CHAPTER 1

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 (EMEA) 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^{TM} (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^{TM} (bupropion hydrobromide) for the treatment of major depressive disorder and Banner Pharmacaps' Stavzor^{TM} (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 be-
tween 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 Uni-
versity 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 dis-
tinction 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 pro-
cess, 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 pharmaceu-
tical firms have been estimated in a number of studies, but the most widely
cited figures come from DiMasi and colleagues [16]. This group utilized pub-
lished cost estimates along with information on success rates and trial dura-
tions 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, depend-
ing 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 ex-
pensive 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 gleam 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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