Antiepileptic Drugs
Combination Therapy and Interactions

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.

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Combination Therapy and Interactions

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Foreword

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 of 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.

Torbjörn Tomson
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