Perspectives in Pharmacology

Challenges in the Search for Drugs to Treat Central Nervous System Disorders

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ABSTRACT

The history of drug discovery spans approximately 200,000 years. For much of this time, the identification of therapeutic agents was empirical, with the shift to a more hypothesis-driven approach occurring in the late 19th century. Since then, the objective has changed from identifying an active drug and its mechanism of action to determining therapeutic potential only after identifying drug-like compounds that interact with a target site. Although the emphasis on target identification, or “targetophilia,” has yielded novel drugs, overall it appears to have slowed the drug discovery process, especially for compounds used in treating central nervous system (CNS) disorders. This is because the “targetophilic” approach requires a good understanding of target physiology and its integration with the target organ, with a hierarchical integration from in vitro cellular and functional tissue studies to animal models that reasonably predict human responses. Because the majority of CNS drugs were discovered empirically, drug discovery in this area appears less amenable to target-based approaches than it seems for other types of therapeutics. Improving the success rate in CNS drug discovery requires a more pharmacometric-based approach, with a renewed emphasis on defining basic CNS function in intact animals and a more systematic in vivo screening of novel structures. Efforts must also be directed toward defining the sites of action of existing CNS drugs to aid in the design of second-generation agents with improved efficacy and safety.

Drug discovery extends back at least to the late Paleolithic period, approximately 200,000 years ago. As a distinct scientific discipline, modern drug discovery had its origins in the 19th century, with the birth of organic chemistry (Chast, 2008). It came of age in the mid-1800s, with the incorporation of the physiological studies of Claude Bernard and others, making the modern era approximately 160 years old (Sneader, 2005). War, economic upheaval, and epidemics, such as the need for morphine during the United States Civil War, the repositioning of the German dyestuffs industry, and acquired immunodeficiency syndrome, have historically been stimuli for the discovery and development of new drugs (Liebenau, 1990).

In the premodern period, Homo sapiens identified novel therapies from natural products using an empirical in vivo approach. Although the drug source was most probably consumed initially for sustenance, therapeutic efficacy or effects on the sensorium may have been noted. Highly toxic or lethal agents were subsequently avoided, with the exception of facile tools for capturing or killing wild game or enemies. If therapeutic efficacy was observed but accompanied by side effects, informal trial and error testing established the utility of the natural product(s), which would then be adopted into the Aryudevic, Kampo, traditional Chinese, or other folk medicine systems. The simple premodern approach focusing exclusively on efficacy and safety (Fig. 1) contrasts markedly with the complexity of the 21st century drug discovery process (Fig. 2) (Hopkins et al., 2007). The latter involves many diverse and focused, yet interrelated, activities that are integrated toward the common goal of identifying a new chemical entity (NCE) interacting at a selected target site. Drug
Evolution of Research Strategies

**Premodern Era**

**Efficacy/Safety**

**Modern Era**

- **Physiology Period**
  **Efficacy/Safety → Organ Systems Analysis**
- **Biochemical Period**
  **Efficacy/Safety ↔ Cellular Analysis ↔ Organ System**
- **Molecular Period**
  **Target Analysis → Cellular Analysis → Organ System → Efficacy/Safety**

Discovery has thus evolved from an empirically driven in vivo enterprise to one based on the testing of hypotheses generated by discoveries in chemistry and biology. Historically, an organ systems approach (physiology) was complimented by the addition of cellular analyses (biochemistry), which then led to the current molecular approach where the indispensable factors of efficacy and safety were assessed only after extensive in vitro testing (Figs. 1 and 2).

The complexity of the contemporary drug discovery process is thought to contribute to the inverse relationship between investments in drug research and development and successful new drug applications (Milne, 2003; U.S. Food & Drug Administration, 2004). For over a decade, it has been argued that drug discovery needs to return to a simpler, more science-driven approach (Weisbach and Moos, 1995; Cuatrecasas, 2006; Shaywitz and Taleb, 2008), with less focus on metrics (Ullman and Boubullier, 2008) and more emphasis on scientific substance (Maienschein et al., 2008). Another major issue with modern drug discovery is an unrealistic but expected time compression of the research and development process that is incompatible with the scientific method.

**Empirically Based Drug Discovery**

Double-blind, placebo-controlled clinical trials indicate that many of the purported therapeutics originating from natural products are of dubious or unproven value such as, for example, the use of St. John’s wort for the treatment of depression (Szegedi et al., 2005). Such data notwithstanding, there has been a renewed interest in recent years in the use of natural products as drug sources (Newman, 2008). This has resulted from the questionable success of the combinatorial chemistry/high-throughput screening approach that was the hallmark of drug discovery in the 1990s (Kaiser, 2008) and from the empirical discovery of two exquisitely potent analgesics: 1) the alkaloid epibatidine, a neuronal nicotinic receptor agonist, from frog skin (Dalay et al., 2000), and 2) the conotoxin peptide ziconitide, an N-type calcium channel blocker isolated from tropical cone snails (Wallace et al., 2008). Although superior to the opioids in terms of potency, efficacy, and lack of tolerance (Scholz and Woolf, 2002; Corbett et al., 2006), both epibatidine and ziconitide have limited therapeutic utility due to off-target activity and side effects. The interest in natural products as a source for new drugs is also driven by improved analytical techniques that permit the identification of active ingredients with minimal amounts (~1 mg) of test material. With the emergence in China and India of a more scientifically rigorous approach to drug discovery, it is anticipated that in the near future, many NCEs will be identified from studies of natural product therapies that have been in use for centuries.

The success of the empirical approach in CNS drug discovery is illustrated by the fact that the mechanisms of action of morphine, salicylates, and barbiturates were unknown when these drugs were introduced for human use. In addition, it is notable that the identification of the target site for these drugs has not generally resulted in improved second generation NCEs (Fitzgerald, 2004; Corbett et al., 2006).

**“Targephilia”: Target-Based Drug Discovery**

Modern drug discovery is almost exclusively focused on the identification of NCEs that interact with discrete molecular targets. This reductionist approach, or “targephilia”, is characterized by an obsession with and excessive focus on sites of drug action. It originated during the molecular biology revolution that had “one gene, one protein, one function” as its mantra. Although useful in developing NCEs, such as the HMG CoA reductase inhibitors (statins), the human immunodeficiency virus protease inhibitors, antibiotics, and the selective serotonin reuptake inhibitors, there is a growing feeling of unease that the reductionistic focus on a single, often unproven, molecular target has resulted in a “less equals less” outcome. In addition, as more is learned about the effectiveness of target-selective NCEs, it is apparent that CNS drugs in particular, such as clozapine (Roth et al., 2004) and dimebon (Doody et al., 2008), owe their clinical utility to actions at multiple molecular targets (Spedding et al., 2005).

Thus, it is unlikely that statin equivalents will be identified from studies of natural product therapies that have been in use for centuries. Likewise, in cancer chemotherapeutics, it has been recognized that drugs active at more than one target have a higher probability of being efficacious (Vogelstein, 2008).

For nearly 25 years, the pharmaceutical industry has dedicated its drug discovery resources to the “targephobic” approach, relying on iterations between chemical synthesis, molecular modeling, fragment-based molecular design, high-throughput screening, in vitro binding, and functional assays...
at selected targets to identify drug-like NCEs (Fig. 2). This has been coupled with an increased focus on the pharmacokinetic and pharmacodynamic properties of NCEs (Abdel-Rahman and Kauffman, 2004). However, with the growing awareness of the complex role of post-translational protein modification in cell function, and as many diseases have been found to have multiple gene associations and major epigenetic components (Jiang et al., 2004), there is now a realization that the “targephilic” approach does not take into full consideration the complexity of native, integrated systems (van der Greef and McBurney, 2005; Spedding et al., 2005).

The exclusionary nature of “targephilia” also minimizes the serendipity, passion, and intellectual rigor that are necessary components of a successful drug discovery program (Kubinyi, 2003; Black, 2005; Shaywitz and Taleb, 2008; Williams, 2008).

**CNS Drug Discovery**

Whereas morphine, salicylates, and caffeine are some of the more prominent premodern CNS drugs that have originated from natural products, many CNS agents developed in the 20th century were also discovered serendipitously (see Sneader, 2005; Klein, 2008). Reserpine, an active alkaloid derived from *Rauwolfia*, was used in India long before its introduction in 1953 to the West as an antihypertensive agent and antipsychotic drug. The use of lithium for treating bipolar disorder resulted from a search for the hormonal...
basis for depression, with this cation being accidentally discovered in urine samples from patients. Iproniazide was originally developed as an antitubercular agent but was subsequently found to display antidepressant activity in patients, and chlorpromazine was first used in 1950 to accelerate the recovery period from surgical anesthesia before it was found to alleviate some symptoms of schizophrenia. Carbamazepine, a tricyclic analog of chlorpromazine, was identified in the 1960s as an anticonvulsant, as was valproic acid, which was used originally as a solvent for testing insoluble drug candidates. The GABA analog, gabapentin, developed as a novel anticonvulsant, is now widely used for treating neuropathic pain. The sedative benzo diazepine chlordiazepoxide was found in 1958 to display unique tranquilizing activity in laboratory animals and selective anxiolytic properties in humans. Adrafinil, the prodrug of modafinil, was originally evaluated as an analgesic (Rambert et al., 2007) but was found to be an atypical psychostimulant. In all of these cases, utility was first noted by astute bench scientists or clinicians who observed potential or actual beneficial effects in laboratory animals or during clinical use for other purposes. Moreover, the mechanisms of action of these drugs were unknown at the time they were first used in humans. Indeed, the precise target site for many of them remains unknown or uncertain to this day, even after years of clinical use and commercial success.

Beyond Small Molecules: The Human Genome and Biologics

A revolution in CNS drug discovery was anticipated with the mapping of the human genome. It was believed these data would prove crucial for understanding disease pathophysiology and for identifying specific disease-associated targets, thereby simplifying the search for improved therapeutics (Williams et al., 2001). However, this early enthusiasm has been tempered by the discovery that neuropsychiatric conditions have dozens of discrete, causal, and susceptibility-related genetic associations. For schizophrenia, more than 30 gene associations are known (Marino et al., 2008, Altar et al., 2009), none of which has yet proven to be viable as a drug target. Interestingly, the dopamine D2 receptor, the primary target of currently used antipsychotic agents, was not among these associations (Marino et al., 2008). Approximately 70 gene associations appear to exist for Alzheimer’s disease, many of which, if replicated, require a reassessment of the amyloid hypothesis (Williams, 2009). Another confound is that some disease-associated genes overlap with one another. For instance, the catechol-O-methyltransferase V158M polymorphism found in some patients with schizophrenia is also associated with gender-related pain sensitivity, obsessive-compulsive disorder, myofacial pain syndrome, breast cancer, anorexia nervosa, anxiety, panic disorder, depression, and Alzheimer’s disease (Marino et al., 2008), limiting its attractiveness as a selective target for treating any of these disorders.

Whereas small molecules active at extracellular receptors represent more than 80% of drugs, there has been considerable interest in antibodies, vaccines, aptamers, small interfering RNA, and other biologics as potential agents for treating neurological and psychiatric conditions (Malik, 2008; De Souza et al., 2009). However, these approaches have yielded mixed results when tested clinically. The success of the Very Late Antigen-4 monoclonal antibody Tysabri (natalizumab) for the treatment of multiple sclerosis has been confounded by cases of progressive multifocal leukoencephalopathy. Likewise, the clinical development of AN1792 and bapineuzumab immunogens designed to remove brain amyloid deposits has been slowed by their possible association with aseptic meningoencephalitis and vasogenic edema, respectively, as well as by their minimal effects on disease progression (Williams, 2009).

Animal Models

Although the therapeutic potential of many CNS drugs was discovered with little or no understanding of their precise targets, clinically active compounds have historically been used to develop animal models for identifying newer agents. In addition to behavioral models, drug and putative-disease-related CNS function is studied using in situ electrophysiology and microdialysis techniques. However, the relevance of behavioral models to human disease is a subject of considerable debate (Horrobin, 2003; Spedding et al., 2005; Day et al., 2008; Markou et al., 2009). For instance, the rat catalepsy model, developed using classic antipsychotics, is more a measure of dopamine receptor blockade than that of schizophrenia. Likewise, the behavioral despair model of depression (Porsolt et al., 1977), while capable of identifying some potential antidepressants, must be modified to detect others (Markou et al., 2009). Likewise, although the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson’s disease has considerable predictive validity for the efficacy of compounds acting upon dopaminergic systems, it has not been useful in assessing novel mechanistic approaches for treating this condition (Waldmeier et al., 2006). Although models of acute and chronic pain (Le Bars et al., 2001; Honore and Jarvis, 2007) have been validated using opioids and nonsteroidal anti-inflammatory agents and seem to display face validity, experience suggests that potential analgesics acting at novel targets often fail in the clinic, even though they are active in these tests. Moreover, whereas NCEs for the treatment of neuropathic pain are typically examined in various rodent nerve ligation models (Honore and Jarvis, 2007), positive results in these assays do not consistently predict clinical efficacy as treatments for diabetic and cisplatin-induced neuropathies. This lack of concordance suggests a mismatch between the nature and extent of nerve damage in the animal ligation models and the human condition. Furthermore, the human condition reflects spontaneous pain resulting from a pathology that develops over years, whereas the majority of animal models involve evoked pain responses in subjects sensitized over days.

The use of transgenic animal models involving the ablation or overexpression of one or more genes was thought to provide a solution to the shortcomings of traditional animal models and for validating targets to accurately define drug mechanisms and disease pathophysiology. However, in many instances, target ablation has no apparent effect on phenotype because of penetrance (Arguello and Gogos, 2006) or homeostatic compensation during development. Animal models where human targets are transfected, such as the Tg2576 mouse amyloid model of Alzheimer’s disease, are useful but, as with the antipsychotic catalepsy model, mimic symptoms
of the disorder rather than the condition itself. Likewise, there is significant controversy regarding the predictive utility of transgenic mouse models of amyotrophic lateral sclerosis (Schnabel, 2008), with concerns regarding the rigor with which NCEs are tested, especially in regard to the blinding, powering, and randomization of such studies (Green, 2008). These examples reflect the “implausibility of a single causal molecular abnormality” in CNS diseases (Spedding et al., 2005).

It is now apparent that in most cases no single animal model can recapitulate the human condition for a variety of reasons. These include 1) dependence on face rather than predictive or construct validity, 2) disconnects in the temporal relationship of animal manipulation to the human disease state, and 3) particularly for CNS research, the fact that animals cannot verbally share their experiences, leaving the experimenter to subjectively surmise causality in a way that may confound the value of the observation (Arguello and Gogos, 2006). In general, human disease states are more subtle and spontaneous than those induced in animal models and have a far longer time to onset, with the exception of overt trauma. Whereas this cataloging of the limitations of the current animal models of CNS disease brings into question their utility in drug discovery, they remain essential for advancing NCEs to the clinic (Markou et al., 2009). At the very least, they are needed to demonstrate that an NCE has CNS activity and to provide an initial, although imprecise, way to select human doses. The use of several models rather than a single one is absolutely necessary to reduce the risk in assessing efficacy and for guiding dose, patient, and disease selection for clinical trials. In short, whereas animal models are an essential component of a drug discovery program, data from these studies must be interpreted with appropriate appreciation for the shortcomings of the system being utilized. This is especially true for most models of neurological and psychiatric disorders, complicating the quest for new CNS drugs. Because of this, greater efforts are being made to use data generated from compounds that advance to the clinic to improve the behavioral models employed for identifying such agents (Fig. 3). This approach is a major component of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; Geyer, 2008) initiative, which is focused on identifying animal models that correlate with human tests of attention, processing speed, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

**The Irwin Test and Pharmacometrics**

A seminal article by Irwin (1968) first described a consolidated neurobehavioral observation battery in rodents that has become part of the mandatory safety pharmacology package necessary for advancing all NCEs to clinical trials. As drug discovery became more target-oriented, the use of the Irwin test as an early screen for CNS activity dwindled. In
the 1970s and 1980s, the Irwin test was used routinely in drug discovery programs to evaluate newly synthesized compounds for potential CNS activity. At that time, gram quantities of NCEs were routinely synthesized and empirically tested in vivo by scientists with years of experience in animal experimentation. Astute observations by such individuals using these pharmacometric screens were used to prioritize and reasonably predict the potential therapeutic potential and possible side effects of the test agent. Although anathema to some “targephilias,” by exploiting the observational powers and expertise of experienced investigators, the pharmacometric approach increases the chances for a serendipitous discovery that could redirect the clinical development of an NCE. Indeed, pharmacometrics has consistently demonstrated its utility. For example, the initial interest in the pharmacological properties of dizocilpine (MK-801) was based on its activity in a substance P-induced reciprocal hind paw scratching test and its anticonvulsant properties in rodents, whereas its mechanism of action as a novel, selective N-methyl-D-aspartate receptor antagonist was not determined until years later (Wong et al., 1986).

The de-emphasis on pharmacometric testing led to a decline in the number of investigators capable of providing informed insights from behavioral observations. Advances in robotics, computer vision, and machine learning have led to the development of high-throughput, automated screens such as Psychogenics’ SmartCube (Tecott and Nestler, 2004) and Pattern Array (Kafkafi et al., 2008) to characterize mouse behavior. SmartCube can collect many thousands of behavioral measurements in seconds, generating detailed behavioral phenotypes in response to an NCE that can then be compared to databases of existing CNS drugs and drug class “fingerprints” to predict therapeutic utility or side effect liability. Although quick and efficient, it remains to be proven whether such automation can substitute fully for an experienced human observer.

Given the value of serendipity in CNS drug discovery, efforts should be made to more fully and formally integrate the “targephilic” and pharmacometric approaches in the search for centrally active agents. The “targephilic” component (Fig. 3) is designed to identify NCEs for screening on the basis of a computer modeling assessment of their molecular space occupancy and diversity or by “patent busting.” For the latter, proprietary NCEs active at the target are examined with the aim of developing novel intellectual property around them. Once a patentable pharmacophore is identified from the screening assay or from a series of known agents, a structure-activity relationship (SAR) is sought. Those with an identifiable SAR are advanced to an iterative lead optimization process to determine the agents with the best efficacy, selectivity, and drug-like properties (solubility, stability, and bioavailability) and the least potential for side effects. These lead candidates are then examined further for potential mutagenicity, effects on human ether-a-go-go-related gene channel function, on drug-metabolizing enzymes and drugability to identify investigational new drug candidates (Fig. 3). The pharmacometric approach (Fig. 3) involves the screening of compounds already known to interact at novel targets or that have unique structures for activity in vivo models (e.g., SmartCube). Compounds are typically tested acutely at a single dose. Active agents are then assessed in a molecular profiling assay (e.g., Cerep Screen; Cerep, Paris, France) involving receptors, enzymes, and channels, as well as in more traditional in vivo models, including behavioral tests, electrophysiological analysis, and microdialysis assays. If a molecular target can be identified for the empirically screened NCEs, an SAR would then be sought and the resultant compounds would be optimized chemically following the same procedures as described for the “targephilic” approach (Fig. 3). The same lead optimization approach would be taken for an NCE known to interact at a novel target with a CNS indication. Even if no molecular target is found, a behaviorally active compound would be optimized for pharmacokinetic properties and advanced to an investigational new drug based on empirical observations indicative of important CNS activity and safety, as was done for valproic acid, pregabalin, modafinil, and most recently, dimebon (Doody et al., 2008). If a compound is inactive in the pharmacometric screen, it is either discarded or tested chronically if there is particular interest in the chemical structure or target. Both acute and chronic studies require pharmacokinetic data to ensure that adequate plasma levels are achieved and that the agent enters the CNS. If active when administered this way, the test agent would re-enter the pharmacometric screening process for further in vivo analyses (Fig. 3).

Combining the “targephilic” and pharmacometric approaches increases the universe of compounds for testing and maximizes the likelihood of identifying agents with novel CNS profiles. This strategy takes full advantage of the ongoing advances in molecular targeting, while at the same time encouraging a serendipitous finding, which has been the driving force for CNS drug discovery for millennia.

Beyond “Targephilia”

The CNS is hierarchically complex and functionally interdependent with a variety of distinct, specialized cell types that are integrated into discrete pathways. Given the complexity of the brain and the multiplicity of diseases that affect brain function, it is remarkable that any CNS medication can be safely used. A highly dynamic organ, the brain shifts between normal and various disease-related states. This may explain why many CNS disorders have a weak genetic component and multiple gene associations and are significantly influenced by environmental factors. A similar complexity of disease causality has been described for cancer. In this case, the same type of tumor differs in genetic profile from patient to patient. Thus, glioblastomas have 60 genetic alterations (Parsons et al., 2008), and pancreatic tumors have 63 (Jones et al., 2008), suggesting that, as with schizophrenia, there is a need to focus on genes that cluster in pathways rather than concentrating on discrete molecular targets (Davies et al., 2006).

Success in CNS drug discovery, as measured by the number of NCEs advancing to and surviving in clinical trials has been challenging (Kola and Landis, 2004), with many hurdles for translating laboratory findings into clinically meaningful treatments (Johnson, 2007). Some needed advances for addressing these issues include real-time brain imaging technologies and predictive biomarkers to quantify drug target interactions to ensure that NCEs actually reach their target (Markou et al., 2009). Such techniques and methodologies...
can also be used for diagnosis and for the assessment of disease progression.

The evolving behavioral data mining approaches (Tecott and Nestler, 2004; Arguello and Gogos, 2006; Kafkafi et al., 2008) recapitulate, to a degree, the pharmacometric approach to CNS drug discovery. They make possible the characterization of NCEs in vivo in a matter of weeks rather than years, are cost- and time-effective, and require only small quantities of test agent. When coupled with more traditional behavioral assays (McArthur and Borsini, 2008), these approaches complement molecular screens (Roth et al., 2004), providing a broader database for selecting NCEs for advancement to the clinic. This design can also be useful in determining the mechanism of action of existing CNS drugs, thereby increasing the likelihood of developing derivatives with greater efficacy and fewer side effects. Indeed, established medications with as yet undefined mechanisms represent some of the best leads for novel CNS agents. Efforts should be increased to identify their sites of action to fully exploit these agents for the development of new drugs.

The Path Forward—Back to the Future?

The CNS drug market is currently valued at more than $50 billion worldwide and is growing ~15% on an annual basis, a number that is likely to increase further as the population ages and as new drugs are discovered that address currently unmet medical needs, such as Alzheimer’s Disease, stroke (O’Collins et al., 2006), and substance abuse (Volkow and Li, 2004). Despite its heuristic value, the “targephilic” approach to drug discovery has not been as efficient in identifying therapeutically useful NCEs as was originally envisioned, making it difficult to meet the demand for new medications. Although targeted screening is an important component of drug discovery, the search for new CNS agents will continue to rely primarily on data from in vivo studies, making it crucial for investments to be made in the characterization and development of improved animal models of CNS disease. The fact that this has not been a priority area in biomedical research in recent years has contributed significantly to the increased rate of NCE attrition and the decline in the discovery of truly novel agents for the treatment of CNS disorders (U.S. Food & Drug Administration, 2004).

In 2004, the U.S. Food & Drug Administration published a guide (U.S. Food & Drug Administration, 2004) that focused on the lack of productivity in drug research and development (www.fda.gov/cder/initiatives/criticalpath/whitepaper.html). This report highlighted the key needs in strengthening and rebuilding the disciplines of physiology, as well as basic and clinical pharmacology. Indeed, in recent years, pharmacology training has diminished as funding agencies underwrote the growth of newer areas. This has led to a decline in the number of pharmacologists and physiologists capable of making translational medicine a reality. To help address this issue, pressure from individual scientists, advocacy groups, and the pharmaceutical industry led to the establishment of National Institutes of Health-sponsored Integrative and Organ Systems Pharmacology courses (Preusch, 2004) and to the support of initiatives by the National Institute of Mental Health to enhance collaborations among industry, academia, and the federal government (Conn and Roth, 2008; Brady et al., 2009).

Conclusion

As with clinical medicine where new and expensive imaging technologies have not rendered the traditional history and physical exam as obsolete, the latest techniques in molecular biology and medicinal chemistry cannot substitute entirely for empirical testing in vivo in assessing the therapeutic potential of NCEs. This is especially true in the search for drugs used to treat CNS disorders. Although the modern empirical approach is more informed than that employed by prehistoric scientists, the objective remains the same: to identify as quickly as possible whether a particular chemical agent displays drug-like characteristics of clinical importance. Although knowledge of site(s) of action is critical for fully characterizing and exploiting a drug class, the primary aim of a drug discovery program must be the identification of new therapeutic agents, not the synthesis of high-affinity ligands for molecular targets of unknown clinical value. Although the pharmacometric approach contrasts markedly with the almost exclusive focus on the human genome as the guide to drug discovery (Wilgenbus et al., 2007), experience has proven that in vivo testing is the most reliable guide for assessing therapeutic potential. Moving animal model assays to an earlier stage in the CNS drug discovery process to compliment and enhance the “targephilic” approach can provide data enriched with an element of calculated serendipity (Fig. 3). It will also yield an earlier indication of a relationship, or lack thereof, between a molecular target and animal behavior, thereby accelerating the discovery of novel drugs for the treatment of psychiatric and neurological disorders.

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