this method cannot be repeated at short time intervals, which limits the obtainable information to one data point per animal.

Seizures are usually considered as a single entity, but an interesting possibility is to analyze separate seizure behavioral components and their time sequence in detail (Della Paschoa et al., 1997, 1998b). Seizure semiology plays an important role in clinical diagnosis, but it is seldom used in pharmacologic studies. The effects of AEDs on specific seizure components have been investigated and it has been shown that they can be selectively suppressed (Jonker et al., 2003, 2004).
Methods, which have been developed in ethology for measuring behavior objectively and reproducibly, are utilized for quantification. If drugs can be found that specifically and selectively suppress certain seizure components, and if these components are generated by separate mechanisms, this might provide an interesting approach to develop putatively successful combinations. Moreover, quantitative behavioral analysis can in principle be applied to any seizure type, irrespective of its origin, and in any experimental animal model or even in humans.

It is also possible to use indirect markers for seizure suppression. For example, if a drug combination is expected to modify GABA_A receptor-mediated inhibition, the increase in the EEG in the β-frequency band can be monitored (Mandema \textit{et al.}, 1992). Such an approach focuses more on mechanisms of interaction and eventually allows conclusions about the contribution of specific mechanisms to the antiepileptic effect.

The methods described above can be applied initially in naive animals and later in one of the experimental models representative for pharmaco-resistant epilepsy. In the final stage the ultimate test will be the efficacy of a drug combination to suppress spontaneous seizures. The frequency of seizure occurrence, or even better, the distribution of the duration of inter-ictal intervals, is in principle a good measure. A low frequency of seizure occurrence and the inherent unpredictability clearly complicate these measurements, but on the other hand in that stage of development, only a limited range of drug plasma concentrations or dose regimens need to be tested.

Design of experiments

An efficient way to establish the response surface of a drug combination is to give drug A as a continuous i.v. infusion in order to establish a steady-state concentration and to add drug B as an i.v. bolus dose on top of the infusion (Della Paschoa \textit{et al.}, 1998a). By measuring the anticonvulsant effect at regular time intervals after administration of the bolus dose, the effect can be determined over the full concentration range of drug B in the presence of a specified concentration of drug A. Repeating the experiment at different steady-state levels of A, characterizes the complete response surface in a relatively small number of experiments. When necessary, alternative concentration–time profiles can be created. For example, a linearly or stepwise increasing plasma concentration can be achieved easily by programming a computer-controlled infusion pump using the pharmacokinetic parameters of the drug (Cleton \textit{et al.}, 1999a). By using this approach to administer two drugs in a fixed ratio, the response surface can be then determined even more efficiently than by the method described above.

These approaches can be used only under certain conditions. In the first place this is possible only when the anticonvulsant effect can be determined repeatedly.
It is therefore very convenient if cortical stimulation with ramp-shaped pulse trains can be applied or if a continuous measure such as the change in the $\beta$-frequency band in the EEG can be used. In the second place, maintaining a steady-state concentration for hours by continuous i.v. infusion is only feasible when the drug is water soluble and available in sufficient amounts. By adding a suitable carrier to the infusion fluid, such as albumin or cyclodextrin, water-solubility might be increased. Alternatively, drugs could be administered by a slow-release device.

Determination of plasma concentrations is of utmost importance when evaluating drug combinations. For the estimation of the concentration of both drugs at the time of effect measurement, it is not sufficient to rely on pharmacokinetic parameters determined for the individual drug in healthy animals. The actual concentrations in combination experiments may be different because of pharmacokinetic interactions, interindividual variability and epilepsy-induced alterations in pharmacokinetics. Furthermore, transport to the brain may be changed as well. Upregulation of transporters in the blood–brain barrier such as P-glycoprotein and multidrug-resistance-associated proteins may lower the brain concentration. Although sophisticated mathematical models may be applied to estimate drug concentrations at the effect site, based on the pharmacokinetics in plasma, this should be confirmed by independent techniques. Methods such as microdialysis, positron emission tomography and magnetic resonance spectroscopy may provide such information.

**Integrated PK/PD modeling**

Superiority of a combination over a single drug needs to be proven. For this purpose, PK/PD modeling, which describes and characterizes the relationship between drug concentration and pharmacologic response by a mathematical model, is a convenient method. There are many applications of PK/PD modeling, such as optimization of dosage regimens, comparison of drug response under physiologic and pathologic conditions, etc. (Lesko *et al.*, 2001; Sheiner and Steimer, 2000). The particular advantage in this case is that both pharmacokinetic and pharmacodynamic interactions can be identified simultaneously.

Models used to characterize drug action in PK/PD modeling have evolved from simple empirical models such as the sigmoidal $E_{\text{max}}$ model to sophisticated mechanistic models that take into account physiologic and pathologic mechanisms, and mechanisms of drug action. Another important development is the application of population modeling (Holford and Peck, 1992; Ouellet *et al.*, 2001), which focuses on characterizing and explaining variability in pharmacokinetics and in pharmacologic response (e.g. inter- and intra-individual variability, influence of covariates such as age, gender, disease, co-medication, etc.). Also the modeling of non-continuous pharmacologic endpoints, such as categorical data, discrete counts or time-to-event
is now feasible. This has greatly enhanced the power and applicability of Pk/Pd modeling and will be particularly useful in drug-related epilepsy research.

Summary and conclusions

Despite a long history of research, the science of truly rational polytherapy is still in its infancy. It is generally believed that combining drugs with different mechanisms of action will give the best chance of improving the anticonvulsant efficacy and/or reducing the number and severity of adverse events. This approach appears logical, but sound experimental evidence is still lacking. Assuming that it is true, it is clear that a detailed knowledge of the mechanisms leading to pharmaco-resistant epilepsy, for which combination therapy is primarily intended, is of crucial importance. Present knowledge of experimental animal models proposed for refractory epilepsy indicates that multiple factors contribute to its emergence. This supports the notion that simultaneously aiming drugs at the different targets is likely to be the most successful way to treat refractory epilepsy. Eventually, combinatorial chemistry may provide agents that combine different anticonvulsant properties in a single molecule. For the present, it is more feasible to combine selectively acting drugs. Exploration of mechanism-based mathematical interaction models may help to improve our understanding of drug interactions and to identify the most synergistic (or antagonistic) combinations. Theory predicts that the translation of receptor activation into pharmacologic response is as important as the drug-receptor interaction itself.

Remarkably, drugs with moderate efficacy are predicted to produce more synergism (or antagonism) than drugs with high efficacy. Results of theoretical interaction studies can be elegantly visualized by constructing three-dimensional plots of the concentration–response surface. A plot of the difference between the interaction model and a reference model immediately identifies the concentration regions of synergism and antagonism. These theoretical predictions may be used to design experiments confined to the most interesting concentration regions, which will considerably reduce the amount of experimental work. Combinations need to be tested after acute and chronic dosing in vivo in experimental models faithfully reflecting refractory epilepsy, in order to account for altered drug responses in the epileptic brain. In addition, a careful study of the pharmacokinetics is an indispensable element in studies on drug combinations to account for pharmacokinetic interactions and epilepsy-induced changes in pharmacokinetics. It is advantageous if the anticonvulsant effect can be measured repeatedly in the same animal, because this makes it possible to establish concentration–effect relations in an efficient way. Integrated PK/PD modeling and population modeling provide the best tools to quantify pharmacodynamic interactions.
More and better experimental models of refractory epilepsy are needed. In nearly all the presently available models, epilepsy is induced in essentially healthy animals. The search for combinations should also be applied to minimize side effects and should include complementary studies in vitro. It is believed that a thorough understanding of the mechanisms of epileptogenesis and ictogenesis will pave the way for development of effective drug combinations. Such combinations may contain even more than two agents.

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Future research: a clinical perspective

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Introduction

Although the best standard guideline for the treatment of epilepsy is to treat patients with monotherapy antiepileptic drugs (AEDs) first, the use of AEDs in combination to treat patients with intractable epilepsy is a long-standing clinical practice. The concept of monotherapy is relatively new, having its origin in the mid-1970s (Leppik, 2000). Monotherapy implies the use of a single active entity and its advantages are recognized. These include avoidance of drug–drug interactions, enhancement of compliance and the reduction of adverse effects. But is this true? What is the benefit/risk ratio of polypharmacy compared with monotherapy? Are all the combinations of AEDs useful and/or equally useful? What doses of AEDs in polypharmacy and in monotherapy must be compared?

With our enhanced understanding of the mechanisms of ictal events and mechanisms of action of the traditional and new (second generation) AEDs, as well as the licensing of new AEDs having a variety of mechanisms for antiepileptic action, the concept of ‘rational polypharmacy’ (RP) has been developed (Homan, 1997). Although it may appear as a paradox, the goals of RP are to minimize total AEDs used, to personalize antiepileptic treatment, to develop more specific targets for therapy and to maximize the therapeutic index. Therefore, the heart of RP is the use of two (and only occasionally more than two) agents to give better seizure control with the lowest dose of each AED and with minimal adverse effects.

Patients with difficult to control epilepsy have traditionally received multiple AEDs in what is essentially random polypharmacy (Homan, 1997). The intent was to develop synergistic therapeutic effects. However, in the majority of cases, although additive efficacy was observed, adverse effects were also significantly potentiated. Consequently, the use of inappropriate drug combinations has long been and remains a problem. RP advocates the use of AEDs with different mechanisms of action and/or appropriate pharmacokinetic properties; however, as to whether this approach is associated with an enhanced risk/benefit ratio compared to monotherapy is unknown.
The inappropriate application of drug combinations has been frequently coupled with inadequate recognition or understanding of epileptic syndromes (Homan, 1997). An individual patient’s epilepsy may be treated as a mixed epileptic condition rather than as a single epileptic syndrome with multiple seizure types (Homan, 1997). Is combination of different AEDs necessary to treat different seizure type and epileptic syndromes? With the improvement in the definition of epileptic syndromes, is there stronger indication for RP? What is the timing and target population of RP? What data are needed to develop RP for a specific patient?

Many of the answers to these questions are proposals for future clinical research. Thus, there are two broad lines of research: one is linked to the development of the so-called ‘rational antiepileptic polypharmacy’, and the other to the study of adverse events induced by drug interactions or combinations.

The development of RP can be supported by an improved definition of epileptic syndromes. Since knowledge about the initiation of the seizure, spread of the ictal activity and arrest of the seizure has been increasing, there are new opportunities to design RP in a single drug (with multiple mechanisms) and/or to design ‘curative’ antiepileptogenic drugs. Of course, all of these ideas and projects must be tested through clinical studies. Even the accepted combinations of AEDs must be tested through well-designed clinical trials. Another avenue which can be of value in AED combinations is the study of the quality of life and of compliance.

The other past, present and future line of research is related to the risk of drug combinations or interactions. Pharmacovigilance is obligatory and must be improved for the study of drug interactions. Another item related to the safe use of drugs is the development of pharmacogenomics with the possibility of choosing the bespoke AED. Finally, it is important to verify whether or not the serum therapeutic ranges, described for antiepileptic monotherapy, are similar to those necessary during the rational combination of AEDs.

**Improved definition of epileptic syndromes: recent and promising tools to study combinations of AEDs**

Pharmacological management of epilepsy has targeted only symptoms (i.e. seizures) and not the disease (i.e. epilepsy), and it has been limited to containment of seizure propagation without attention to initiation or rates and routes of the spread of seizure activity (Löscher and Ebert, 1996). There is some evidence indicating that some generalized seizures in children may be exacerbated by carbamazepine (Snead and Hosey, 1985), myoclonic seizures worsened by vigabatrin
and juvenile myoclonic epilepsy aggravated by phenytoin, carbamazepine or gabapentin (Leppik, 2000). Therefore, the diagnosis of the epileptic syndrome is useful and when possible must be obtained.

The goal of developing more specific targets for RP includes treatment of the onset of seizures (ictogenesis) and of the onset and maintenance of epilepsy (epileptogenesis) (Lothman, 1996).

Other advances can be obtained through the use of animal models of epilepsy, namely genetic models which are a source that is yet to be optimally used and has the potential to allow evaluation of AEDs, not only for anti-ictal potential but also for antiepileptogenic potential (Homan, 1997). This can be associated with the more classical animal models to study AEDs. Debate over an appropriate model to study polypharmacy continues (Homan, 1997) and must be one of the goals for future research.

Another technique is computer modelling, which may provide the means to develop potential drug combinations. This approach is most relevant to predict rational drug combinations at the pharmacodynamic level (Homan, 1997). Of course, well-designed clinical trials with such suggested drug combinations must always be performed.

In addition to the significant contribution to epilepsy treatment by localizing epileptic foci for surgical excision, functional neuroimaging (e.g. positron emission tomography, PET; single photon emission computed tomography, SPECT) may also contribute by refining the definition of epilepsy (for instance, to demonstrate different epileptic syndromes with the same seizure type).

Probably of still greater potential value are studies designed to define receptor sites. These offer the possibility of refinement diagnosis and, therefore, pharmacological management. Some neurotransmitter systems have been studied, such as the benzodiazepine and the opioid receptors, since there is evidence for their involvement in epilepsy. The opioid receptors appear to be related to seizure termination (Theodore, 1990).

Functional neuroimaging using receptor ligands could give information regarding ictal onset, propagation and containment (Homan, 1997), and could be used to formulate a rational plan for pharmacological management. This would be another area for future research.

Almost all the available drugs have been extensively evaluated for simple and complex partial seizures. Many double blind, placebo-controlled clinical trials are available for the second generation AEDs; initial efficacy studies were done as adjunct therapy with one or two marketed AEDs. The first generation AEDs did not undergo such rigorous testing. The effect of drugs on syndromes of primarily generalized epilepsies have not been studied as extensively, and surely these studies must be developed in the near future.
During the past two decades, our knowledge of the mechanisms of seizures has greatly expanded. Distinct events occur during a seizure: initiation of the seizure, spread of the ictal activity and arrest of the seizure. Different mechanisms support these steps (Leppik, 2000), since sodium conductance initiates and maintains the ictal activity, calcium conductance initiates and maintains seizure activity and also contributes to neuronal injury, and potassium conductance is essential in the arrest of a seizure discharge. The principal neurotransmitters involved are the inhibitory gamma amino butyric acid (GABA) neurotransmitter and the excitatory glutamate neurotransmitter. Since AEDs show distinct profiles regarding these different ion conductances, their combination may be rational. Therefore, it is reasonable that a seizure may be suppressed in its initiation by one drug, another may be more effective in limiting its propagation and a third may enhance the probability of its arrest. In addition, other drugs may need to be developed to shorten the post-ictal state or to limit the neuronal damage caused by the seizures. Thus, sodium conductances are modified by phenytoin, carbamazepine, primidone, valproate, lamotrigine, oxcarbazepine and zonisamide, although some of these drugs have other actions as well; calcium conductance (T-calcium channels) may be modified by ethosuximide and valproate; GABA-mediated chloride conductance may be reinforced by vigabatrin, tiagabine, gabapentin and barbiturates; N-methyl-D-aspartate (NMDA) receptors are affected by topiramate (Table 25.1). Although an AED might have many mechanisms of action, only a few are relevant for the antiepileptic effect. In general, it can concluded that the traditional AEDs act via an action on cation currents, whereas the more recent AEDs reinforce the GABA and/or inhibit the glutamatergic systems.

Based on this knowledge, some AED combinations may be proposed, whereas other might be avoided (Table 25.2). However, this apparent RP must be tested through controlled randomized clinical trials, double blind, and with correct sample size, inclusion and exclusion patient criteria, time of treatment and statistical analysis (including per protocol and intention-to-treat analyses, and characterization of dropouts). This area for research is substantial.

**Designing RP in a single drug (with multiple mechanisms)**

Many studies suggest that multiple neurotransmitters and subtypes of their receptors are involved in the abnormal neuronal excitability that underlies some models of the epilepsies. For instance, the glutamatergic system (NMDA and non-NMDA mechanisms) may have an important role in excitability, whereas the GABAergic system may play a role in decreasing the epileptiform activity. The RP may use several drugs with a different pharmacodynamic profile or, better, may use a single drug
Carlos A. Fontes Ribeiro

with affinity for multiple systems. Therefore, the possibility exists that a drug with affinity for multiple receptors or systems (e.g. inhibiting the glutamatergic system and reinforcing the GABAergic system) may have a considerable efficacy. In addition, if the efficacy for the multiple receptors is low, then the compound may show low toxicity (Sankar and Weaver, 1997) compounds with a high affinity and potency may carry unacceptable toxicity (e.g. sedation when the GABA system is strongly activated). Topiramate, an AED with a broad antiepileptic activity, has at least six mechanisms of action (Table 25.1) and, therefore, may show high efficacy. However, these hypothesis must be confirmed by randomized, controlled clinical trials.

**Designing ‘curative’ antiepileptogenic drugs**

The drugs currently available for treating epilepsy are little more than symptomatic agents (Sankar and Weaver, 1997), failing to stop the fundamental pathologic

<table>
<thead>
<tr>
<th>Table 25.1 AEDs and their mechanisms of action</th>
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<tbody>
<tr>
<td><strong>Blockade of the Na(^+)</strong> current</td>
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<tr>
<td><strong>Inhibition of L- and N-Ca(^{++})</strong> currents</td>
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<tr>
<td><strong>Inhibition of T-Ca(^{++})</strong> current</td>
</tr>
<tr>
<td><strong>Enhancement of GABA-evoked Cl(^-)</strong> current</td>
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<tr>
<td><strong>Antagonism of AMPA receptor subtype</strong></td>
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<tr>
<td><strong>Blockade of NMDA responses</strong></td>
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<td><strong>Increase of brain GABA</strong></td>
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<tr>
<td><strong>Decreased glutamate release</strong></td>
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<tr>
<td><strong>Antagonism of adenosine receptors</strong></td>
</tr>
<tr>
<td><strong>Increase of 5-HT release</strong></td>
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</tbody>
</table>

Adapted from Macdonald (1997) and Moshé (2000).

5-HT: 5-hydroxytryptamine.

**Table 25.2 Combinations based on the mechanisms of action of AEDs**

*Most useful (due to widely different mechanisms of action): Carbamazepine or phenytoin with gabapentin, tiagabine and topiramate*

*Least useful (similar mechanisms of action): Carbamazepine and phenytoin; tiagabine, gabapentin and vigabatrin*
process that initially causes and maintains the susceptibility to seizures. Two important concepts are ictogenesis and epileptogenesis. Ictogenesis is the initiation and propagation of a seizure (in time and space), occurring within seconds or minutes and being a rapid electrical/chemical event, whereas epileptogenesis is the gradual process (occurring through a period of months or years), whereby normal brain is transformed into a state susceptible to spontaneous and recurrent seizures (through the initiation and maturation of an epileptogenic focus) (Sankar and Weaver, 1997).

If the chemistries of these two processes are different, their treatment may also be different, by use of different drugs or a single drug with different mechanisms. To treat ictogenesis, it is necessary to control the opening of Na\(^+\) channels (which underlies brain electrical discharges) and the subsequent involvement of K\(^+\) channels and the Na\(^+/\)K\(^+\)-ATPase pump, often associated with neurotransmitter systems; since the electrical activity passes from neuron to neuron via the Ca\(^++\) channel-mediated release of neurotransmitters, these channels represent another process to control. Thus, ictogenesis may be inhibited through the blockade of ion channels involved in depolarization, antagonism of excitatory neurotransmitter and/or activation of inhibitory neurotransmitter systems (Sankar and Weaver, 1997).

The fundamental disturbance that yields epileptogenesis seems to represent a combined, concurrent imbalance of an excessive excitation and a weak inhibition (Sankar and Weaver, 1997). Although glutamatergic and GABAergic processes are leading candidates, some studies (Ernfors et al., 1991) suggest other factors such as the nerve growth factor (NGF), whose production is enhanced in the limbic system of animal models (with the experimental form of epileptogenesis known as kindling). The fact that the intracerebroventricular injection of antibodies to NGF delays the onset of kindled seizures (Fundabashi et al., 1988) seems to confirm the role of this protein. The future design of antiepileptogenic compounds must identify the full range of target molecules (NMDA antagonists, GABA agonists, NGF antagonists and others).

**Clinical studies to test combinations of AEDs**

Studies designed to test efficacy (and safety) of drug combinations can be observational or experimental (Waning and Montagne, 2001). Investigators in observational studies may plan and identify variables to be measured, but human intervention is not a part of the process. Experimental studies, in contrast, involve intervention in ongoing processes to study any resulting change or difference; they are clinical trials and intervention studies designed to compare outcomes between two or more treatment or intervention groups.

Observational study designs include case reports, cross-sectional studies, case–control studies and cohort studies. A case report is a descriptive study of a single
patient, and a case series is a collection of case reports; a cross-sectional study is a prevalence study, examining relationships between a drug use (or interaction) problem and other characteristics of people in a population at one point in time; a case–control study compares people who have the disease or problem or drug interaction (cases) to those who do not have (controls) with respect to characteristics of interest (i.e. potential causes); a cohort study is an incidence study that measures characteristics free of drug problem and relates them to subsequent development of the disease or event in that population as it is followed over time (a longitudinal study).

The majority of studies on AED combinations (random or RP) have been observational, although there are a few cohort studies. These studies are less expensive than the experimental ones and the ethical concerns are less. However, the results obtained are weak and, therefore, there is a need to undertake experimental studies in order to provide sound scientific evidence upon which recommendation of RP can be based.

An experimental study is designed to compare benefits of an intervention with a standard treatment, or no treatment, to show cause and effect. This type of study is performed prospectively. Both study groups (the experimental group receives the drug under investigation; the control group receives the traditional or approved treatment or no treatment or placebo) are studied over the same time period using the same measures of safety and efficacy/effectiveness. The gold standard of an experimental clinical study is the randomized, controlled trial (RCT). RCTs are in general studies of Phase III, performed to submit an application of the AED to the European Agency for the Evaluation of Medicinal Products (EMEA), Food and Drug Administration (FDA) or any national drug agency. It must be emphasized that almost all the studies with new AEDs are add-on studies – all the epileptic patients are treated with a standard AED and then they are randomized to placebo or the new AED (crossover or parallel-group add-on RCT design). The efficacy and the risk of the added active drug or of the placebo can then be calculated and compared. This type of design hardly characterizes the new drug and now study designs are being proposed (Loiseau and Jallon, 2001) (e.g. therapeutic failure design trials, attenuated active-control designs, presurgical withdrawal designs).

A supplemental new drug application is submitted when a drug’s sponsor requests approval to promote an existing drug with either a new indication or new labeling (for instance, when two AEDs were used in combination in clinical trials and the sponsor wants the reference to this in the summary product characteristics (SPC), or when there are reports of adverse reactions with some drug combinations and the sponsor is obliged to refer this in the SPC).

Although Phase III clinical trials are the gold standard for demonstrating treatment efficacy, pitfalls can include the selected nature of the subjects, the small number
of subjects included, the usually brief follow-up period and the missing intention-to-treat analysis (without characterization of the dropouts). Some of these deficiencies may be addressed by a Phase IV clinical trial, usually called a post-marketing study. This type of trial may establish the effectiveness of the combination of drugs, in the routine setting or in some subgroups of patients. Included in these Phase IV trials are the large, simple trials (LSTs) (Lesko and Mitchell, 2001), which can be designed in order to study AED combinations.

LSTs may be the best solution when it is not possible to completely control confounding by means other than randomization. This approach has also been used successfully to evaluate the risk of adverse drug effects when the more common observational designs have been judged inadequate. These studies are really just very large randomized trials made simple by reducing data collection to the minimum needed to test only a single hypothesis (or at most a few hypotheses). Randomization of treatment assignment is the key feature of the design, which controls for confounding by known and unknown factors. The large study size provides for AED combinations the power needed to evaluate small risks, either absolute or relative, and small differences in effectiveness.

The combination of AEDs will only be considered acceptable if the proposed combination is based on valid therapeutic principles. For this, it can be adopted from the guideline CPMP/EWP/240/95 of the CPMP (Committee for Proprietary Medicinal Products) and of the EMEA, although this guideline had been developed for fixed drug combinations. It is necessary to assess the potential advantages in the clinical situation against possible disadvantages, in order to determine whether the combination meets the requirements with respect to efficacy and safety.

Potential advantages of AED combinations include an improvement of the risk/benefit assessment due to:

(a) addition or potentiation of the therapeutic activities of the two drugs, which results in a level of efficacy similar to the one achievable by each active drug used alone at higher doses than in combination, but associated with a better safety profile, or a level of efficacy above the one achievable by a single drug with an acceptable safety profile;

(b) the counteracting by one drug of an adverse reaction produced by another drug.

Disadvantages of combinations of AEDs include the addition of the different adverse reactions specific to each substance.

Adverse reactions are of two principal types: Type A reactions, which will occur in everyone if adequate amount of the drug is given, because they are due to excess of normal, predictable, dose-related, pharmacodynamic effects. Type B reactions are those that will occur only in some people. They are not dose-related and are due to
unusual attributes of the patient interacting with the drug. This class of adverse effects includes unwanted effects due to inherited abnormalities (idiosyncrasy) (differences in pharmacogenetics) and/or immunological processes (drug allergy).

Three subordinate adverse reaction types can also be recognized: Type C reactions due to long-term use (for instance, hyponatremia with carbamazepine or oxcarbazepine, behaviour changes with the majority of the AEDs, weight changes with many AEDs). Type D effects, for example teratogenesis, carcinogenesis (with the majority of AEDs, but particularly with valproic acid and phenytoin – do these adverse effects increase with the combination of drugs, in comparison with monotherapy?). Type E reactions, where discontinuation is too abrupt (increased seizures due to interruption of medication – what happens with polypharmacy when one of the drugs is stopped?). Of course, AED combinations may increase Type B and in certain circumstances Type A reactions. The latter may occur when drugs act through the same mechanism and their sum at the sites of action exceeds the maximal dose of one of them at that site. However, as one of the objectives of RP is to use moderate doses of two or more AEDs, Type A adverse reactions should be avoided but with and increasing efficacy.

Another Type A adverse reaction comprises a failure in increasing efficacy and an increase in the number and severity of seizures. This type of reaction can happen with the prescription of different drug formulations, principally due to the increasing number of generic preparations. The resulting variation in steady-state plasma levels, after substitution of one preparation for another may cause gradual loss of seizure control or the gradual development of drug intoxication. Thus, studies of bioequivalence between generics and reference drugs are necessary and they must be a priority for patients, physicians and national regulatory authorities.

Two main objectives in AED combination therapy that could be researched are as follows:

(a) **Pharmacodynamic objectives**: Frequently, the addition or the potentiation of the pharmacodynamic effects of drugs may constitute the rationale of the AED combination. In this case, several dose combinations for each drug might have to be tested and the concentration–response information can help to select the combination leading to a satisfactory response.

(b) **Pharmacokinetic objectives**: In general, it must be demonstrated that the various drugs do not affect each other’s respective pharmacokinetic patterns. These interactions should be studied primarily in healthy volunteers; however, patients should also be studied if the disease modifies the pharmacokinetics of a drug or if high-risk subgroup is to be prescribed the drug combination (elderly, patients with renal failure or hepatic impairment).
Future research: a clinical perspective

Table 25.3 Rational AED combinations

<table>
<thead>
<tr>
<th>Primary generalized epilepsies</th>
<th>Localization-related epilepsies</th>
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</thead>
<tbody>
<tr>
<td>Valproate and propranolol</td>
<td>Carbamazepine or phenytoin and intermittent clobazam</td>
</tr>
<tr>
<td>Valproate and ethosuximide</td>
<td>Carbamazepine or phenytoin and valproate</td>
</tr>
<tr>
<td>Valproate and phenytoin or primidone</td>
<td>Carbamazepine or phenytoin and gabapentin</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine or phenytoin and lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine and vigabatrin</td>
</tr>
</tbody>
</table>

Adapted from Homan (1997).

Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel or crossover group comparisons in which the combination is compared to its individual (multilevel factorial design). Inclusion of a placebo group is recommended when feasible, but in patients with epilepsy there are concerns about the use of placebo. However, there are now new trial designs which have been specifically designed to overcome this problem.

In some cases, studies have to be specifically designed to determine the minimal effective dose and usual effective dose of the combination. Multiple dose-effect studies may be required.

Although there are some examples of RP (Table 25.3), these combinations have not been tested in rigorous factorial clinical trials; instead their use is based on anecdotal evidence. In factorial trials the combination of active drugs must be compared with each one. This type of clinical trial has been used to study antihypertensive drugs and could be applied for the studies of AEDs. However, one problem with these studies is that of choosing the dose of each drug to be studied.

Safety aspects

In the case of combinations of AEDs, which are for long-term use, safety data on 300–600 patients for 6 months or longer will be required. Where there are grounds to expect that the combination of AEDs may be substantially more harmful or give rise to much more frequent adverse effects than any individual substances given alone, evidence should be obtained that this does not occur in therapeutic use, or that the advantages of the combination, for example increased efficacy, outweigh such disadvantages.

One of the major problems related to clinical research is the non-publication of trials with negative findings, thus enhancing the risk of bias from omitted research. The communication of these trials must be obligatory, in order to develop potent and useful databases.
Quality of life and RP

Assessing the impact of health care interventions is increasingly shifting from biologic and physician-determined parameters to patient-focused parameters. Although they can be more difficult to quantify, patient-centered outcomes, such as functional status, life satisfaction and health-related quality of life (HRQOL), are often more clinically relevant.

Fundamental dimensions essential to HRQOL have been proposed and include physical, psychological and social functioning, role activities, overall life satisfaction and perceptions of health status (Berzon et al., 1993; Williams, 2001).

Once the decision to assess patients' HRQOL has been made, an investigator must choose which type of HRQOL assessment is most likely to help for answering the research question. Of course, all the instruments used must show validity and reliability. As no standard measure exists, responsiveness is often measured in several ways; most of the statistics involve dividing change in scores by some indicator of the precision of measurement. General guidelines for interpreting HRQOL data in RCTs have been suggested (Guyatt et al., 1997). Important issues addressed (Williams, 2001) are:

1. how to assess the validity of the HRQOL measures used;
2. whether the HRQOL measures performed as expected;
3. how to evaluate the magnitude of effect on HRQOL outcomes;
4. how to translate HRQOL data from an RCT to daily clinical practice.

Compliance

The process of taking medications as prescribed can be an extremely difficult task during AED polypharmacy, particularly in old age. The complexity of the polypharmacy can be further complicated by cognitive abnormalities, poor vision, motor disturbances and adverse reactions.

The patient's compliance in adhering to drug combinations must be studied and enhanced. Questions that need answering in this regard include: at what time of the day must an AED be ingested? Should AEDs be administered together or should they be separated by a specific time interval? These questions might be best answered by first attaining the optimal dose for each patient and then the best regimen of administration studied and used.

Pharmacovigilance

AEDs, either in monotherapy or in polytherapy, can only be useful if there is scientific evidence of relevant efficacy and a low risk of adverse effects. This risk/benefit ratio
is established through pre-marketing and post-marketing drug surveillance. Therefore, drug surveillance or pharmacovigilance is applied to drug interactions or to AED combinations. Regarding AEDs, interactions can happen between each other or between AEDs and other drugs or substances, such as food.

The consequences of these drug interactions can be lower efficacy and/or lower safety, both of concern and a reason for pharmacovigilance. Concerning AEDs, less efficacy resulting from AED interactions must be classified as an adverse drug reaction, and thus it must be subjected to pharmacovigilance.

AEDs can also adversely affect the course of a concomitant medical condition; alternatively, drugs used to treat a medical condition can at times exacerbate epilepsy. Carbamazepine occasionally precipitates arrhythmias in patients with cardiac conduction system disease (Scheuer, 1997). Theophylline can lower seizure threshold in susceptible persons and psychotropic agents also occasionally precipitate seizures (Scheuer, 1997).

Taking into account the pre-clinical studies and clinical trials, either of Phases I, II or III, some drug interactions, at the pharmacokinetic or pharmacodynamic level, are expected. Of course these interactions are fundamental to establish the risk/benefit ratio and they must be specified in the SPC of the respective AED. But there are other adverse events that can occur after licensing of the AED, since the drug is then used in a clinical setting different from that of clinical trials, where restricted inclusion and exclusion criteria are inevitable. Unexpected or serious adverse reactions may happen, which oblige us to re-evaluate the risk/benefit ratio and to add these reactions to the SPC.

During post-marketing pharmacovigilance the majority of adverse events are spontaneously reported by physicians, pharmacists and – in some countries – nurses. They use, for instance, the yellow card to communicate the adverse event to the national pharmacovigilance system. This is the principal way for pharmacovigilance (to follow the drug in the market), since all drugs and health professionals belong to the system. But other studies may be performed during the post-marketing surveillance, such as observational cohort studies, case–control studies, case surveillance and clinical trials.

For any surveillance study, their following phases are essential:

1. report of the adverse event;
2. validation of the report;
3. establishment of causality between drug and event.

Unexpected or serious adverse events must always be reported; the communication of other adverse events is country dependent. The term adverse event or adverse experience intentionally avoids implying a necessary cause-and-effect relationship between the use of the drug and the event. The term includes adverse events that
occur during the use of the drug in professional practice or drug study, during a drug overdose, as a result of drug withdrawal and as a result of the failure of the expected pharmacological action (Greenwood, 2000). Regarding AED interactions, namely with the new drugs, the increase of adverse event frequency or the decrease of efficacy must also be reported, whether or not it is clearly considered to be drug-related.

In the European Union each National Pharmacovigilance System is linked to the EMEA. The section of EMEA for pharmacovigilance is the pharmacovigilance working party, which belongs to the CPMP, a part of EMEA. In addition, each member state and EMEA collaborates with the World Health Organization (WHO) (via the Collaborating Centre for International Drug Monitoring, in Uppsala, Sweden). Therefore, each National Pharmacovigilance System is connected to EMEA and both are connected to the WHO Collaborating Centre.

To characterize an adverse event as an adverse reaction due to the AED there must be the establishment of causality. This can be made by different methods of importability that take into account chronological and semeiological criteria and an extrinsic importability (with the classifying of bibliographic data). The majority of the methods of importability take only one drug into account at a time. The other drug may be ‘another explanation’, decreasing the power of the causal relationship. The relationship between the adverse event and the drug can be definite, probable, possible, conditional or not related. If two drugs are used simultaneously the causal relationship will be rarely identified; however, if the one drug is taken after the other the causality can be more readily established.

Adverse reactions can be characterized as serious and/or unexpected and, as highlighted earlier, they must be reported to the pharmacovigilance system. However, as far as the combination of drugs is concerned, all the aspects of safety must be studied in order to clarify the risk/benefit ratio of the combination (at lower doses of each drug, for instance) compared with the single drug, either used at a high dose or at a mean dose, and in populations of different age, sex or susceptibility. Pre-existing medical conditions must also be known so as to characterize the target population for drug combinations.

The consequences of the adverse drug reaction assessment are as follows:

• To establish the overall risk/benefit ratio.
• To begin a rapid alert for the scientific community.
• To withdraw or to reduce the use of the medicinal product.
• To complete the SPC.
• To develop pharmacoepidemiology and databases.
• To design other studies to confirm or explain the adverse reaction.
• To design rational AED combinations (an example of a possible AED combination whose individual knowledge indicates less adverse effects is the combination of...
Future research: a clinical perspective

valproate (or gabapentin, vigabatrin or carbamazepine) with topiramate, since the first ones induce weight gain and the latter weight loss (Greenwood, 2000)).
• To define the non-epileptic drugs which can be associated with an AED.

In addition, each medicinal product must, of course, have periodic safety update reports, which permits the drug to be reanalyzed.

The lack of uniformity of populations, terminology, methods for collecting data, patient experiences and the absence of formal methods for testing for adverse reactions make comparisons of adverse reactions among studies difficult. In spite of these problems, pharmacovigilance is the best way to characterize the safety of drug combinations, since all the epileptic population may be followed (through the spontaneous reporting system) or some specific groups of epileptic patients (case–control or cohort studies or through the prescription monitoring system). Of course, during the Phase III or IV post-marketing clinical trials, important and useful data are collected but the less frequent adverse reactions can only happen during the extensive use of the combination of drugs in the general patient population. Thus, pharmacovigilance is an integral component of all future research of all health systems.

To overcome the problem of terminology to describe patient reports of adverse experiences or events, the terminology used in the United States (Coding Symbols for a Thesaurus of Adverse Reactions Terms: COSTART) and the World Health Organization’s Adverse Reaction Terminology (WHO-ART), used in the European Union, will be replaced with the Medical Dictionary for Regulatory Activities (MedDRA). To accomplish this goal, the International Conference on Harmonization (ICH), an organization made up of representatives of industry associations and regulatory authorities in United States, Europe and Japan, has agreed upon the structure and content of the MedDRA. The descriptive terms used for adverse events are expanded and this source has a hierarchical structure to allow greater specificity (Brown et al., 1999). Thus, the international use of MedDRA will make it easier to compare adverse events when characterizing AEDs and their combinations.

In the future prospective, comparative studies of adverse events will be essential. With a better understanding of the circumstances in which each adverse effect occurs, we may be able to know the mechanisms that mediate the adverse reactions and ultimately find ways to prevent them and/or to combine AEDs rationally (or to combine an AED with other non-AEDs). Clearly, more research is needed in this area.

Pharmacogenomics and choice of the personal AED

Genetic factors can contribute in the genesis of unexpected or idiosyncratic adverse reactions, through, for example, the synthesis of variant plasma proteins (which
can cause atypical drug–protein binding) or in the existence of abnormal or variant metabolic capacity (e.g. slow phenytoin para-hydroxylators may lead to higher than expected drug levels and unexpected toxicity).

A great part of the interactions of AEDs with other AEDs or with other non-epileptic drugs occur at the metabolic level, principally through the cytochrome P450 system. Practically, only five CYP isoenzymes account for the metabolism of most therapeutic agents studied to date (Levy and Bourgeois, 1997) – CYP1A2, CYP2C9/10, CYP2C19, CYP2D6, CYP3A4. CYP2C19 and CYP2D6 exhibit known genetic polymorphism. The major pathway (60–80%) in phenytoin metabolism is hydroxylation to \( p \)-hydroxyphenol-5-phenylhydantoin (\( p \)-HPPH) by CYP2C9, whereas the metabolism of carbamazepine to carbamazepine-10,11-epoxide (40–60%) is through the isoenzyme CYP3A4 (Levy and Bourgeois, 1997). Now it is possible to characterize each individual regarding his or her CYP isoenzymes. Thus, if a subject does not have genetic polymorphisms, drug interactions during combination therapy will be minimal. Therefore, a bespoke treatment regimen would be possible in the future.

**Validation of therapeutic ranges**

For many AEDs, therapeutic serum level ranges are more or less well defined. However, the increasing application of serum AED monitoring led to an awareness that use of multiple AEDs altered the pharmacokinetics of the individual drugs, thereby complicating their use. Drugs with a narrow therapeutic range or low therapeutic index are more likely to be the objects for serious drug interactions. In RP, it is necessary to correlate serum levels with clinical efficacy since the combined drugs may be more active if the serum levels attained by each one in combination therapy are similar to those attained when the drug is used in monotherapy. Moreover, the serum concentrations must be correlated with the type and severity of epilepsy.

**REFERENCES**


Index

Page numbers in italic, e.g. 195, refer to figures. Page numbers in bold, e.g. 183, signify entries in tables.

ABCB1 gene 29
absences in childhood 265
acetaminophen (paracetamol), interactions with AEDs
  lamotrigine (LTG) 147
  phenytoin (PHT) 157
acetazolamide, interactions with AEDs
  primidone (PRM) 161
acquired immunodeficiency syndrome (AIDS) 373
acyclovir, interactions with AEDs
  phenytoin (PHT) 154
additive drug interactions 183, 183, 193–4
  isobolographic analysis 195, 195, 197, 198
adverse drug reactions, pharmacogenetic aspects 37–9
  distribution of positive results 39
  genetic susceptibility factor 38
  prevalence 38–9
  susceptibility factor 38
affective disorders, interaction between AEDs and antidepressants (ADs) 242–3
albumin, effect on drug distribution 49
aminoglycoside
  combination therapies, general principles 7
1-(4-aminophenyl)-4-methyl-7,8-methylene-dioxo-5H-2,3-benzodiazepine hydrochloride (AMPA/KA) receptor antagonists, interactions with AEDs 216–18, 218
aminophylline 101
amiodarone, interactions with AEDs
  phenytoin (PHT) 154
amitriptyline 244
amphetamines 249
analgesics and anti-inflammatory agents, interactions with AEDs 250
  elderly patients 281–2
  opioids in valproic acid overdose 251
  seizure threshold 251
  treatment of pain 250–1
anesthetic agents, interactions with AEDs 250
angiotensin converting enzyme (ACE) inhibitors
  combination therapies, general principles 6, 7
antacids
  effect on AED absorption
    phenytoin (PHT) 98
  interactions with AEDs
    gabapentin (GBP) 147
    phenytoin (PHT) 154
antibiotics, interactions with AEDs
  carbamazepine (CBZ) 140–1
anticoagulants/antiplatelet agents 10
  interactions with AEDs in the elderly 279–81
anticonvulsants
  interactions with antipsychotics (APs)
    benzisoxazoles and benzisothiazoles 358–9
    thienobenzodiazepine, dibenzothiazepine and dibenzothiazepine derivatives 359
  interactions with anxiolytics 359–60
anticonvulsants (contd)
interactions with psychotropic drugs, role of CYP450 system 353–5
interactions with selective serotonin-reuptake inhibitors (SSRIs) 355–7
interactions with serotonin–noradrenergic re-uptake inhibitors (NSRIs) 355–7
interactions with tricyclic antidepressants (TCAs) 357
pharmacodynamic interactions with antidepressants (ADs) 360, 361, 362
pharmacodynamic interactions with antipsychotics (APs) 360–2, 361, 362
antidepressants (ADs) 350–1, 351
inhibition of CYP enzymes 355
interactions with AEDs 242
adverse effects 245–6
affective disorders 242–3
effects on seizure threshold 243–5, 244
pharmacodynamic interactions with anticonvulsants 360, 361, 362
antihyperlipidemics, interactions with AEDs in the elderly 278–9
antihypertensive drugs, interactions with AEDs
carbamazepine (CBZ) 143–4
elderly patients 278
antineoplastic therapy
effect on AED absorption
phenytoin (PHT) 98
interactions with AEDs
phenytoin (PHT) 154–5
antipsychotics (APs) 351, 352
inhibition of CYP enzymes 355
interactions with AEDs 246
adverse effects 248
convulsant effect of atypical APs 247–8
effects on seizure threshold 246–7, 247
psychosis 246
interactions with anticonvulsants
benzisoxazoles and benzisothiazoles 358–9
phenothiazines–butyrophenones 358
thienobenzodiazepine, dibenzothiazepine and dibenzothiazepine derivatives 359
pharmacodynamic interactions with anticonvulsants 360–2, 361, 362
antiviral agents, interactions with AEDs
carbamazepine (CBZ) 141
anxiolytics, interactions with anticonvulsants 359–60
arene oxide metabolites of phenytoin 35
aspirin 7
astemizole 10
barbexaclone 249
barbiturates 18, 249
benign myoclonic epilepsy 265
benign partial epilepsy 265
benign partial seizures 265
benzodiazepines (BZDs) 352
action 210
effect upon excitatory amino acid receptors 214
fetal syndrome 311
GABA receptors 33–4
handicapped and mentally retarded patients 332
interactions with flumazenil 241
beta-blockers 7
biguanides 9
bioavailability of AEDs, influence of food and drugs 93
general principles 93–5
interactions with established AEDs
carbamazepine (CBZ) 100–1
ethosuximide (ESM) 102
phenobarbital (PB) 101–2
phenytoin (PHT) 96–100
valproic acid (VPA) 101
interactions with new AEDs 102
felbamate (FBM) 103
gabapentin (GBP) 103–4
lamotrigine (LMT) 104
levetiracetam (LEV) 105
oxcarbazepine (OCBZ) 104–5
tiagabine (TGB) 103
topiramate (TPM) 104
vigabatrin (VGB) 102–3
zonisamide (ZNS) 105
birth defects
infants of mothers with epilepsy (IME) 298–300
teratogenicity of phenytoin (PHT) 301–2
bishydroxycoumarin, interactions with AEDs
phenytoin (PHT) 155
borax (sodium biborate) 17
bromides 9, 17
bupropion 244
interactions with AEDs
lamotrigine (LTG) 148
calcium channel blockers, interactions with AEDs
phenytoin (PHT) 155
cannabis and cannabinoids 3
carbamazepine (CBZ) 18
absence seizures 30
action 210
sodium channels 32
active metabolites 22
adverse effects 18, 21
clinical trials 231–2
effect upon excitatory amino acid receptors 214
effect upon NMDA and AMPA/KA receptors 218
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
FEC and FEC index 201
fetal syndrome 311
handicapped and mentally retarded patients 331
influence of excitatory amino acid receptor antagonists 215
influence of food and drugs on bioavailability 100–1
interactions in children 259–60
interactions in the elderly
analgesics 281
anticoagulants/antiplatelet agents 279
antihyperlipidemics 278–9
antihypertensives 278
CNS agents 285–6
endocrine/metabolic agents 283
gastrointestinal agents 282
interactions with newer AEDs 213
interactions with non-AEDs 140, 143
antibiotics 140–1
antihypertensive drugs 143–4
antiviral agents 141
cimetidine 141
cisplatin 141
cyclosporin 144
danazol 142
dicoumarol 144
diltiazem 142
doxycycline 144
fentanyl 144
fluconazole 142
indinavir 144
isoniazid 142
itraconazole 144
ketoconazole 142
methotrexate 145
metronidazole 142
nicotinamide 143
phenprocoumon 145
propoxyphene 143
quinine 143
rocuronium 145
steroids 145
teniposide 145
ticlopidine 143
verapamil 143
vincristine 145
interactions with other AEDs
effect of other drugs 117–18
effect on other drugs 116–17
levels through pregnancy 297
nicotinic receptor 30
non-epileptic disorders 375
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
selection for combination therapy 22
therapeutic range 393
cefotaxime, interactions with AEDs
phenobarbital (PB) 151
central nervous system (CNS) agents, interactions with AEDs in the elderly 285–7
central nervous system (CNS) stimulants, interactions with AEDs 248–9
adverse effects 249
charcoal, activated
effect on AED absorption
phenytoin (PHT) 97–8
interactions with AEDs
phenobarbital (PB) 150–1
phenytoin (PHT) 154
children, AED interactions 257–9, 268
childhood
absences 265
benign partial epilepsy 265
continuous spike waves in slow sleep 266
Lennox–Gestaut syndrome 266
myoclonic–astatic epilepsy 265–6
combining AEDs with non-AEDs 266–8
infancy
benign partial seizures and benign
myoclonic epilepsy 265
Dravet syndrome 264
infantile spasms 264
interactions between AEDs 259
carbamazepine (CBZ) 259–60
felbamate (FBM) 261
gabapentin (GBP) 261
lamotrigine (LTG) 261
oxcarbazepine (OCBZ) 261
phenobarbital (PB) 259–60
phenytoin (PHT) 259–60
valproic acid (VPA) 260
pragmatic aspects of treatment
epilepsy resistant to a first-line
monotherapy 262–3
epilepsy resistant to a second AED 263
first-line treatment 262
treatment according to epilepsy type or syndrome
cryptogenic or symptomatic partial epilepsy 263–4
Chinese medicines 3
chloramphenicol, interactions with AEDs
phenobarbital (PB) 151
phenytoin (PHT) 155, 157
chlorpromazine 352
cholestyramine, interactions with AEDs
valproic acid (VPA) 164
cimetidine, interactions with AEDs
carbamazepine (CBZ) 141
gabapentin (GBP) 147
lamotrigine (LTG) 148
oxcarbazepine (O CBZ) 149
phenobarbital (PB) 151
phenytoin (PHT) 155
tiagabine (TGB) 162
valproic acid (VPA) 164
ciprofloxacin 99
cirrhosis of the liver 372
cisapride 10
cisplatin, interactions with AEDs
carbamazepine (CBZ) 141
valproic acid (VPA) 164
citalopram 350, 356
clarithromycin 99
clobazam 352, 359
pharmacokinetic characteristics 50
clomipramine 244
clonazepam
action 30
effect upon NMDA and AMPA/KA receptors 218
pharmacokinetic characteristics 50
clozapine 247–8, 247, 352, 359
cognitive side-effects of AED therapies and interactions 403–4, 414–15
clinical effects 411–12
topiramate (TPM) 412
psychometric studies 404–8
design nomenclature and classification 408
findings about cognitive effects 410–11
methodological considerations 408–10
summary 406–7
subjective patient complaints 412–14, 413
comparison of complaints 415
combination therapies, drug monitoring 392–3, 400
future of monitoring 399
indications 393–4, 394
avoidance of intoxication and side effects 395–7
avoidance of under dosage 394–5
monitoring concomitant medication 397
laboratory tests 399
limits and dangers of serum AED
collection determination 398
measurement of free AED concentration 397–8
prerequisites for serum AED determination 397
therapeutic ranges 393
combination therapies, general principles 12
advantages
enhanced efficacy 7–8
prevention of resistance 8
reduced risk of adverse reactions 8
disadvantages
increased risk of medication error 11
increased risk of non-compliance 11
poor evidence of benefits 8–9
risk of greater toxicity 9–11
epidemiology 6
historical perspective 3–5
monotherapy versus combination therapy 190–1
polypharmacy 5–6, 9, 228
polytherapy 6
principles in oncology 5
combination therapy with antiepileptic drugs (AEDs) 23
advantages 17, 17
additional efficacy/infra-additive adverse effects 18
counteracting adverse effects 19
different mechanisms 18
different seizure types 18
pharmacoeconomic benefits 19
benefits compared with monotherapy 19–20
potential problems 20, 21
active metabolites 22
additive adverse effects 21
clinical responses to combinations 23
expense 23
pharmacokinetic interactions 21
selection of combinations 22
rationale 16–17
background 17
constitutive androstane receptor (CAR) 68
corticosteroids 10
cryptogenic partial epilepsy 263–4
cyclophosphamide, interactions with AEDs
phenytoin (PHT) 157
cyclosporin 10
interactions with AEDs
carbamazepine (CBZ) 144
phenobarbital (PB) 151
phenytoin (PHT) 158
cytochrome P450 (CYP) system 27, 51, 52,
58–9, 94–5
CYP1A2 59
CYP2C9 and CYP2C19 59–62
CYP2D6 62–3
CYP2E1 63
CYP3A4 63–4
identification of isoforms 76
inhibition by psychotropic drugs 355
interactions between psychotropic drugs
and anticonvulsants 353–5
psychotropic drug metabolism 354
substrates, probe drugs, inhibitors and
inducers 60–1
danazol, interactions with AEDs
carbamazepine (CBZ) 142
defined daily dose (DDD) 188
developmental delay associated with AEDs 313–14
dexamethasone, interactions with AEDs
phenobarbital (PB) 151
phenytoin (PHT) 158
dextropropoxyphene, interactions with AEDs
oxcarbazepine (OCBZ) 149
diabetes 9
diazepam 359
effect upon NMDA and AMPA/KA
receptors 218
pharmacokinetic characteristics 50
dicoumarol, interactions with AEDs
 carbamazepine (CBZ) 144
phenytoin (PHT) 158
digitoxin, interactions with AEDs
phenytoin (PHT) 158
digoxin, interactions with AEDs
levetiracetam (LEV) 148, 149
phenytoin (PHT) 158
tiagabine (TGB) 163
topiramate (TPM) 164
dilantin 17
dilantin, interactions with AEDs
carbamazepine (CBZ) 142
diphenylhydrantoin
action 210
effect upon excitatory amino acid receptors 214
effect upon NMDA and AMPA/KA receptors 218
influence of excitatory amino acid receptor antagonists 215
interactions with newer AEDs 213
disopyramide, interactions with AEDs
phenytoin (PHT) 158
distal digital hypoplasia (DDH) 308–9
disulfiram, interactions with AEDs
phenytoin (PHT) 155
doxorubicin, interactions with AEDs
valproic acid (VPA) 164
doxycycline, interactions with AEDs
carbamazepine (CBZ) 144
phenytoin (PHT) 158
Dravet syndrome 264
drug combination selection 421–2
combination therapies AEDs with non-AEDs 431
gabapentin (GBP) 428
lamotrigine (LTG) 427–8
tiagabine (TGB) 429
topiramate (TPM) 428–9
vigabatrin (VGB) 429
combination therapies with older AEDs 425–7
combination therapies with three or more AEDs 429–30
general principles 426
pharmacotherapy-resistant seizures 422–3, 423
rational polytherapy 424–5
resistance to pharmacotherapy 431–4
scale of the epilepsy problem 423–4,
drug interactions, investigation
in vitro systems 74

cell-based techniques 75
enzyme-based techniques 74–5
drug interactions, pharmacokinetic principles 47
absorption 48
characteristics of AEDs 50
distinction between pharmacodynamic and pharmacokinetic interactions 181–2
distribution 49–51
elimination 53–4
enzyme induction 66–7
as a cause of drug interactions 69–70
constitutive androstane receptor and phenobarbital-type induction 67–8
induction by ethanol 68
induction by peroxisome proliferators 68–9
induction mediated by aryl hydrocarbon receptor 67
induction mediated by pregnane X receptor (PXR) 68
enzyme inhibition 70–1
as a cause of drug interactions 72–4
irreversible inhibition 72
reversible inhibition 71
slowly reversible inhibition 71–2
mechanisms 47–8
metabolism 51–3, 57–8

cytochrome P450 (CYP) system 58–64
epoxide hydrolases (EHs) 65
drug interactions, prediction 87
in vitro systems 75–6
assessment of influence on activity of drug-metabolizing isoenzymes 79–80
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
identification of enzymes involved in drug metabolism 76–7
predicting effects on metabolism of other drugs 80–2
predicting interactions 77–9
test drug affecting metabolism of other drugs 79–82

test drug as substrate 76–9

in vitro–in vivo correlations 82–3

complex or biphasic interactions 85–6

drug pharmacokinetic characteristics and administration route 85

metabolism of substrate 83–4

other sources of variability 86–7

role of metabolites 84–5

therapeutic index of the substrate 83

drugs, influence on AED bioavailability 93

general principles 93–5

interactions with established AEDs

carbamazepine (CBZ) 100–1

ethosuximide (ESM) 102

phenobarbital (PB) 101–2

phenytoin (PHT) 96–100

valproic acid (VPA) 101

interactions with new AEDs 102

felbamate (FBM) 103

gabapentin (GBP) 103–4

lamotrigine (LTG) 104

levetiracetam (LEV) 105

oxcarbazepine (OCBZ) 104–5

tiagabine (TGB) 103

topiramate (TPM) 104

vigabatrin (VGB) 102–3

zonisamide (ZNS) 105

elderly patients, AED interactions 273, 287

AEDs versus other drug combinations 278

analgesics 281–2

anticoagulants/antiplatelet agents 279–81

antihyperlipidemics 278–9

antihypertensives 278

CNS agents 285–7

endocrine/metabolic agents 283–4

gastrointestinal agents 282–3

respiratory agents 285

contributing factors 273

age-related alterations in pharmacodynamics 274–5

age-related alterations in pharmacokinetics 275–7

age-related alterations in physiology 276

pharmacoepidemiology 273–4

medication used in addition to AEDs on nursing home residents 275

endocrine/metabolic agents, interactions with AEDs in the elderly 283–4

epilepsy

mentally retarded patients

differential diagnosis 328

epidemiology 326–7, 326, 327

intractability of seizures 327, 329

problems diagnosing epilepsy 327

psychotropic drugs 353

epoxide hydrolases (EHs) 65

erthyromycin 6, 99

interactions with AEDs

oxcarbazepine (OCBZ) 150

tiagabine (TGB) 162

ethambutol 8

ethanol 68

interactions with AEDs

phenobarbital (PB) 151

phenytoin (PHT) 155

tiagabine (TGB) 163

ethosuximide (ESM)

action 30, 210

clinical trials 233

effect upon excitatory amino acid receptors 214

effects on drug-metabolizing enzyme systems 81

elimination pathways 78

FEC and FEC index 201

influence of food and drugs on bioavailability 102

interactions with non-AEDs 146

isoniazid 146

rifampicin 146

interactions with other AEDs 119

levels through pregnancy 297

pharmacokinetic characteristics 50

therapeutic range 393

ethotoin 302

felbamate (FBM) 18

action 210

adverse effects 34

effect upon excitatory amino acid receptors 214
felbamate (FBM) (contd)
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 334
influence of food and drugs on bioavailability 103
interactions in children 261
interactions in the elderly anticoagulants/antiplatelet agents 279 endocrine/metabolic agents 283
interactions with conventional AEDs 213
interactions with non-AEDs 146
interactions with other AEDs effect of other drugs 121 effect on other drugs 120–1
metabolic interactions 84 pharmacokinetic characteristics 50 therapeutic range 393
felodipine, interactions with AEDs oxcarbazepine (OCBZ) 150 phenobarbital (PB) 151 fentanyl, interactions with AEDs carbamazepine (CBZ) 144 phenobarbital (PB) 152 fetal complications associated with AEDs 298–300 fetal hydrantoin syndrome (FHS) 301, 308–10 fetal trimethadione syndrome 308 fetal valproate syndrome 310 fluconazole, interactions with AEDs carbamazepine (CBZ) 142 phenytoin (PHT) 155–6, 158
flumazenil 241 fluoxetine 244, 348, 353–4 fluvoxamine 244, 348, 354 folic acid and folates 100 deficiency as a potential mechanism for AED teratogenicity 304–6 pre-conceptual folate 305 interactions with AEDs phenobarbital (PB) 152 phenytoin (PHT) 159 primidone (PRM) 162 folk medicines 374 food, influence on AED bioavailability 93

felbamate (FBM) (contd)
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 334
influence of food and drugs on bioavailability 103
interactions in children 261
interactions in the elderly anticoagulants/antiplatelet agents 279 endocrine/metabolic agents 283
interactions with conventional AEDs 213
interactions with non-AEDs 146
interactions with other AEDs effect of other drugs 121 effect on other drugs 120–1
metabolic interactions 84 pharmacokinetic characteristics 50 therapeutic range 393
felodipine, interactions with AEDs oxcarbazepine (OCBZ) 150 phenobarbital (PB) 151 fentanyl, interactions with AEDs carbamazepine (CBZ) 144 phenobarbital (PB) 152 fetal complications associated with AEDs 298–300 fetal hydrantoin syndrome (FHS) 301, 308–10 fetal trimethadione syndrome 308 fetal valproate syndrome 310 fluconazole, interactions with AEDs carbamazepine (CBZ) 142 phenytoin (PHT) 155–6, 158
flumazenil 241 fluoxetine 244, 348, 353–4 fluvoxamine 244, 348, 354 folic acid and folates 100 deficiency as a potential mechanism for AED teratogenicity 304–6 pre-conceptual folate 305 interactions with AEDs phenobarbital (PB) 152 phenytoin (PHT) 159 primidone (PRM) 162 folk medicines 374 food, influence on AED bioavailability 93
general principles 93–5 interactions with established AEDs carbamazepine (CBZ) 100–1 ethosuximide (ESM) 102 phenobarbital (PB) 101–2 phenytoin (PHT) 96–100 valproic acid (VPA) 101 interactions with new AEDs 102 felbamate (FBM) 103 gabapentin (GBP) 103–4 lamotrigine (LTG) 104 levetiracetam (LEV) 105 oxcarbazepine (OCBZ) 104–5 tiagabine (TGB) 103 topiramate (TPM) 104 vigabatrin (VGB) 102–3 zonisamide (ZNS) 105 fractional effective concentration (FEC) and FEC index 199–201, 200, 201 frusemide 7 furosemide 99–100 interactions with AEDs phenytoin (PHT) 159 future clinical research 458–9 compliance 468 designing curative AEDs 462–3 designing rational polytherapy 461–2 improved definition of epileptic syndromes 459–60 pharmacogenomics and personalized AEDs 471–2 pharmacovigilance 468–71 quality of life and rational polytherapy 468 safety aspects 467 seizure initiation and progression 461 studies to test combinations 463–7 validation of therapeutic ranges 472 future experimental research 441–2, 453–4 assessment of drug combination efficacy 449–50 controlled seizure activity and pharmacologic endpoints 450–1 experimental design 451–2 integrated Pk/Pd modelling 452–3 factors affecting AED response disease progression 444–5
experimental animal models 442–4
influence of chronic medication 445
mechanisms of epileptogenesis 442
modelling new drug combinations 446–9, 447, 448
pharmacokinetic factors and interactions 445–6

gabapentin (GBP)
action 210
combination therapies 428
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 333
influence of food and drugs on bioavailability 103–4
interactions in children 261
interactions in the elderly gastrointestinal agents 282
interactions with conventional AEDs 213
interactions with non-AEDs 147 antacids 147
cimetidine 147
interactions with other AEDs
effect of other drugs 122
effect on other drugs 121–2
non-epileptic disorders 375–7
pharmacokinetic characteristics 50
pregnancy, use in 306
therapeutic range 393
gamma amino butyric acid receptors (GABA-A and GABA-B) 18, 30–1, 32–4
gastrointestinal agents, interactions with AEDs in the elderly 282–3
genetic susceptibility factor (G) for adverse drug reactions 38
genetic tests, misconceptions about 35–9 discriminative value 36
pre-test probability 37
genotyping 28
Gilbert’s syndrome 28, 372
glibenclamide 9
glucuronidation 28
gonadotropic-releasing hormone (GnRH) 297
grapefruit juice 97
griseofulvin 102
Gull, William Withey 4
haloperidol 352, 358
handicapped and mentally retarded patients 325, 335
drug interactions and adverse effects 328–9
benzodiazepines (BZP) 332
carbamazepine (CBZ) 331
felbamate (FBM) 334
gabapentin (GBP) 333
lamotrigine (LMT) 332–3
levetiracetam (LEV) 334–5
oxcarbazepine (OCBZ) 331
phenobarbital (PB) 329–30
phenytoin (PHT) 330
tiagabine (TGB) 333
topiramate (TPM) 333–4
valproate (VPA) 330–1
vigabatrin (VGB) 332
zonisamide (ZNS) 334
epidemiology of epilepsy 326–7
failure to recognise seizures 327
occurrence in certain syndromes 326
intractability of seizures 327, 329
outcome of epilepsy 335
problems diagnosing epilepsy 327
differential diagnosis 328
hepatocytes, use in drug metabolism tests 75
herbal remedies 3–4
Herpes Zoster infections 10
holocrania 303–4
human genome project 26
human immuno virus (HIV) infection 373
human leukocyte antigen (HLA) 34
hyperbilirubinemia 372
hypertension 7
hypertension optimal treatment (HOT) study 7
ibuprofen, interactions with AEDs
valproic acid (VPA) 164–5
ifosfamide, interactions with AEDs
phenobarbital (PB) 152
imipramine 244
indifferent drug interactions 183
isobolographic analysis 195, 196
indinavir, interactions with AEDs
  carbamazepine (CBZ) 144
infantile spasms 264
infants of mothers with epilepsy (IME) 298
malformations 298, 299–300
infra-additive drug interactions 183
isobolographic analysis 195, 196, 197
inhibition constant (K_i) 80
insertion or deletion (INDELS) polymorphisms 26
interactions between AEDs 111–12, 129
  carbamazepine (CBZ)
    effect of other drugs 117–18
    effect on other drugs 116–17
children 259
  carbamazepine (CBZ) 259–60
  childhood 265–6
  felbamate (FBM) 261
  gabapentin (GBP) 261
  infancy 264–5
  lamotrigine (LTG) 261
  oxcarbazepine (OCBZ) 261
  phenobarbital (PB) 259–60
  phenytoin (PHT) 259–60
  pragmatic aspects of treatment 262–3
  treatment according to epilepsy type or syndrome 263–4
  valproic acid (VPA) 260
clinical studies of pharmacodynamic interactions 228–9
negative interactions affecting efficacy 235–6
positive interactions affecting efficacy 229–35
side effects 236–7
trial designs 237–8
conventional AEDs
  experimental studies 208–10, 210
conventional and newer AEDs
  experimental studies 211–12, 213
ethosuximide (ESM) 119
felbamate (FBM)
  effect of other drugs 121
  effect on other drugs 120–1
gabapentin (GBP)
  effect of other drugs 122
  effect on other drugs 121–2
lamotrigine (LTG)
  effect of other drugs 123–4, 124
  effect on other drugs 122–3
levetiracetam (LEV) 128
methsuximide (MSM)
  effect on other drugs 119–20
newer AEDs
  experimental studies 212–13
  oxcarbazepine (OCBZ)
    effect of other drugs 125–6
    effect on other drugs 124–5
  phenobarbital (PB)
    effect of other drugs 113–14
    effect on other drugs 112–13
phenytoin (PHT)
    effect of other drugs 115–16
    effect on other drugs 114–15
primidone (PRM)
  effect of other drugs 116
  effect on other drugs 116
therapeutic implications 130
  tiagabine (TGB)
    effect of other drugs 128
    effect on other drugs 128
topiramate (TPM)
  effect of other drugs 127
  effect on other drugs 127
valproic acid (VPA)
  effect of other drugs 118
  vigabatrin (VGB)
    effect of other drugs 127
    effect on other drugs 126–7
zonisamide (ZNS)
  effect of other drugs 130
  effect on other drugs 128
interactions of AEDs with non-AEDs 139–40, 363–4
AEDs in general
  excitatory amino acid antagonists 213–19, 214
  voltage-dependent calcium channel inhibitors 219–20
carbamazepine (CBZ) 140, 143
  antibiotics 140–1
  antihypertensive drugs 143–4
  antiviral agents 141
  cimetidine 141
<table>
<thead>
<tr>
<th>Drug</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisplatin</td>
<td>141</td>
</tr>
<tr>
<td>cyclosporin</td>
<td>144</td>
</tr>
<tr>
<td>danazol</td>
<td>142</td>
</tr>
<tr>
<td>dicoumarol</td>
<td>144</td>
</tr>
<tr>
<td>diltiazem</td>
<td>142</td>
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<tr>
<td>doxycycline</td>
<td>144</td>
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<td>144</td>
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<td>142</td>
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<td>indinavir</td>
<td>144</td>
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<tr>
<td>isoniazid</td>
<td>142</td>
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<tr>
<td>itraconazole</td>
<td>144</td>
</tr>
<tr>
<td>ketoconazole</td>
<td>142</td>
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<tr>
<td>methotrexate</td>
<td>145</td>
</tr>
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<td>metronidazole</td>
<td>142</td>
</tr>
<tr>
<td>nicotinamide</td>
<td>143</td>
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<tr>
<td>phenprocoumon</td>
<td>145</td>
</tr>
<tr>
<td>propoxyphene</td>
<td>143</td>
</tr>
<tr>
<td>quinine</td>
<td>143</td>
</tr>
<tr>
<td>rocuronium</td>
<td>145</td>
</tr>
<tr>
<td>steroids</td>
<td>145</td>
</tr>
<tr>
<td>teniposide</td>
<td>145</td>
</tr>
<tr>
<td>ticlopidine</td>
<td>143</td>
</tr>
<tr>
<td>verapamil</td>
<td>143</td>
</tr>
<tr>
<td>vincristine</td>
<td>145</td>
</tr>
<tr>
<td>clinical studies of pharmacodynamic interactions</td>
<td>241, 251–2</td>
</tr>
<tr>
<td>analgesics and anti-inflammatory agents</td>
<td>250–1</td>
</tr>
<tr>
<td>anesthetic agents</td>
<td>250</td>
</tr>
<tr>
<td>antidepressants (ADs)</td>
<td>242–6, 244</td>
</tr>
<tr>
<td>antipsychotics (APs)</td>
<td>246–8</td>
</tr>
<tr>
<td>CNS stimulants</td>
<td>248–9</td>
</tr>
<tr>
<td>ethosuximide (ESM)</td>
<td>146</td>
</tr>
<tr>
<td>isoniazid</td>
<td>146</td>
</tr>
<tr>
<td>rifampicin</td>
<td>146</td>
</tr>
<tr>
<td>felbamate (FBM)</td>
<td>146</td>
</tr>
<tr>
<td>gabapentin (GBP)</td>
<td>147</td>
</tr>
<tr>
<td>antacids</td>
<td>147</td>
</tr>
<tr>
<td>cimetidine</td>
<td>147</td>
</tr>
<tr>
<td>lamotrigine (LTG)</td>
<td>147</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>147</td>
</tr>
<tr>
<td>bupropion</td>
<td>148</td>
</tr>
<tr>
<td>cimetidine</td>
<td>148</td>
</tr>
<tr>
<td>rifampicin</td>
<td>148</td>
</tr>
<tr>
<td>levetiracetam (LEV)</td>
<td>148</td>
</tr>
<tr>
<td>digoxin</td>
<td>148, 149</td>
</tr>
<tr>
<td>probenecid</td>
<td>148–9</td>
</tr>
<tr>
<td>warfarin</td>
<td>149</td>
</tr>
<tr>
<td>oxcarbazepine (OCBZ)</td>
<td>149</td>
</tr>
<tr>
<td>cimetidine</td>
<td>149</td>
</tr>
<tr>
<td>dextropropoxyphene</td>
<td>149</td>
</tr>
<tr>
<td>erythromycin</td>
<td>150</td>
</tr>
<tr>
<td>felodipine</td>
<td>150</td>
</tr>
<tr>
<td>verapamil</td>
<td>150</td>
</tr>
<tr>
<td>phenobarbital (PB)</td>
<td>150</td>
</tr>
<tr>
<td>activated charcoal</td>
<td>150–1</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>151</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>151</td>
</tr>
<tr>
<td>cimetidine</td>
<td>151</td>
</tr>
<tr>
<td>cyclosporin</td>
<td>151</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>151</td>
</tr>
<tr>
<td>ethanol</td>
<td>151</td>
</tr>
<tr>
<td>felodipine</td>
<td>151</td>
</tr>
<tr>
<td>fentanyl</td>
<td>152</td>
</tr>
<tr>
<td>folic acid</td>
<td>152</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>152</td>
</tr>
<tr>
<td>itraconazole</td>
<td>152</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>152</td>
</tr>
<tr>
<td>metronidazole</td>
<td>152</td>
</tr>
<tr>
<td>nimodipine</td>
<td>152</td>
</tr>
<tr>
<td>prednisolone</td>
<td>153</td>
</tr>
<tr>
<td>teniposide</td>
<td>153</td>
</tr>
<tr>
<td>theophylline</td>
<td>153</td>
</tr>
<tr>
<td>tirilazad</td>
<td>153</td>
</tr>
<tr>
<td>tolbutamide</td>
<td>153</td>
</tr>
<tr>
<td>verapamil</td>
<td>153</td>
</tr>
<tr>
<td>warfarin</td>
<td>153</td>
</tr>
<tr>
<td>phenytoin (PHT)</td>
<td>154</td>
</tr>
<tr>
<td>acetaminophen (paracetamol)</td>
<td>157</td>
</tr>
<tr>
<td>activated charcoal</td>
<td>154</td>
</tr>
<tr>
<td>acyclovir</td>
<td>154</td>
</tr>
<tr>
<td>amiodarone</td>
<td>154</td>
</tr>
<tr>
<td>antacids</td>
<td>154</td>
</tr>
<tr>
<td>antineoplastic agents</td>
<td>154–5</td>
</tr>
<tr>
<td>bishydroxycoumarin</td>
<td>155</td>
</tr>
<tr>
<td>calcium channel blockers</td>
<td>155</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>155, 157</td>
</tr>
<tr>
<td>cimetidine</td>
<td>155</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>157</td>
</tr>
<tr>
<td>cyclosporin</td>
<td>158</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>158</td>
</tr>
<tr>
<td>dicoumarol</td>
<td>158</td>
</tr>
</tbody>
</table>
interactions of AEDs with non-AEDs (contd) phenytoin (PHT) (contd)
digitoxin 158
digoxin 158
disopyramide 158
disulfiram 155
doxycycline 158
ethanol 155
fluconazole 155–6, 158
folic acid 159
furosemide 159
isoniazid 156
itraconazole 159
ketocanazole 159
meperidine (pethidine) 159
methadone 159
methotrexate 159
mexiletine 159
miconazole 156
misonidazole 160
nisoldipine 160
omeprazole 156
phenylbutazone 156
praziquantel 160
prednisolone 160
propoxyphene 156
quinidine 160
rifampin 156–7
rocuronium 160
salicylates 157
sulfonamides 157
teniposide 160
theophylline 160
ticlopidine 157
tolbutamide 157
trilazad 161
vecuronium 161
warfarin 161
primidone (PRM) 161
acetazolamide 161
folic acid 162
isoniazid 161
nicotinamide 162
tiagabine (TGB) 162
cimetidine 162
digoxin 163
erthyromycin 162
ethanol 163
theophylline 163
triazolam 163
warfarin 163
topiramate (TPM) 163
digoxin 164
valproic acid (VPA)
cholestryramine 164
cimetidine 164
cisplatin 164
doxorubicin 164
ibuprofen 164–5
isoniazid 165
ketoconazole 165
mefenamic acid 165
methotrexate 165
naproxen 165
rifampicin 165
salicylic acid 165
tolbutamide 166
tolmetin 166
warfarin 166
zidovudine 166
vigabatrin (VGB) 166
zonisamide (ZNS) 167
sulfonamides 167
isobolographic analysis 194–9, 198, 199
types of interactions 195, 197
isoniazid, interactions with AEDs
carbamazepine (CBZ) 142
ethosuximide (ESM) 146
phenytoin (PHT) 156
primidone (PRM) 161
valproic acid (VPA) 165
itraconazole, interactions with AEDs
carbamazepine (CBZ) 144
phenobarbital (PB) 152
phenytoin (PHT) 159
kernicterus 372
ketoconazole, interactions with AEDs
carbamazepine (CBZ) 142
phenytoin (PHT) 159
valproic acid (VPA) 165
lamotrigine (LTG) 18
absence seizures 30
action 210
sodium channels 32
adverse effects 21
combination therapies 427–8
effect upon excitatory amino acid receptors 214
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 334–5
influence of food and drugs on bioavailability 105
interactions 28
interactions in children 261
interactions in the elderly analgesics 281
CNS agents 286
interactions with non-AEDs 147
acetaminophen 147
bupropion 148
cimetidine 148
rifampicin 148
interactions with other AEDs
effect of other drugs 123–4, 124
effect on other drugs 122–3
non-epileptic disorders 377
oral contraceptives (OCs) 346
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
pregnancy, use in 306–7
selection for combination therapy 22
therapeutic range 393
latin square design 233
Lennox–Gestaut syndrome 266
leukemia 28
levetiracetam (LEV) 18
interactions with non-AEDs 148
digoxin 148, 149
probenecid 148–9
warfarin 149
interactions with other AEDs 128
non-epileptic disorders 377–8
pharmacokinetic characteristics 50
therapeutic range 393
lidocaine 250
ligands of metabotropic glutamate receptors:
interactions with AEDs 218–19
Lind, James 3–4
lipophilic drugs 27
lithium 352, 363
liver
cirrhosis 372
hepatocytes, use in drug metabolism tests 75
microsomes, use in drug metabolism tests 75
role in drug metabolism 57–8
lutenizing hormone (LH) 297
maprotiline 244
maximal electroshock (MES) 195, 199
maximal tolerated dose (MTD) 204–6
median effective dose (ED₅₀) 196–7
medroxyprogesterone 295, 345
mefenamic acid, interactions with AEDs
valproic acid (VPA) 165
menstruation 295
mentally retarded patients see handicapped and mentally retarded patients
meperidine (pethidine), interactions with AEDs
phenytoin (PHT) 159
mercaptopurine 28
metformin 9
methadone, interactions with AEDs
phenytoin (PHT) 159
methotrexate, interactions with AEDs
carbamazepine (CBZ) 145
phenytoin (PHT) 159
valproic acid (VPA) 165
methotrexate (MST), interactions with other AEDs
effect on other drugs 119–20
N-methyl-D-aspartate receptor antagonists, interactions with AEDs 213–16, 214
methylenetetrahydrofolate reductase (MTHFR) gene 35
methylprednisolone, interactions with AEDs phenobarbital (PB) 152
metolazone 7
metronidazole, interactions with AEDs carbamazepine (CBZ) 142
phenobarbital (PB) 152
mexiletine, interactions with AEDs phenytoin (PHT) 159
mibefradil 10–11
miconazole, interactions with AEDs phenytoin (PHT) 156
microsomes, use in drug metabolism tests 75
mirtazapine 351
misonidazole, interactions with AEDs phenytoin (PHT) 160
monitoring of drugs in combination therapies 392–3, 400
future of monitoring 399
indications 393–4, 394
indications
avoidance of intoxication and side effects 395–7
avoidance of under dosage 394–5
monitoring concomitant medication 397
laboratory tests 399
limits and dangers of serum AED concentration determination 398
measurement of free AED concentration 397–8
prerequisites for serum AED determination 397
therapeutic ranges 393
muscarinic receptor 30
myoclonic–astatic epilepsy 265–6
naloxone 251
interactions with AEDs
valproic acid (VPA) 165
nefazodone 350–1, 356–7
neonatal complications with AEDs 312–13
neural tube defects (NTDs) 303–4
nicotinamide, interactions with AEDs carbamazepine (CBZ) 143
primidone (PRM) 162
nicotinic receptor 30
nifedipine, interactions with AEDs phenobarbital (PB) 152
nimodipine, interactions with AEDs phenobarbital (PB) 152
nisoldipine, interactions with AEDs phenytoin (PHT) 160
non-epileptic health conditions, possible AED interactions 369–70, 370, 371–3, 382–3
carbamazepine (CBZ) 375
folk medicines 374
gabapentin (GBP) 375–7
lamotrigine (LTG) 377
levetiracetam (LEV) 377–8
oxcarbazepine (OCBZ) 378
phenobarbital (PB) 378–9
phenytoin (PHT) 379–80
pregabalin (PGB) 380
primidone (PRM) 380
rationale for AED use 370–1
tiagabine (TGB) 380–1
topiramate (TPM) 381–2
unpredicted interactions 373–4
non-epileptic health conditions, possible AED interactions
valproate (VPA) 382
non-steroidal anti-inflammatory drugs (NSAIDs) 9–10
noradrenergic re-uptake inhibitors (NARIs) 350
olanzapine 247–8, 247, 352, 359
omeprazole
effect on AED absorption carbamazepine (CBZ) 100–1
phenytoin (PHT) 98
interactions with AEDs phenytoin (PHT) 156
opioids in valproic acid overdose 251
oral contraceptives (OCs) 295–6
management of women 347
mechanism of AED interactions and contraceptive failure 343–4
specific interactions with AEDs 344–5, 345
lamotrigine (LTG) 346
oxcarbazepine (OCBZ) 18
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 331
influence of food and drugs on bioavailability 104–5
interactions in children 261
interactions in the elderly
anticoagulants/antiplatelet agents 279–80
endocrine/metabolic agents 283–4
interactions with non-AEDs 149
cimetidine 149
dextropropoxyphene 149
erythromycin 150
felodipine 150
verapamil 150
warfarin 150
interactions with other AEDs
effect of other drugs 125–6
effect on other drugs 124–5
non-epileptic disorders 376
pharmacokinetic characteristics 50
pregnancy, use in 307
selection for combination therapy 22
therapeutic range 393
paracetamol (acetaminophen), interactions with AEDs
phenytoin (PHT) 157
paradoxical intoxication 189
paroxetine 350
penicillin in combination therapies, general principles 7
perospirone 359
peroxisome proliferator-activated receptors (PPARs) 68–9
pethidine (meperidine), interactions with AEDs
phenytoin (PHT) 159
pharmacodynamics, genetic dependency 29–34
pharmacodynamics, methods for assessing interactions
clinical methods and studies 228–9, 241
basic principles 203–4
latin square design 233
negative interactions affecting efficacy 235–6
other studies 231–5
placebo-controlled trials 230–1, 231
positive interactions affecting efficacy 229–30
side effects 236–7
trial designs 204–6, 237–8
experimental methods and studies 208, 220–2
basic principles 193–4
blockade of ionotropic receptors for glutamate 219
interaction of AEDs with voltage-dependent calcium channel inhibitors 219–20
interactions between AEDs and excitatory amino acid antagonists 213–19, 214
interactions between conventional AEDs 208–10, 210
interactions between conventional and newer AEDs 211–12
interactions between newer AEDs 212–13, 213
isobolographic analysis 194–9, 195, 197, 198, 199
methodological pitfalls 202–3
other methods 199–202, 200
pharmacodynamics, principles and mechanisms of drug interactions
clinical significance of interactions 184–5
spectrum of interactions 184–5, 185
desirable interactions 186–7, 186
distinction between pharmacodynamic and pharmacokinetic interactions 181–2
monotherapy versus combination therapy 190–1
relationship between drug dose, concentration and response 183–4, 184
types of interactions 182–4, 183
undesirable interactions 186, 187–9
antagonism 190
seizure aggravation and paradoxical intoxication 189
Index

pharmacogenetics 26–7
adverse effects 34–5
central pharmacokinetics 28–9
genetic tests 35–9
discriminative value 36
distribution of positive results 39
genetic susceptibility factor 38
pre-test probability 37
prevalence of adverse drug reactions 38–9
susceptibility factor 38
metabolism 27–8
pharmacodynamics 29–34
pharmacokinetics, genetic dependency 28–9
phelatin 17
phenobarbital (PB) 17
action 18, 210
adverse effects 18
clinical trials 232
effect upon excitatory amino acid receptors 214
effect upon NMDA and AMPA/KA receptors 218
effects on drug-metabolizing enzyme systems 81
elimination pathways 78
FEC and FEC index 201
handicapped and mentally retarded patients 329–30
influence of excitatory amino acid receptor antagonists 215
influence of food and drugs on bioavailability 101–2
interactions in children 259–60
interactions in the elderly analgesics 281
anticoagulants/antiplatelet agents 280
antihyperlipidemias 279
antihypertensives 278
CNS agents 286
endocrine/metabolic agents 284
gastrointestinal agents 282
respiratory agents 285
interactions with newer AEDs 213
interactions with non-AEDs 150
activated charcoal 150–1
cefotaxime 151
chloramphenicol 151
cimetidine 151
cyclosporin 151
dexamethasone 151
ethanol 151
felodipine 151
fentanyl 152
folic acid 152
ifosfamide 152
itraconazole 152
methylprednisolone 152
metronidazole 152
nifedipine 152
nimodipine 152
prednisolone 153
teniposide 153
theophylline 153
tirilazad 153
tolbutamide 153
verapamil 153
warfarin 153
interactions with other AEDs
effect of other drugs 113–14
effect on other drugs 112–13
levels through pregnancy 297
metabolism 27–8
non-epileptic disorders 378–9
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
therapeutic range 393
phenobarbitone see phenobarbital (PB)
phenothiazines 247
phenprocoumon, interactions with AEDs
carbamazepine (CBZ) 145
phenylbutazone 50
interactions with AEDs
phenytoin (PHT) 156
phenytoin (PHT) 4, 17
absence seizures 30
absorption 48
action 18
sodium channels 32
active metabolites 22
adverse effects
gum hypertrophy 35
metabolites 35
clinical trials 232
drug interactions 49–50, 51–2
drugs, effect on absorption
activated charcoal 97–8
antacids 98
interactions during parenteral administration 99
sucralfate 98
effect of gastrointestinal diseases on bioavailability 97
effects on drug-metabolizing enzyme systems 81
effects on pharmacokinetics/pharmacodynamics of other drugs 99–100
elimination pathways 78
foods, effect on absorption 97
handicapped and mentally retarded patients 330
influence of food and drugs on bioavailability 96
interactions in children 259–60
interactions in the elderly analgesics 282
anticoagulants/antiplatelet agents 280
antihyperlipidemics 279
antihypertensives 278
CNS agents 286
endocrine/metabolic agents 284
gastrointestinal agents 282–3
respiratory agents 285
interactions with non-AEDs 154
acetaminophen (paracetamol) 157
activated charcoal 154
acyclovir 154
amiodarone 154
antacids 154
antineoplastic agents 154–5
bishydroxycoumarin 155
calcium channel blockers 155
chloramphenicol 155, 157
cimetidine 155
cyclophosphamide 157
cyclosporin 158
dexamethasone 158
dicoumarol 158
digitoxin 158
digoxin 158
disopyramide 158
disulfiram 155
doxycycline 158
ethanol 155
fluconazole 155–6, 158
folic acid 159
furosemide 159
isoniazid 156
itraconazole 159
ketoconazole 159
meperidine (pethidine) 159
methadone 159
methotrexate 159
mexiletine 159
miconazole 156
misonidazole 160
nisoldipine 160
omeprazole 156
phenylbutazone 156
praziquantel 160
prednisolone 160
propoxyphene 156
quinidine 160
rifampin 156–7
rocuronium 160
salicylates 157
sulfonamides 157
teniposide 160
theophylline 160
ticlopidine 157
tolbutamide 157
trilazad 161
vecuronium 161
warfarin 161
interactions with other AEDs
effect of other drugs 115–16
effect on other drugs 114–15
levels through pregnancy 297
metabolism 27
non-epileptic disorders 379–80
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
selection for combination therapy 22
teratogenicity 301
birth defects and epoxide hydrolase activity 301–2
birth defects and lymphocyte cytotoxicity 301
formation of arene oxides 301
therapeutic range 393
placebo-controlled trials 230–1, 231
polycystic ovarian syndrome (PCOS) 297, 298
polypharmacy 5–6, 9, 228
polytherapy 6
drug selection 421–2
combination therapies AEDs with non-AEDs 431
combination therapies with newer AEDs 427–9
combination therapies with older AEDs 425–7
combination therapies with three or more AEDs 429–30
general principles 426
pharmacotherapy-resistant seizures 422–3, 423
resistance to pharmacotherapy 431–4
scale of the problem 423–4, 424
rational polytherapy 424–5
potassium channels 30
potentiation of drugs 183
praziquantel, interactions with AEDs
phenytoin (PHT) 160
prednisolone, interactions with AEDs
phenobarbital (PB) 153
phenytoin (PHT) 160
pregabalin (PGB), non-epileptic disorders 380
pregnancy and AED interactions 294, 314
AEDs and hormonal contraceptives 295–6
mechanism of interactions and contraceptive failure 343–4
specific interactions with oral contraceptives (OCs) 344–5, 345
specific interactions with parental sex steroid administration 345–6
developmental delay 313–14
epoxides 300–1
fetal complications 298–300
folate deficiency as a potential mechanism for teratogenicity 304–6
pre-conceptual folate 305
free radical intermediates and teratogenicity 302
maternal complications 296–7
mechanisms of teratogenicity 300
neonatal complications 312–13
neural tube defects (NTDs) 303–4
new AEDs 306
gabapentin (GBP) 306
lamotrigine (LTG) 306–7
oxcarbazepine (OCBZ) 307
topiramate (TPM) 307
zonisamide (ZNS) 307
phenytoin (PHT) teratogenicity 301–2
polycystic ovaries 297–8
syndromes of anomalies 308
benzodiazepine syndrome 311
cambamazepine syndrome 311
fetal hydrantoin syndrome (FHS) 301, 308–10
fetal trimethadione syndrome 308
fetal valproate syndrome 310
newer AEDs 311–12
primidone embryopathy 310
pregnane X receptor (PXR) 68
prescribed daily dose (PDD) 188
primidone (PRM) 20
embryopathy 310
interactions with non-AEDs 161
acacetazolamide 161
folic acid 162
isoniazid 161
nicotinamide 162
interactions with other AEDs
effect of other drugs 116
effect on other drugs 116
levels through pregnancy 297
non-epileptic disorders 380
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
therapeutic range 393
probenecid, interactions with AEDs
levetiracetam (LEV) 148–9
propranolol 371
psychosis, interaction between AEDs and antipsychotics (APs) 246
psychotropic drugs
interactions with anticonvulsants
role of CYP450 system 353–5
use in epilepsy 353
pyrazinamide 8
quetiapine 247–8, 247, 352
quinidine, interactions with AEDs
  phenytoin (PHT) 160
quinine, interactions with AEDs
  carbamazepine (CBZ) 143
reboxetine 350
renal dysfunction 373
respiratory agents, interactions with AEDs in
  the elderly 285
rifampicin, interactions with AEDs
  ethosuximide (ESM) 146
  lamotrigine (LTG) 148
  phenytoin (PHT) 156–7
  valproic acid (VPA) 165
risperidone 247–8, 247, 352, 358–9
rocuronium, interactions with AEDs
  carbamazepine (CBZ) 145
  phenytoin (PHT) 160
roxithromycin 99
salicylic acid and salicylates, interactions with
  AEDs 7
  phenytoin (PHT) 157
  valproic acid (VPA) 165
seizure aggravation by AEDs 189
selective serotonin-reuptake inhibitors
  (SSRIs) 243, 350
  interactions with anticonvulsants 355–7
serotonin–noradrenergic re-uptake inhibitors
  (NSRIs) 350
  interactions with anticonvulsants 355–7
sertraline 350, 356
sex hormone-binding globulin (SHBG) 295
sex steroids and AEDs 341, 347
  awareness of issues 342
  frequency and importance of reactions 341–2
  management of women on oral
     contraceptives (OCs) 347
  mechanism of interactions and
     contraceptive failure 343–4
  specific interactions with oral
     contraceptives (OCs) 344–5, 345
  lamotrigine (LTG) 346
  specific interactions with parental sex
     steroid administration 345–6
     testosterone 346
single nucleotide polymorphisms (SNPs) 26, 29
sodium channels 31–2
sorivudine 10
spina bifida (SB) 303
spironolactone 7
statins 7
steroids, interactions with AEDs
  carbamazepine (CBZ) 145
Stevens–Johnson syndrome (SJS) 36–7
  discriminative value of genetic tests 36
  pre-test probability 37
streptomycin 4–5
Sturge–Weber disease 263
sucralfate, effect on AED absorption
  phenytoin (PHT) 98
sulfonamides, interactions with AEDs
  phenytoin (PHT) 157
  zonisamide (ZNS) 167
sulfonylureas 9
supra-additive drug interactions 183, 193–4
  isobolographic analysis 195, 196, 197
susceptibility factor (R) for adverse drug
  reactions 38
symptomatic partial epilepsy 263–4
synergism between drugs 183
synergism in combination therapies, general
  principles 7
teniposide, interactions with AEDs
  carbamazepine (CBZ) 145
  phenobarbital (PB) 153
  phenytoin (PHT) 160
teratogenicity, AED mechanisms 35, 300
  folate deficiency 304–6
    pre-conceptual folate 305
  free radical intermediates 302
  neural tube defects (NTDs) 303–4
  phenytoin (PHT) 301
  birth defects and epoxide hydrolase
    activity 301–2
  birth defects and lymphocyte cytotoxicity
    301
  formation of arene oxides 301
terfenadine 10
testosterone, interaction with AEDs 346
theophylline
 - drugs, effect on absorption
 - antineoplastic therapy 98
 - other drugs 99
 - theophylline 98
 - interactions with AEDs
   - phenobarbital (PB) 153
   - phenytoin (PHT) 157
   - valproic acid (VPA) 166
tolmetin, interactions with AEDs
   - valproic acid (VPA) 166
topiramate (TPM) 18
   - action 210
   - combination therapies 428–9
   - effect upon excitatory amino acid receptors 214
   - effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 333–4
influence of food and drugs on bioavailability 103
interactions with non-AEDs 162
 - cimetidine 162
 - digoxin 163
 - erythromycin 162
 - ethanol 163
 - theophylline 163
 - triazolam 163
 - warfarin 163
 - interactions with other AEDs
   - effect of other drugs 127
   - effect on other drugs 127
 - metabolic interactions 84
 - non-epileptic disorders 381–2
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
pregnancy, use in 307
side effects in polytherapy and monotherapy 412
therapeutic range 393
total AED load 188
toxic epidermal necrolysis (TEN) 36–7
discriminative value of genetic tests 36
pre-test probability 37
trial designs 204, 237–8
 - invalid design 206
 - optimal design 204–5
 - probably valid design 205
 - questionably valid design 205–6
 - triazolam, interactions with AEDs
 - ticlopidine, interactions with AEDs
 - carbamazepine (CBZ) 143
 - phenytoin (PHT) 157
 - tirilazad, interactions with AEDs
 - phenobarbital (PB) 153
tolbutamide 50
interactions with AEDs
 - phenobarbital (PB) 153
 - phenytoin (PHT) 157
 - valproic acid (VPA) 166
 - tiagabine (TGB) 163
therapeutic index 83, 197
thiopurine S-methyltransferase deficiency 28
thioridazine 358
tiagabine (TGB) 18
   - action 30, 210
   - combination therapies 429
   - effect upon excitatory amino acid receptors 214
   - effects on drug-metabolizing enzyme systems 81
elimination pathways 78
handicapped and mentally retarded patients 333–4
influence of food and drugs on bioavailability 104
interactions in the elderly
 - anticoagulants/antiplatelet agents 280
 - endocrine/metabolic agents 284
interactions with conventional AEDs 213
interactions with non-AEDs 163
 - digoxin 164
interactions with other AEDs
   - effect of other drugs 127
   - effect on other drugs 127
metabolic interactions 84
non-epileptic disorders 381–2
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
pregnancy, use in 307
side effects in polytherapy and monotherapy 412
therapeutic range 393
total AED load 188
toxic epidermal necrolysis (TEN) 36–7
discriminative value of genetic tests 36
pre-test probability 37
trial designs 204, 237–8
 - invalid design 206
 - optimal design 204–5
 - probably valid design 205
 - questionably valid design 205–6
 - triazolam, interactions with AEDs
 - ticlopidine, interactions with AEDs
 - carbamazepine (CBZ) 143
 - phenytoin (PHT) 157
 - tirilazad, interactions with AEDs
 - phenobarbital (PB) 153

tolbutamide 50
interactions with AEDs
 - phenobarbital (PB) 153
 - phenytoin (PHT) 157
 - valproic acid (VPA) 166
 - tiagabine (TGB) 163
tricyclic antidepressants (TCAs) 10, 243
interactions with anticonvulsants 357
trilazad, interactions with AEDs
phenytoin (PHT) 161
tuberculosis 4–5, 8

uridine diphosphate (UDP)-glucuronosyl-
tranferases (UDPGTs) 65–6
uridine glucuronyl transferases (UGTs) 28, 51

valproic acid and valproate (VPA) 18
action 210
active metabolites 22
adverse effects 21
effect upon excitatory amino acid receptors 214
effect upon NMDA and AMPA/KA
receptors 218
effects on drug-metabolizing enzyme
systems 81
elimination pathways 78
FEC and FEC index 201
fetal valproate syndrome 310
handicapped and mentally retarded
patients 330–1
influence of excitatory amino acid receptor
antagonists 215
influence of food and drugs on
bioavailability 101
interactions in children 260
interactions in the elderly
analgesics 282
anticoagulants/antiplatelet agents 280–1
CNS agents 287
gastrointestinal agents 283
interactions with newer AEDs 213
interactions with non-AEDs 163
cholestyramine 164
cimetidine 164
cisplatin 164
doxorubicin 164
ibuprofen 164–5
isoniazid 165
ketocnazole 165
mefenamic acid 165
methotrexate 165
naproxen 165
rifampicin 165
salicylic acid 165
tolbutamide 166
tolmetin 166
warfarin 166
zidovudine 166
interactions with other AEDs
effect on other drugs 118
levels through pregnancy 297
non-epileptic disorders 382
pharmacokinetic characteristics 50
pharmacokinetic interactions 21
therapeutic range 393
use of opioids in overdose 251
vecuronium, interactions with AEDs
phenytoin (PHT) 161
venlafaxine 350
verapamil, interactions with AEDs
carbamazepine (CBZ) 143
oxcarbazepine (OCBZ) 150
phenobarbital (PB) 153
vigabatrin (VGB) 18
action 30, 210
clinical trials 232
combination therapies 429
effect upon excitatory amino acid receptors
214
effects on drug-metabolizing enzyme
systems 81
elimination pathways 78
handicapped and mentally retarded
patients 332
influence of food and drugs on
bioavailability 102–3
interactions with non-AEDs 166
interactions with other AEDs
effect of other drugs 127
effect on other drugs 126–7
pharmacokinetic characteristics 50
selection for combination therapy 22
viloxazine 244
vincristine, interactions with AEDs
carbamazepine (CBZ) 145
warfarin, interactions with AEDs
levetiracetam (LEV) 149
oxcarbazepine (OCBZ) 150
warfarin, interactions with AEDs (contd)
phenobarbital (PB) 153
phenytoin (PHT) 161
tiagabine (TGB) 163
valproic acid (VPA) 166

zidovudine, interactions with AEDs
valproic acid (VPA) 166
ziprasidone 359
zolpidem 33
zonisamide (ZNS)
effects on drug-metabolizing enzyme systems 81

elimination pathways 78
handicapped and mentally retarded patients 334
influence of food and drugs on bioavailability 105
interactions with non-AEDs 167 sulfonamides 167
interactions with other AEDs effect of other drugs 130
effect on other drugs 128
pharmacokinetic characteristics 50 pharmacokinetic interactions 21
pregnancy, use in 307