

Critical Pathways to Success in CNS Drug Development

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Contents

Acknowledgments, vi

Foreword, vii

- 1** The impending crisis in CNS drug development, 1
 - 2** Animal models and procedures for CNS disorders, 14
 - 3** Preclinical antecedents to early human clinical trials, 70
 - 4** Biomarkers and surrogate markers in drug development, 101
 - 5** Neuroimaging and cognitive assessments in early drug development, 167
 - 6** Bridging and CSF studies, 187
 - 7** A case study from preclinical to early clinical trials, 230
- Index, 254

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Foreword

The process of drug development has never been as complex and costly as it has become in the twenty-first century. Encouraged by sensationalistic and inaccurate reporting in the lay press, many citizens are convinced of the unrealistic fantasy that prescription pharmaceutical products should be risk-free. When effective medications cause adverse reactions—as they inevitably do—the response from the public and from politicians is outrage, with accusations of greed and malfeasance on the part of the pharmaceutical manufacturers and incompetence on the part of regulatory agencies. The outcome has been a development process driven by avoidance of liability and blame, with an increasing maze of paperwork and regulation that work against true innovation.

For developers of new drugs in the area of neuropsychopharmacology, the already difficult process is further complicated by features intrinsic to the discipline. Mood, affect, thought, behavior, and cognition are not easily measured. Outcome instruments are “soft,” and responses potentially modulated by research setting, experience, expectations, and practice. Experimental animal models and surrogate markers of disease and treatment are less well developed than in other disciplines. Placebo response rates in trials of neuropsychiatric agents are uncomfortably high, leading to many “failed” studies in which even an established active comparator does not separate from placebo.

I have known Dr. Neal Cutler and his work for more than three decades. His career represents a remarkable blend of academic achievement and entrepreneurial success. A physician and board-certified psychiatrist, Dr. Cutler spent his early professional career as an academic psychiatrist, both at the University of California and at the National Institutes of Health. In 1987 he started a successful clinical trial site, and subsequently a contract research organization (CRO) in Beverly Hills, specializing in clinical trials of marketed and candidate drugs in psychiatry and neurology. His work in the CRO industry has brought him to his present position as President and Chief Executive Officer of Worldwide Clinical Trials in Beverly Hills.

The accomplishments of Dr. Cutler and his associates demonstrate that a financially successful CRO can not only serve the drug development objectives of the pharmaceutical industry, but also advance basic and clinical knowledge in neuropsychopharmacology. Over the years their work has resulted in hundreds of publications in the peer-reviewed medical and scientific literature. The vast experience of the group ranges from strategic scientific and conceptual aspects of drug development in psychopharmacology to practical issues

of protocol design and execution, avoidance of typical problems and pitfalls, and compliance with regulatory requirements.

This book collates and summarizes the experiences of Dr. Cutler and his professional colleagues. It is not an anthology of chapters from different authors at different institutions—each chapter is written by Dr. Cutler and his collaborating scientists at Worldwide Clinical Trials, Inc. It is *their* experience, expertise, and achievement that are represented on the printed page. For those determined enough to face the hazardous landscape of drug development in neuropsychopharmacology, this book will help.

David J. Greenblatt, MD
Boston, MA

The impending crisis in CNS drug development

Introduction

A plethora of information has been gathered across the fields of neuroimaging, genetics/genomics, proteomics, neurobiology, and epidemiology that have greatly enhanced our basic knowledge of the pathophysiological and genetic underpinnings of many common central nervous system (CNS) disorders such as schizophrenia, Alzheimer's disease (AD), Parkinson's disease, depression, and anxiety disorders. In fact, most of what is currently known about these CNS disorders has been discovered in the past decade. However, these breakthroughs in the CNS basic sciences have too often failed to translate into more effective, more affordable, and safer pharmaceutical products for patients suffering from these disorders. Much of the information resulting from these innovations has had little clinical relevance, and despite the newly acquired knowledge gained throughout the past few years, CNS drug development has been characterized by relative stagnation. In fact, the number of approvals for CNS drugs over the past several years has actually declined!

Given the current economic climate in the US and around the world, this situation appears to be only getting worse—there are reduced resources available for drug development and reduced capital to fund this development. In addition, the drug development pathway is typically cumbersome and expensive, requiring fresh ideas and streamlined procedures to make development programs run faster and cheaper, as well as updated regulations from the Food and Drug Administration (FDA) to simplify the drug approval process. Many of these innovations already exist, and are beginning to be integrated into the drug development pipeline. Others are being validated and may soon become vital components of this pathway. The pharmaceutical and biotechnology industries are on the cusp of a major revolution in technology, procedures, and regulations regarding drug development—not because they wish to improve upon an already successful system, but because they need to replace a flawed and broken system if they wish to be relevant in coming decades, and create new, effective treatments for the patients who need them the most.

It is with this idea in mind that we have decided to write this book. We have compiled the latest advances in early CNS drug development from a vast body of literature, from clinical studies, and from our own experience. We have explained these advances in sequential, clearly organized chapters, beginning with preclinical models and going through first-in-man clinical trials. We have provided concise, relevant summaries and reviews of the newest techniques, markers, and models being used and introduced into the CNS drug development pipeline, and determined how they can be best utilized and what further validation is required. We have also reviewed the latest FDA regulations and guidelines, and discussed how each of these affects the drug development industry for better or for worse.

However, before we discuss the many innovations and regulations designed to address the problems the drug development industry faces, we wish to briefly explain the problems themselves; this way you will have a better understanding of what requires fixing, why it needs to be fixed, and just how serious the problems really are.

Stagnation in CNS drug development

The current stagnation in CNS drug development is evidenced by the lack of novel treatments across a number of neurologic and psychiatric disorders, with two of the most representative indications from the therapeutic area of CNS (AD and schizophrenia) serving as compelling illustrations of this stagnation. For example, the lack of approvable therapies that would hope to modify disease progression of AD has been truly frustrating—not only for physicians and family members who are caregivers for patients with AD, but also for society as a whole, given the looming financial and healthcare crisis associated with the ever-increasing prevalence of the disease. To date, all the drugs approved to treat AD, including the *N*-methyl-*D*-aspartic acid (NMDA) antagonist Namenda[®] (memantine), as well as all of the cholinesterase inhibitors, including Razadyne[®] (galantamine/previously known as Reminyl[®]), Exelon[®] (rivastigmine), and Aricept[®] (donepezil), are prescribed for the treatment of the symptoms of AD and carry the label that there is “no evidence that any of these drugs alter the course of the underlying dementing process.”

As an example, despite an explosion of publications advancing our understanding of the diagnostics, pathophysiology, genetics, and imaging associated with AD, there have not been any drugs that have successfully been shown to act as “disease modifiers.” This is certainly not for a lack of effort: In early 2007, there were approximately 12 drugs in US phase III clinical trials for AD, all of which showed great promise to slow or stop the progression of the disease based on their mechanisms of action. Additionally, the European Medicines Agency (EMA) reported consulting on at least 15 different AD drugs, with 79% of their advice stemming from queries surrounding disease modification (20% were on symptomatic treatment and

1% were on diagnostics) [1]. Despite some early signals to the contrary, there are no development programs to date (including Neurochem's Alzhemed[®], Myriad Genetics' Flurizan[™], and Wyeth/Elan's bapineuzumab) that have unequivocally shown positive trial results, although some interesting trends were noted that will be discussed below.

The lack of disease modifiers is especially dire when considering that the Alzheimer's Association report from March of 2007 concluded that there were over 5 million people in the United States living with AD [2]. This number includes 4.9 million people over the age of 65 and between 200,000 and 500,000 people under the age of 65 with early-onset AD and other dementias. Equally alarming are the projections for the future. The prevalence of AD is predicted to increase 27% by 2020, an astonishing 70% by 2030, and nearly 300%, to approximately 13.2 million people, by 2050—unless a way can be found to slow the progression of the disease or prevent it [3]. Remarkably, it has been suggested that even a “5-year delay in onset could reduce the prevalence of AD by almost 50%” [4], underscoring the need for a drug that will delay the onset or progression of dementia. The prevalence projections for AD are in stark contrast to other indications such as heart disease and cancer, which are projected to remain stable or actually decline over time. From 2000 to 2005, death rates have declined for most major diseases—including heart disease, breast cancer, and prostate cancer—while deaths from AD continue to trend upward, and are expected to increase 44% by 2025 [5].

Another regrettable example of stagnation in the field of CNS therapies comes from psychiatry, and is evidenced by the lack of novel antipsychotic drugs to treat schizophrenia and other psychotic disorders. The three-phase Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, one of the longest drug trials ever conducted in psychiatry, began in 2000 and data were analyzed beginning in 2005. In that time period, only two new antipsychotic drugs (ziprasidone [marketed as Geodon[®] and Zeldox[®]] in 2001 and Abilify[®] in 2002) were approved. Since then, only one other drug has been approved for the treatment of schizophrenia—Janssen's Invega[™] (paliperidone), which was approved in 2006. Invega is an oral extended-release (ER) major active metabolite of risperidone and would not be considered to be a novel molecular entity or new molecular entity (NME).

In the first phase of the CATIE study, 1493 patients with schizophrenia were recruited at 57 US sites and were randomly assigned to receive the antipsychotics olanzapine (7.5–30 mg/day), perphenazine (8–32 mg/day), quetiapine (200–800 mg/day), or risperidone (1.5–6.0 mg/day) for up to 18 months. Ziprasidone (40–160 mg/day) was added in 2002 following its approval by the FDA. The study concluded that the majority of patients in each treatment group discontinued due to inefficacy or intolerable side effects or for other reasons. Patients on olanzapine had the best record for continuing treatment, but this treatment was associated with greater weight gain and increases in measures of glucose and lipid metabolism. Overall, 74% of patients

discontinued the study medication before 18 months. Surprisingly, the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of the atypical antipsychotics quetiapine, risperidone, and ziprasidone, suggesting no difference between first- and second-generation antipsychotics [6].

In the second phase of the CATIE study, 543 participants were selected who did not benefit from the first phase of the study. Patients were divided into two groups. In one group, patients were randomly assigned to get one of four medications: clozapine, olanzapine, quetiapine, or risperidone. In the other group, clozapine was not included, and ziprasidone, the newest of the atypical medications available in the early stages of CATIE, was compared with the other three (olanzapine, quetiapine, or risperidone). Clozapine, one of the earliest atypical antipsychotics, was found to be remarkably effective and substantially better than all the other, newer atypical medications in the study [7]. Unfortunately, clozapine is associated with serious side effects, including life-threatening blood and heart complications, requiring careful monitoring of the patients taking this medication. It is often underprescribed because of this reason [8].

In the third phase of the CATIE study, 270 patients who had discontinued antipsychotic treatment in both first and second phases were enrolled. Patients and their doctors selected one of nine antipsychotic regimens (aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, the long-acting injectable fluphenazine decanoate, or a combination of any two of these treatments). Symptoms showed modest improvement for most patients [9]. Clozapine was underprescribed due to safety issues, although it had been recommended as the only treatment consistently shown to be effective when others were not [10].

Predictions of better efficacy and safety of second-generation antipsychotics over conventional antipsychotics were not realized in the CATIE study, leaving CNS drug developers wondering what the second-generation antipsychotics actually added to treatment options. Importantly, during the 8 years since the start of the CATIE initiative, there has been a lack of novel “third-generation” antipsychotic treatment for psychotic disorders.

True third-generation antipsychotic medications would essentially be a new class of antipsychotic medications that differs substantially from older agents in terms of clinical effectiveness, reduced side effects, basic mechanisms, or some combination of these factors [11]. Based on these criteria, none of the approved antipsychotic medications would be considered third generation. Eli Lilly and Company has a promising third-generation antipsychotic with its compound LY2140023, but this agent is only in phase 2 of development and is far from approval.

Thus, despite innumerable advances in basic research improving our understanding of the pathophysiology of schizophrenia, practicing psychiatrists anxiously await the arrival of a true third-generation antipsychotic compound that has novel therapeutic mechanisms of action.

Drug development stagnation: an industry-wide problem

Regrettably, the stagnation in drug development is not restricted to the development of drugs for schizophrenia or AD or even limited to CNS drug development, but rather appears to be the prevailing trend across a number of therapeutic areas. In fact, despite the great increase in broad scientific/medical developments, the number of new drug and biologic applications submitted to FDA has declined significantly over the past decade. The FDA approved 17 new molecular entities (NMEs) and 2 biologic license applications (BLAs) in 2007—the lowest number recorded since 1983, a year that had 14 approvals [12]. Of these 17 NMEs approved in 2007, only 2 were in CNS indications—New Rivers' Vyvanse™ (lisdexamfetamine) for attention-deficit/hyperactivity disorder and Schwarz BioSciences' dopamine receptor agonist rotigotine (Neupro®) for early stage idiopathic Parkinson's disease. Of the 18 NMEs approved by the FDA in 2006 (the same number as in 2005), only 3 could be considered to fall under the CNS therapeutic realm: Pfizer's Chantix® (varenicline) for smoking cessation, Teva's Azilect® (rasagiline) for Parkinson's disease, and Janssen's Invega® (paliperidone) for schizophrenia. Of note, there was only one psychiatric drug approved in 2004—Lilly's Cymbalta® (duloxetine HCL), and no psychiatric drugs at all approved in 2003 or 2005. 2008 has fared better with two psychiatric drug approvals, but there is still a dearth of NMEs. Approvals included Biovail's Aplenzin™ (bupropion hydrobromide) for the treatment of major depressive disorder and Banner Pharmacaps' Stavzor™ (valproic acid delayed release) for the treatment of bipolar manic disorder, seizures, and migraine headaches. There have been an additional five neurologic drug approvals (not just NMEs), including Prestwick Pharma's Xenazine® (tetrabenazine) for the treatment of chorea due to Huntington's disease; Eisai's Banzel (rufinamide) for the treatment of seizures associated with Lennox-Gastaut syndrome in pediatrics and adults; Lusedra® (fospropofol disodium), a sedative-hypnotic agent indicated for monitored anesthesia care sedation; Sirion Therapeutics' Durezol® (difluprednate) for the treatment of inflammation and pain associated with ocular surgery; and Schwarz Pharma's Vimpat® (lacosamide) for the treatment of partial-onset seizures in adults with epilepsy.

An inspection across multiple years in other indications does not make the picture any brighter. The FDA approved more than 30 NMEs in only 1 year in the present decade. This is in stark contrast to the second half of the 1990s, in which the FDA approved more than 30 NMEs every year [13]. Stated another way, over the past 3 years, the FDA has approved a total of 53 NMEs—the same number approved in 1996 alone. The EMEA is also approving fewer products than the FDA, even though processing speed and volume have been significantly improved. Both the FDA and EMEA are asking for more data in drug applications that pose heightened safety concerns, although there have been no official changes in overall drug approval standards.

Additionally, there does not appear to be much distinction in success between the pharmaceutical and biotechnology sectors, despite the fact that products originating from the biotech industry account for approximately two-thirds of all new drug applications. Henry Grabowski from Duke University reported that biotech drugs are slightly more successful in early-phase clinical trials than those of traditional pharmaceutical companies, but are more likely to fail in the larger phase III trials [14]. This is an important distinction as the basic questions concerning efficacy are largely determined in phase IIa and IIb studies. On average, 24.2% of biotech drugs are scrapped after phase III trials versus 12.6% of traditional drugs. Thus, biotech drugs account for more than 90% of phase III failures. These facts support the long-held views of biotechnology companies being more skilled at innovation and pharmaceutical companies being more skilled in the drug development process, and suggest that an alliance of these two might result in higher drug approval rates. Unfortunately, these alliances have not historically produced such results [15].

The decline in drug approvals is in harsh disparity to the ever-burgeoning costs and timelines required in drug development. The costs of developing the types of new drugs that have been pursued by traditional large pharmaceutical firms have been estimated in a number of studies, but the most widely cited figures come from DiMasi and colleagues [16]. This group utilized published cost estimates along with information on success rates and trial durations from a publicly available data set. They proposed that the cost associated with a new drug entering human clinical trials for the first time between 1989 and 2002 was estimated at \$800 million, and for several years this figure has been widely used by the lay public and by politicians seeking to understand the cost of prescriptions. Estimates have generally supported this figure, citing costs that vary from around \$500 million to more than \$2000 million, depending on the type of therapy [17]. For example, it has been generally suggested that drugs for neurologic and psychiatric conditions tend to be the most expensive drugs to develop. In contrast, drugs targeted for infectious diseases and analgesia indications tend to be the least expensive to develop.

Specific difficulties with CNS drug development

Despite the advent and acceptance of biological psychiatry and the abundant awareness campaigns by patient advocacy groups, the National Institutes of Health (NIH) and other government agencies often still inaccurately view CNS drugs as somehow less important than other drugs. This is because these drugs are often viewed as treatments for people who are fundamentally healthy but are seeking to improve a lifestyle problem, such as sadness, anxiety, addiction, or phobias. While CNS drugs may make it through the approval process at the FDA as quickly as their counterparts in other divisions, they often start off in a worse position by being viewed as having a relatively higher risk and lower priority due to the indications that they treat.

Furthermore, CNS drug developers are simply not utilizing the regulatory tools available to them, such as Priority Review or Fast Track designation, to have these drugs designated differently from the start.

There are many CNS conditions (i.e., suicide) that would be considered to be serious or life threatening. In addition, given the historically poor treatment response to psychiatric drugs, the growing number of treatment refractory patients, and the degree of intolerable side effects, many CNS development programs would be considered to address an unmet medical need. In fact, the FDA Guidance for Industry on Fast Track Drug Development Programs—Designation, Development, and Application Review cites several CNS examples of whether the drug development plan addresses an unmet medical need:

Effect(s) on serious outcomes of the condition not known to be affected by the alternatives (e.g., progressive disability in multiple sclerosis when the alternative treatments have shown an effect on exacerbations but have not shown an effect on progressive disability).

Ability to provide benefit(s) in patients who are unable to tolerate or are unresponsive to alternative agents (e.g., an antipsychotic agent that is effective in people failing standard therapy), or an ability to be used effectively in combination with other critical agents that cannot be combined with available therapy. [18]

Products that receive Priority Review or Fast Track designation are not necessarily more likely to be approved by the FDA than products that do not receive any such designation. However, the Fast Track designation enables early interaction with the FDA that can help clarify elements of clinical study design and data presentation, whose deficiency upon New Drug Application (NDA) submission could delay approval decisions. Although the FDA makes similar interactions available to any sponsor who seeks their consultation throughout the stages of drug development, these meetings are not always guaranteed. A unique option within the Fast Track designation is the opportunity to submit sections of an NDA to the FDA when they become ready, rather than the standard requirement to submit a complete application at one time. Thus, many CNS development programs miss out on some very important advantages associated with special designations.

The disparity in trial sample size is yet another manifestation of stigma or bias against CNS drug development. Charles B. Nemeroff, MD, PhD, noted large differences in number of patients in cardiovascular trials versus psychiatry trials [19]. Cardiovascular trials are strikingly larger than psychiatry trials. It would not be unusual to have 10,000 patients in a single cardiovascular study, while most psychiatry studies have less than one-tenth of that number (300–500 patients). Even the relatively large psychiatry trials sponsored by the NIH, such as the CATIE trial, have no more than a thousand patients, which results in a relative reduction of statistical power for CNS trials compared to

cardiovascular trials. Nemeroff suggests that this is an artifact of the pharmaceutical industry's reluctance to invest in psychiatry trials, and cites two main reasons for this. One reason is that psychiatry as a field is forced to deal with active "antipsychiatry" movements that do not believe in the benefit of psychiatric treatment. There appears to be no such movement for other disorders seen as purely "physical." He also noted that the pharmaceutical industry is reluctant to get involved in psychiatry trials because the difference between active drug and placebo is often more difficult to demonstrate statistically.

The general notion that drug-placebo differences are more difficult to discern in CNS trials is well acknowledged, and the conduct of CNS trials are often regarded as being as much art as science. It is certainly true that compound development in the CNS areas is more costly and often more difficult than compound development in other therapeutic areas, such as infectious disease. Some of the more salient reasons for this increased difficulty include:

1. The lack of correspondence between animal models and early patient studies in which very sophisticated and well-accepted animal models have failed to predict patient response to CNS therapeutics;
2. The difference seen in absorption, distribution, metabolism, and excretion (ADME) between normal healthy volunteers and patients, especially in AD, Parkinson's disease, and schizophrenia;
3. The uncoupling of pharmacokinetic and pharmacodynamic measures, often seen across a multitude of psychiatry trials;
4. The lack of accepted biomarkers and surrogates by regulatory authorities and the scientific community, even in areas such as cerebral structural and functional imaging;
5. The use of subjective investigator and patient-rated diagnostic scales and endpoints, leading to rater inflation and regression to the mean following randomization (this is seen across a variety of psychiatry trials, but is especially problematic in trials of depression and anxiety);
6. The related issue of heightened placebo response (which is endemic in studies of depression and anxiety and is becoming more commonplace and troublesome in studies of schizophrenia and AD);
7. The often mismatch between clinical meaning and statistical significance across a variety of indications, especially in studies of analgesia;
8. Very high attrition rates with upward of 60% attrition in substance abuse and AD and schizophrenia/bipolar trials, making trials cumbersome, biasing treatment effects, and reducing statistical power and generalizability;
9. Very high levels of comorbid substance abuse rates, especially in trials of psychotic patient populations such as schizophrenia and bipolar mania; and
10. The large number of failed trials (not just nonsignificant trials) in which an already approved active comparator failed to differentiate from placebo, thus requiring a larger number of trials in order to secure two adequate and well-controlled studies.

Although most companies entering into a CNS development program are aware of these issues, they tend to ignore them in favor of the potential

payoff of a CNS drug approval. In short, there is a great deal of money to be made by marketing to an ever-growing CNS customer base, especially in neurodegenerative disorders. The number of patients with CNS disorders far surpasses those with cardiovascular disorders, and given the population trend (in which those who are 85 years and older will quadruple by 2050), this difference and growth in CNS disorders that affect patients later in life (such as AD and Parkinson's disease) is only likely to expand.

No matter what the explanation for the lack of CNS studies (whether societal stigma, trial complexity, or difficulties in study conduct), most drug developers agree that there is room for expansion in the CNS marketplace. The potential size of the untreated CNS markets is so large that the future growth of the global neuropharmaceutical market could outpace the growth in the other sectors of the pharmaceutical industry. This fact alone makes CNS development attractive to the pharmaceutical and biotech sectors. In addition, the prospect of reducing patient suffering, prolonging life, and responding to important public health problems all demand greater efficiency in the clinical trial process, including a greater ability to secure approval for CNS drugs in a more timely and less costly manner.

A new outlook on CNS drug development

The industry and the FDA must rethink and improve upon the typically cumbersome and expensive path of drug development, and come up with creative solutions that expedite the process and reduce costs while still producing effective new therapies. We view the drug development process as a creative opportunity that must be approached by drug developers cognizant of the entire multivariate processes involved. This can be seen as somewhat analogous to the role of a contractor constructing a new skyscraper. The contractor may not have degrees in the chemistry and physics of the materials, nor in engineering and geology, but he or she must fully comprehend the application of all physical principles in constructing a solid foundation. Once the foundation and first few floors have been prepared and properly constructed, the rest of the floors can rise mechanically and repetitively. If there are any problems encountered with the structural integrity as the floors rise, it is difficult if not impossible to correct it.

Similarly, once the foundations of CNS development have been properly laid, and one understands early on the pharmacology of the compound and its potential for efficacy, the latter development stages can be executed with aplomb. The most elementary information about the compound, particularly the dose and regimen that will be used to maximal effect in the latter developmental stages, must be acquired in the early developmental stages. The CNS drug developer must fully understand the preclinical programs that have brought the compound to the point of human studies. He or she must be able to glean any important data that could impact the clinical development. For example, the animal toxicity data provide important indications about the

underlying pharmacology and toxicity of a compound, which may be encountered in man, either initially or as long-term, late-onset events, or differences in gender, etc. Thus, the clinical program should be responsive to the appearance of such signals in man. If medicinal chemistry has provided a number of potential candidates, such data, in combination with animal models, can help the developer choose the most appropriate compound to proceed in human development.

Ultimately, given the tremendous costs and resources associated with clinical trials, it is vital to determine in early human studies whether the potential drug candidate is worth continued development. In the CNS area, a thorough understanding of the available potential biomarkers, combined with novel designs and strategies for determining the safety and tolerance of the compound, as well as determining a useful dose range early on in the critical patient population, will enable the later stages to proceed on a solid foundation. For example, there may be biomarkers that can be employed to help confirm the mechanism of action, the best dose range, or even markers of unwanted side effects early in development.

The latter stages of CNS development have their own complexities too, which will only be compounded if the early stages have not yielded useful information. For example, later stages of CNS drug development involve testing the often subjective effects of a compound in relation to placebo, and one does not need to have the added complexity of determining the proper dose and regimen in these stages—this should already have been determined early on. Every creative effort must be employed in the initial human program to understand the critical factors upon which the rest of the program will be built.

The recent surge in development of biotechnology compounds has impacted the CNS area as well, adding layers of complexity to the drug development process due to interactions between these products and other biological processes. In addition, compounds produced from biotechnology often have unique patterns of administration, absorption and metabolism, and end organ effects. On the positive side, biotechnology compounds are often able to target specific underlying pathological processes, such as the pathways to formation of abnormal β -amyloid. This offers truly exciting potential for disease-modifying effects that cannot be duplicated by the more traditional small molecule therapies, which typically offer symptomatic improvement at best.

The early development process can be accelerated by getting the compound into the target population as soon as possible and understanding its pharmacology (including adverse event profile) and dose range as quickly as possible. Application of new technologies in these early studies, particularly cerebrospinal fluid sampling of pharmacokinetic and pharmacodynamic endpoints, can greatly enhance the information we glean about the compound at an early stage, and build a better foundation for future development. Most biomarkers will not provide definitive information that will direct subsequent

development, but nonetheless they can provide important clues and offer the opportunity for hypothesis generation that can be tested in other novel designs. In this book we will outline the known preclinical structures that are important to the early human studies, and elaborate on these early studies and the opportunities they yield in speeding the development process. In addition, in the last chapter of this book, we will provide a fictional case study of the drug development process, demonstrating how preclinical data of a novel compound can be used to construct early clinical studies. A solid foundation of these studies allows the first critical efficacy studies to provide a confident decision about the value of continuing the process. If the compound has failed at this point, there may be little point to expending further resources. If there is success, however, then the pathway for developing the program, including the time and commitment of hundreds of investigators and thousands of patients, will be justified.

In this book, we take as our starting point the availability of a viable compound that enters preclinical development. A compound arrives at this point by often differing routes. Some will be identified for specific targets (such as receptor binding or enzyme inhibition) or by the screening of large chemical libraries of compounds. In other cases, new compounds will be generated by combinatorial chemistry. Yet in other cases, medicinal chemists will synthesize compounds, generally in series, based on alterations to an existing molecule through structure–activity relationship studies, in order to improve or strengthen its activity for a given target, such as receptor fit or binding. A new neuroscience discovery of a promising biochemical pathway linked to a disease state can rapidly push discovery efforts to screen for compounds with the potential to affect that pathway. After such efforts at synthesis and screening of compounds, preclinical studies are then undertaken mainly in the areas of pharmacology and toxicology to further screen these chemical candidates for activity. A full receptor screen for putative CNS compounds will be undertaken to assess the binding potential at all the major receptors and ion channels. For example, inhibition of reuptake or binding on the major monoamines (dopamine, serotonin, and norepinephrine) can be assessed in animal and human cells, as well as in animal brain structures. Potential candidates that have the desired pharmacological profile for a given disorder will then typically enter testing in animal models for efficacy (discussed in Chapter 2). Promising candidates will then often enter toxicity screening at an early stage (discussed in Chapter 3). Initially, because of the high cost of animal toxicity testing, *in vitro* toxicology tests will be conducted on the promising candidates before live animal studies. Thus, the activities discussed in the next two chapters will often progress somewhat concurrently, as promising candidates need to be quickly identified in today's competitive environment and screened for safety prior to consideration for human trials. There are numerous potential CNS indications for promising compounds, but in this book the focus is on four of the major CNS indications which comprise the lion's share of CNS drug sales today—depression, anxiety, schizophrenia, and

Alzheimer's Disease—as a grounding, and appreciation of these indications is fundamental to drug development issues for other CNS indications.

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Animal models and procedures for CNS disorders

Introduction

There are a large number of animal models and behavioral procedures used to test the efficacy of novel compounds in treating central nervous system (CNS) disorders. These models work under the premise that there is consistency among the physiological and behavioral characteristics of various species; therefore, extrapolation from animals to humans is possible. Animal models are used to screen compounds before they are tested in humans, and can provide insight into the mechanism of action and also provide the rationale for clinical trials. In this chapter, we will be primarily concerned with animal models that are predictive of a compound's efficacy rather than safety or toxicity (these areas are discussed in Chapter 3).

While an ideal animal model would reproduce the neuropathology, etiology, and symptoms of the condition it is modeling, this is not feasible for many CNS disorders because the neurological basis of the disorder is unknown, and animal species differ markedly in their ability to express an equivalent human condition. For example, disorders involving thought dysfunction, including anxiety, schizophrenia, and depression, are not possible to fully mimic in animals. Therefore, most animal models are only capable of reproducing certain aspects of the neurological condition they are attempting to model. Because it is not always possible to evaluate an animal model based on its faithful replication of a human CNS disorder, many models are evaluated based on their sensitivity to existing drugs which treat that disorder; i.e., using the known clinical utility of an agent in current use to infer clinical utility of a new chemical biological entity. A major drawback to this approach is that established animal models tend to work for compounds that are similar to preexisting drugs, but not for distinct and novel compounds [1, 2].

Validating an animal model provides an estimate of how relevant it is to the clinical condition it is modeling. The more limited a model is at representing the underlying complexity of a clinical condition, the more limited the range of compounds it can identify which treat that condition. A model that better approximates the neuropathology of a clinical condition will be able to identify more therapeutic compounds with a greater diversity of structure

Table 2.1 Types of validity

Predictive validity	How well the results of an action (i.e., administration of a drug) on a model predict the results of the same action on the disorder
Face validity	How well a model recreates the phenomenology of a condition
Construct validity	How well a model recreates the underlying pathology of a condition
Convergent validity	How well a model's results correlate with those from other models of the same condition
Discriminant validity	How well a model measures components of a condition that are unique from other models of the same condition

and mechanism of action because it provides more pathways and targets for treatment. It modulates processes that are more “upstream” from the clinical expression of the illness. There are many different criteria used to evaluate animal models, including predictive, face, construct, convergent, and discriminant validity, as well as general reliability (see Table 2.1 for a list of validity terms). As these concepts are commonly cited within the literature, each is separately reviewed.

A model has good *predictive validity* if the results in the model predict the results in the clinical disorder [3]. For example, a drug which is known to alleviate the symptoms of a particular disorder in humans should also have a similar effect in the model of that disorder. In addition, there should be a low incidence of false negatives (drugs that do not work in the model but do work in humans) and false positives (drugs that work in the model but not in humans), as well as a similar potency of any observed effect. For certain classes of drugs, interspecies differences in drug metabolism, pharmacokinetics, and pharmacodynamics make predictive validity difficult.

Face validity refers to how well an animal model appears to recreate the phenomenology of a clinical condition. It evaluates a model based on the expression of observable characteristics or symptoms that are similar to the human disorder it is modeling. Because of the superficial similarities it measures, and the frequent lack of correlation to underlying etiology, many consider face validity to be of limited use in determining the ability of an isolated animal model to mirror the clinical condition [4, 5].

Construct validity of a test is commonly defined as the accuracy with which an animal model recreates the disorder it is intended to model, typically in terms of the underlying neuropathology [6]. A model that accurately reproduces the neural origins of a human condition or disease has good construct validity. This is a fundamental principle of any sound animal model, but it is very difficult to determine because the pathology behind many CNS disorders is still not well understood, and biological systems as well as their interrelatedness can differ appreciably by species.

Convergent and *discriminant validity* base their analysis of a model on comparisons with other tests of the same disorder. Convergent validity refers to how well a model's results correlate with the results from other tests of the

same disorder. Discriminant validity refers to the uniqueness of a model; how well a model measures components of a disorder that are unique from those measured in other tests of the same disorder. Both forms of validity are necessary in order to have an accurate model of a disorder which does not measure the exact same parameters as a preexisting model [7].

The *reliability* of a model refers to the consistency and stability with which the measurements of interest are observed. Results should be consistent with each test animal used, across trials with the same animal, under similar testing conditions, and after similar manipulations [8].

The selection algorithm

Every animal model has inherent strengths and weaknesses. Multiple animal models are needed for each neurological or psychiatric disorder to allow investigation into the different components of the condition and to provide a more complete assessment of the pharmacological profile of a compound designated to treat that disorder. These models complement each other without significant overlapping to provide the fullest representation of the underlying disorder. In addition, new models that address unique components of the disorders, expand on more rudimentary screens, or amplify insights regarding a particular mechanism of action may be developed.

Determining the best set of models to be used for testing a novel CNS therapeutic compound can be a daunting task and the process is colloquially assumed to be “sponsor’s risk.” Specifically, since the pathophysiological processes of many neuropsychiatric conditions remain fundamentally speculative, the credence and weight given to the results of any one paradigm fundamentally reflect the belief system of the organization sponsoring that study, and the state-of-the-art methodology in existence for that therapeutic target at the time of the paradigm initiation. The evolution of therapeutic agents for the treatment of Alzheimer’s disease, for example, provides a classic example of increasingly sophisticated preclinical models suggesting efficacy as the biological data regarding Alzheimer’s disease became more extensively defined. Even here, fundamental concepts regarding the genesis of episodic disease remain argumentative in the absence of a specific therapeutic agent that would abort disease progression. The following sections describe the most widely used animal models for four prominent CNS disorders, including their strengths, weaknesses, design characteristics, output measurements, and correlations to their associated human condition.

Animal models of anxiety

Many behavioral animal models of anxiety have been developed and used for the screening of compounds with anxiolytic activity. Numerous neurotransmitters and neuromodulators have been implicated in anxiety disorders, including the γ -aminobutyric acid (GABA)/benzodiazepine chlorine ionophore complex, serotonin and serotonin receptors (5-HT_{1A}, 5-HT₂, and 5-HT₃),

N-methyl-*D*-aspartate (NMDA), cholecystokinin, and others [9]. In animals, the distinctions between fear and anxiety are blurred, and behavioral tests assumed to be a proxy for fear are used to measure anxiety. Two categories of fear are measured; conditioned fear (i.e., fear that is learned by association with an aversive stimulus) and unconditioned fear (i.e., fear that is spontaneous and not learned). Anxiolytic compounds are evaluated for their ability to reduce fear-associated behaviors in animals compared to control groups in the absence of other adverse pharmacological effects, using models which have historically produced reliable estimates of drug efficacy in human clinical trials. Anxiety presents as an emotion in a spectrum of disorders, which includes generalized anxiety disorder, panic attacks, and obsessive-compulsive disorder (OCD). Tests that are sensitive to certain categories of anxiety may not be sensitive to others. This section summarizes some of the most widely used unconditioned and conditioned fear tests in animals. Anxiolytic compounds are listed that produce the most consistent and representative results. Test limitations with the major rodent strains will be discussed. See Table 2.2 for a review of the animal models and Table 2.3 for a review of the genetic models of anxiety covered in this section.

Open field and light/dark transition tests

Rodents typically have a desire to explore novel environments, yet avoid brightly lit, open spaces, which are believed to induce anxiety [10]. The *open field test* takes advantage of these two characteristics by placing a rodent in a brightly lit, open environment where it cannot return to its home cage. Each rat is left in a corner of the environment and its behavior is recorded for 3–15 minutes. Measurements include total distance traveled in the field, average speed, rearing/elongation behavior, and time spent in various parts of the environment. Increased anxiety is associated with a decrease in locomotor activity and rearing, more activity in the periphery versus the central part of the testing area (thigmotaxis), and defecation [11]. Anxiolytic compounds are evaluated based on their ability to reduce these behaviors. The paradigm has been shown to be generally sensitive to classical treatments for anxiety disorder, as mentioned above [12]. It does not appear to work for selective-serotonin reuptake inhibitors (SSRIs) that have a different spectrum of therapeutic efficacy in anxiety disorders such as panic attacks, generalized anxiety disorder, or OCD [13].

The *light/dark transition test* is similar to the open field test, and also capitalizes on an animal's fear of brightly lit spaces. The test apparatus consists of a dark compartment connected to an adjacent illuminated compartment. Measurements include the latency to leave the dark compartment, the time spent and distance walked in the light compartment, and the number of crossings between the two compartments. Anxiolytic compounds are evaluated based on their ability to increase the amount of time the animal spends in the light compartment. Classic anxiolytics (benzodiazepines) as well as the

Table 2.2 Animal models of anxiety

<i>Test type</i>	<i>Description of test</i>	<i>Major responsive drug classes</i>	<i>Limitations</i>
Open field test	Fear-associated behaviors due to bright, open environments can be ameliorated with anxiolytics	BZDs ¹ , 5-HT _{1A} agonists and 5-HT ₂ antagonists	Certain SSRIs unresponsive or even anxiogenic
Elevated maze tests	Avoidance of elevated, unenclosed maze arms reduced by anxiolytics	BZDs, 5-HT _{1A} agonists	Strain/species specific; BZD produces attenuation
Predator exposure tests	Escape/risk assessment behavior in response to a predator reduced by anxiolytics	BZDs, 5-HT _{1A} agonists, 5-HT ₂ antagonists	Reliance on olfactory cues may be confounding; SSRI results contradictory
Fear-potentiated startle (FPS) test	Startle reflex in response to a shock-associated tone reduced by anxiolytics	BZDs, 5-HT _{1A} agonists, SSRIs	Low predictive validity: responsive to some nonanxiolytics
Punishment/conflict test	A pleasurable behavior attenuated by punishment is increased with anxiolytics	BZDs, 5HT _{2A} agonists, SSRIs	5-HT _{1A} agonists, 5-HT ₃ antagonists less responsive
Passive avoidance test	Exploratory behavior attenuated by shock administration is increased by anxiolytics	5-HT agonists, 5-HT _{2A} antagonists, SSRIs	Limited response to BZDs; responsive to some nonanxiolytics
Social interaction test	Decreased social behavior under a stress-inducing environment is corrected by anxiolytics	BZDs (acute only), 5HT _{1A} agonists, and 5-HT ₂ antagonists	Limited response to chronic BZD administration; SSRIs can be anxiogenic

¹BZD, benzodiazepines.

newer anxiolytic-like compounds (e.g., serotonergic drugs or drugs acting on neuropeptide receptors) can be detected using this paradigm.

Elevated maze tests

The elevated plus maze balances an animal's fear of heights and open spaces with its natural tendency to explore novel environments [14, 15]. A mouse or a rat is put on an elevated, plus-shaped platform that has two enclosed arms and two open, unenclosed arms. The open arms are believed to trigger anxiety in rodents. This is supported by higher blood corticosterone levels (the equivalent of human cortisol levels), increased freezing of motion, and increased defecation in animals confined to this part of the maze [16]. Anxiolytic compounds are tested for their ability to increase the time the animal spends