

DRUG DISCOVERY AND EVALUATION

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It is fitting to include in *Neuropsychopharmacology: The Fifth Generation of Progress* a group of chapters concerned with many of the important issues related to: (a) the development of new drugs (e.g., the role of preclinical models to develop and test targets for new drugs; (b) the role of biological markers and imaging studies to provide indices of drug action in humans or predict clinical response; (c) advances in clinical trial design; (d) the optimal utilization of existing drugs (e.g., pharmacokinetics); (e) pharmacogenomics in relation to drug metabolism, discovery, and development; (f) the ethical issues concerning clinical trials and neuropsychiatric research in general; (g) governmental (at least United States) regulation of the process of developing and utilizing new drugs; and (h) the evaluation of the impact of drug treatment on outcome of neuropsychiatric disorders from the perspectives of economics, clinical endpoints, and humanistic considerations. Although the majority of these issues are the same in many parts of the world where this book will be read, there are clear differences in ethical attitudes toward clinical research and governmental regulation of drug development and utilization around the world (despite the Declaration of Helsinki). It is beyond the scope of this volume to consider the worldwide variations in these issues. All the chapters that have preceded this section bear on the subject matter addressed here because new drug development depends so heavily on our understanding of the function of the brain in general, neurotransmitter and modulator receptors and elimination mechanisms, theories of the etiology of the major neuropsychiatric disorders, efficacy and side effects of existing treatments, and an understanding of the mechanism of action of existing drugs.

The process of new drug development has changed greatly in the few years since the last volume in this series and is likely to change even more rapidly in the immediate

future. A great advance was the development of combinatorial chemistry and rapid, robotic characterization of the pharmacologic profile of the vast libraries of compounds produced by this shotgun approach, which, when successful, leads to the elegant and expensive custom syntheses of candidate compounds by sophisticated organic chemical procedures that are now often computer-derived or by methods involving cell and molecular biology to produce peptides or other organic substances. Together with greatly improved methods for analysis of structure–activity relationships, it has been possible to develop putative pharmaceuticals with the desired pharmacologic profile. The old cliché, beware what you desire because you may get it, is relevant here, because it is much easier now to come up with the desired pharmacologic profile than it is to be certain that what is sought is what should be sought. There is not yet sufficient understanding of what is needed in the way of an optimal antidepressant, anxiolytic, antipsychotic, mood stabilizer, antimentia, or other type of drug, especially when a truly novel compound is sought.

The chapter by Geyer and Markou on the role of preclinical models in the development of psychotropic drugs mainly focuses on animal models for the major psychiatric disorders. These authors point out that this approach may seem somewhat old-fashioned compared to approaches such as high throughput screening and utilization of molecular biological techniques to develop targets based on gene expression and identification methods; however, they correctly state that preclinical models are *required* (emphasis added) to provide initial assessment of the functional effects of novel compounds in the integrated organism. We are not yet to the point where new chemical entities go directly into patients or even normal volunteers without some evidence that clinically relevant effects might be present. We

can expect major advances in the development of preclinical models as our knowledge of disease processes and our ability to alter the genome in laboratory animals increase. Knock-out and knockin mouse models will increasingly guide drug discovery and testing. The importance of research designed to identify new drug targets based on the Human Genome Project and the ensuing effort to characterize the genes involved in neuropsychiatric disorders and the action of drugs used to treat neuropsychiatric illness is discussed in various chapters throughout this volume rather than in a single chapter in this section.

The use of biomarkers (i.e., natural history markers), biological activity marker, and surrogate markers is thoroughly explored by Wong and colleagues, who note that the importance of biomarkers as a means to reduce the cost of drug development, improve the ability to predict outcome, and expedite the identification of desired endpoints (e.g., no more than 80% occupancy of striatal D₂ receptors in order to minimize the development of extrapyramidal side effects), is increasing all the time. The extraordinary development of a variety of brain imaging methods, including magnetic resonance imaging, functional magnetic resonance imaging, single photon emission computed tomography, and positron emission tomography, appears to be particularly suited for this purpose. Given the cost associated with a failed clinical trial, someday it may be possible to bring brain imaging into routine clinical practice to guide drug dosage and choice. However, more classical methods such as neuroendocrine testing or examining the effect of treatments on peripheral processes such as changes in saliva, serum, and blood cells still can be valuable at various stages of drug development.

Clinical trials abound in psychiatry. Good clinical trials are much more rare. Problems in trial design, identification of appropriate patients, recruitment, retention, and ethical issues surrounding the use of placebos are very much with us and show signs of becoming more rather than less intractable in the near future. The cost of clinical trials in Western countries has grown enormously, leading to fewer and smaller trials that are often market-driven rather than designed to answer the most important research questions. Kane describes a number of efforts that have been made to improve clinical trial design and to cope with the increasing limitations that current ethical viewpoints have placed on this process. It is a sign of progress that broader outcome measures other than global psychopathology are increasingly the focus of clinical trials. For example, the recognition that cognition may be a more important endpoint than the reduction of positive or negative symptoms in the evaluation of a new drug for schizophrenia is an enormous advance because it refocuses the goal of new drug development and allows for distinguishing between new and existing drugs on a much more meaningful basis.

Pharmacokinetics, pharmacodynamics, and drug disposition in relation to new drug development and their subse-

quent utilization have never been better summarized than they are in the chapter by Greenblatt and colleagues. Advances in this area yield the information needed to use drugs wisely. This area of research has matured to the point where the fundamental principles are well understood and can be readily incorporated into the processes of drug development and utilization. Information about drug interactions that affect efficacy, elimination, and toxicity are ever more essential in the current area of polypharmacy.

Özdemir and colleagues discuss pharmacogenetics, the field that explores individual differences in drug responses that depend on genetic factors and genetic–environmental interactions. A key part of this refers to genetic variations in the liver enzymes that metabolize drugs. Greenblatt and colleagues consider this as well as the genetic factors that determine pharmacodynamics, and thus directly impact on efficacy and side effects. It is clear that this is critically important to psychopharmacology and will become even more so with the completion of the Human Genome Project. They also consider how genomic research will play an increasingly important role in drug discovery and development, including the design of safer and more efficient clinical trials. Their term “personalized therapeutics” is provocative. Have doctors not tried to do this since time immemorial? Genetic information will aid the process to be more science than art (rather than the reverse).

Is medicine in need of new ethical compasses in clinical research? This would seem to be the view of the authors of the United States-based National Bioethics Advisory Commission (NBAC) or the newest version of the Declaration of Helsinki. NBAC, in particular, has singled out research on the mentally ill for more stringent regulation and unique standards. The chapter on ethical aspects of neuropsychiatric research by Pinals and Appelbaum thoughtfully analyzes these recommendations as well as the fundamental principles that should guide policy in this area. Professional societies such as the ACNP have developed guidelines for investigators in an effort to show that there is an awareness of the obligation to protect subjects who agree to research to the greatest possible extent with minimal diminution of the information to be gained from the study. A “safe” study from which we can learn little or nothing of use because of design flaws may be less ethical than others where the absolute risk may be greater, but still within acceptable limits, whereas the potential gain in knowledge is far higher. Institutional review boards (IRB) are becoming increasingly restrictive around clinical research with the mentally ill, based in part on a poor understanding of the intactness of their decisional capacities. It is imperative that methods to assure competence to give consent that meets the legitimate concerns of IRBs are employed in all trials.

Paul Leber, formerly head of the Division of Psychopharmacology of the United States Food and Drug Administration (FDA), explicates the policies of his former employer with the oratorical flourish he is renowned for now transmuted into the written word with equal elegance. This chap-

ter explains what was (and probably still is) guiding the policies of the regulators of the FDA, which has worldwide influence directly and indirectly. This chapter can serve as a primer on getting a new drug application approved by that agency.

Mahmoud and colleagues succinctly and clearly describe the process of evaluating treatment outcomes utilizing the Economic, Clinical, Humanistic outcomes (ECHO) model. These three perspectives on outcome are intimately intertwined. Trouble arises when any one of the aspects is over-emphasized to the neglect of the others. There has been increasing awareness of the need for societal consensus on the importance of outcomes as the cost of achieving the

best outcomes now possible has risen greatly as a percentage of gross national product in both developing and developed countries. Advances in medical research will surely suffer if there is insufficient attention to demonstrating that new therapies are more cost-effective, not just more effective, than previous methods. The critical issue of distinguishing between efficacy and effectiveness research and the need for both are thoroughly discussed.

In conclusion, this section on new drug development and clinical research issues should be of great importance to any reader who is interested in the broader picture of alleviating neuropsychiatric disease burden through psychopharmacology.

