Chapter 1

The discovery and development of drugs to treat psychiatric disorders: Historical perspective

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Drugs to treat psychiatric disorders have added immeasurably to societal well-being, providing many patients with the ability to function adequately and productively under serious and often life-threatening psychiatric disorders. The initial discovery of drugs for the treatment of depression and schizophrenia was made over 50 years ago and was based on clinical observations of drugs used for indications other than depression and schizophrenia (Klein 2008; Preskorn 2010*a*). The mechanisms of these drugs were unknown at the time their efficacy in these disorders was established; however, the subsequent identification of these mechanisms was then used to define the mechanistic causality of the disease state. A historical perspective of these developments serves to underline and highlight a number of important aspects that have had a significant impact on the emergence of drug treatments for psychiatric disorders and is intended to provide focus for the chapters that follow as part of a current translational context.

First, there was and continues to be limited understanding of the molecular causality of psychiatric disorders, which are usually polygenomic, multifactorial, and complex (Enna and Williams 2009). This situation continues to exist despite the availability of effective drugs and represents a significant challenge in moving pharmacological treatment forward into new therapeutics. Second, the presumed mechanism of action of these drugs and their efficacy in treating disorders like schizophrenia, depression, and anxiety not only served to define these conditions biochemically but also provided the basis for the development of a variety of animal models (Day *et al.* 2008; Markou *et al.* 2009; Millan 2008; Spedding *et al.* 2005; van der Greef and McBurney 2005). Despite the proliferation of such models, both wild-type and transgenic, marked disconnects remain between putative animal models of human diseases and the human disease state itself (Nestler and Hyman 2010). Finally, because of historical precedents, the clinical trial paradigm continues to operate in a very opportunistic clinical mode with the expectation that any preclinical data are far from an absolute in terms of predicting what may happen in the clinic.

Psychiatric disorders are frequently treated with drugs that have diverse and often complex mechanisms of action that engage multiple targets. Conversely, different psychiatric disorders are often treated with the same agent, tending to confuse the disease/disorder cause-and-effect paradigm in addition to posing questions regarding diagnostic sensitivity. The paucity of new and improved psychoactive drugs has led to a renewed focus on hierarchical brain networks, neuronal plasticity, and signaling processes (Akil *et al.* 2010) as well as to the renewed interrogation of the predictive value of animal models in defining both psychiatric disorder causality and current translational approaches to psychiatric drug discovery. As many pharmaceutical companies appear to be abandoning their efforts in neuropsychiatric disorders (Miller 2010a; Nierenberg 2010; Nutt and Goodwin 2011; Stovall 2011), there is a pressing need to develop more in-depth information on the pathophysiological mechanisms contributing to these disorders and to develop innovative and alternative strategies for drug discovery and development.

Historical background

Although the origins of mood-altering substances like alcohol, nicotine, mescaline, and cocaine stretch back to antiquity, the utility for the CNS of other compounds like chloral hydrate, barbital, phenytoin, and epinephrine was only established in the late

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nineteenth and early twentieth centuries (Preskorn 2010*a*, 2010*b*). The "golden" age of psychopharmacology (Barrett 2002; Klein 2008) dates back to the late 1940s with the use of lithium urate for the treatment of mania (Cade 1949). The latter is widely considered a serendipitous discovery that was based on the ability of lithium to reverse urea toxicity in guinea pigs, the latter being a toxic agent present in the urine of manic patients. Lithium was in fact in use as a psychoactive drug in the late nineteenth century. At that time, excess uric acid had been linked to depression and mania. Because lithium could dissolve uric acid crystals, it had been used to treat mania in the 1870s but was abandoned as a therapeutic agent by 1900 due to the discrediting of the uric acid diathesis theory (Mitchell and Hadzi-Pavlovic 2000). Thus Cade more properly "rediscovered" the utility of lithium. This event was followed in the 1950s by the discovery of chlorpromazine (Ban 2007) and reserpine (Barsa and Kline 1955) for the treatment of schizophrenia, the monoamine oxidase (MAO) inhibitor, iproniazid, for the treatment of depression (Crane 1956; Zeller *et al.* 1952), and the benzodiazepine (BZ), chlordiazepoxide, for the treatment of anxiety (Sternbach 1979). These discoveries had a major impact in defining the neuropharmacology of the CNS (Jacobsen 1986) and were further aided by the emergence of the discipline of neurochemistry, which focused on the study of enzymes and receptors in the brain (Feldberg 1963; Foley 2007; McIlwain 1958). These discoveries also heralded an effort to develop appropriate animal behavior models in which these compounds could be assayed and which could serve as the basis for the discovery of new drugs (McArthur and Borsini 2008). In short, the identification of drugs to treat major psychiatric disorders launched the fields of biological psychiatry, behavioral pharmacology, and neuropsychopharmacology and had a profound impact not only on individuals suffering from these disorders and on the care and hospitalization of patients but also on the emergence of entirely new disciplines.

Neurochemical studies in cell homogenates, in situ, and in brain slices (McIlwain 1963) coupled with electrophysiological approaches (Llinas 1988) provided a facile means to measure the functional effects of transmitters on cell and tissue function and on metabolism and receptor signaling in relatively intact brain systems and provided the necessary context for the development of receptor binding assays (Snyder 2008). These created a new, target-based interface between small-molecule-based medicinal chemistry strategies and biological testing to advance the process of drug discovery via the rapid development of structure–activity relationships (SARs) for new chemical entities (NCEs) directed toward putative disease targets.

Shortly after its validation, the technique of radioligand binding was used to identify the first *drug* receptor, that for the BZ, diazepam (Braestrup and Squires 1978; Mohler and Okada 1977), the endogenous ligand for which, despite many interesting candidates, has still to be confirmed. With the ability to measure receptor interactions at a binding site as distinct from a functional tissue or whole animal response, a rapid, iterative strategy then became possible where the potency and the SAR of compounds or new chemical entities (NCEs) could be determined in vitro using small quantities (~ 1–2 mg) of newly synthesized NCEs. This process contrasted with the need for the 0.5 to 1 g or greater quantities that had been necessary to study compound effects in intact tissues and animals. In time, this process went through various iterations that further transformed the CNS drug discovery process and eventually led to industrial-level, high-throughput screening assays (Macarron *et al.* 2011) and combinatorial/parallel synthesis chemistry that could screen millions of compounds in the space of a week. The result was the generation of more data within a month than previously had been generated in several decades. These advances also unfortunately tended to replace the intellectual component of the research endeavor with a more technically biased, metrics-driven approach (Kubinyi 2003; Williams 2011).

Second-generation psychoactive agents

The astute observations in the clinical setting that led to the first generation of psychoactive drugs also created the putative framework for the potential discovery of new generations of psychotropic agents. Thus, by identifying the mechanistic attributes of clinically efficacious agents, a better understanding of the molecular causality of the disease could, theoretically, also be achieved. Newly identified targets could then be interrogated using the new tools of receptor binding and functional neurochemistry to identify second-generation compounds for evaluation in animal models that, theoretically, would be more

selective in their actions and thus have improved efficacy, safety, and pharmacokinetic properties. A large number of second-generation compounds have been identified using this approach, some of which are now in clinical use. It is, however, the subject of considerable debate as to whether these NCEs represent clinical improvements over the agents initially discovered, especially in the case of the second-generation or atypical antipsychotics. The National Institute of Mental Health-sponsored CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) (McEvoy *et al.* 2006; Stroup *et al.* 2006) and National Health Service-sponsored CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) (Jones *et al.* 2006) clinical trials, part of a comparative effectiveness research initiative, have led to the highly controversial (Insel 2010; Lewis and Lieberman 2008; Meltzer and Bobo 2006) conclusion that there are few major differences in the clinical effectiveness and safety of first- and second-generation antipsychotics.

Antipsychotics

The search for newer antipsychotics has been ongoing for the better part of the past 60 years. It has resulted in many thousands of compounds that have iterations on the receptor-binding properties of the seminal antipsychotics, haloperidol and chlorpromazine. These efforts have been largely based on the dopamine (DA) hyperfunction hypothesis of schizophrenia (Carlsson and Lindqvist 1963) that was substantiated by the finding that the binding of antipsychotics to brain DA receptors correlated with clinical potency (Creese *et al.* 1976). The additional finding that the presence of 5-HT_{2A} antagonist activity improved the negative symptoms of the disease supported a role for 5-HT in the treatment of schizophrenia, as had been previously suggested by phenotypic similarities between LSD-induced hallucinations and schizophrenic psychosis (Meltzer 1999). This approach helped redefine the characteristics thought to be necessary in a second-generation antipsychotic agent (Kuroki *et al.* 2008; Marino *et al.* 2008) as did the discovery of the dibenzodiazepine antipsychotic, clozapine (Crilly 2007). The latter drug is generally considered the prototypic "second-generation" or atypical antispychotic agent (see Chapter 4, this volume). Identified as a D_2 receptor antagonist with broad-spectrum efficacy in schizophrenia, clozapine was found to be effective in patients with treatment-resistant refractory schizophrenia. It also had a reduced incidence of extrapyramidal symptom liability (Bagnall *et al.* 2003; Wahlbeck *et al.* 2000) and could be used for longer periods prior to patient discontinuation compared with other antipsychotics. The positive attributes of clozapine were, however, limited by a high incidence of potentially fatal agranulocytosis that led to the compound being withdrawn in 1975. Following a subsequent trial in patients with treatment-resistant schizophrenia where it was found to be superior to first-generation compounds, clozapine was reintroduced in 1990 with labeling for continuous monitoring for blood dyscrasias in patients with nonresponsive positive symptoms.

Given its demonstrated superior therapeutic profile, considerable efforts have been directed toward identifying "clozapine-like" NCEs that have the improved antipsychotic efficacy but lack the risk of agranulocytosis. The search for "the mechanism of action" of clozapine was driven by the possibility that this drug might interact with a target that would provide insights into the mechanisms underlying its superior efficacy and side-effect profile and, by default, also provide a better understanding of the mechanistic nuances of schizophrenia. However, with the discovery of each new CNS receptor, the receptor-binding profile of clozapine – its "molecular fingerprint" – was similarly expanded, serving to emphasize the polypharmic profile of this unique antipsychotic drug. Clozapine appears to possess a classical privileged pharmacophore (Evans *et al.* 1988), making it truly a "magic shotgun"-like compound (Roth *et al.* 2004) and thus extremely challenging to replicate in an SAR-focused medicinal chemistry effort (Marino *et al.* 2008). The discovery and approval of another second-generation, atypical antipsychotic, aripiprazole (Shapiro *et al.* 2003), a partial agonist at the DA D_2 receptor, also focused attention on partial agonism/antagonism as an approach to what has been termed "third-generation" DA-based antipsychotics (Mailman and Murthy 2010).

The findings that psychotomimetics like phencyclidine and ketamine, antagonists of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, could mimic the positive, negative, and cognitive symptoms of schizophrenia (Javitt and Zukin 1991) has led to an alternative mechanistic hypothesis for the etiology of schizophrenia, namely that of glutamate hypofunction (Coyle *et al.* 2003; Jentsch and

Roth 1999; Kantrowitz and Javitt 2010; Millan 2005). NMDA receptor antagonists have been shown to exacerbate symptoms in patients with schizophrenia (Lahti *et al.* 1995) and trigger the re-emergence of symptoms in stable patients (Javitt and Zukin 1991). NMDA receptor co-agonists, including glycine, D-serine, and D-cycloserine, while having some beneficial effects in the treatment of schizophrenia (Heresco-Levy *et al.* 2005), have failed to show robust activity in subsequent trials (Buchanan *et al.* 2007). Inhibitors of the glycine transporter type 1 (GlyT1), e.g., sarcosine (Lane *et al.* 2006) and RG1678, that increase endogenous glycine have shown efficacy as an add-on therapy to antipsychotic agents. However, sarcosine and more potent GlyT1 inhibitors, e.g., ALX-5407, can produce hypoactivity/motor impairment and respiratory distress (Perry *et al.* 2008), an apparent function of compound residence time (Kopec *et al.* 2010), which has led to questions regarding the validity of GlyT1 inhibition as an approach to reversing NMDA hypofunction in schizophrenia. Endogenous sarcosine production may, however, be amenable to modulation using PPARα agonists including clofibrate and gemfibrozil (McBurney 2009), suggesting another mechanism for the NMDA receptor co-agonist approach.

Treatment of schizophrenic patients with LY404039, a group 2/3 metabotropic glutamate receptor agonist prodrug, resulted in significant improvements in both the positive and negative symptoms of schizophrenia compared with placebo without causing prolactin elevation, extrapyramidal symptoms, or weight gain (Patil *et al.* 2007). However, these initial results await further confirmatory studies. Positive allosteric modulators of the mGluR2 receptor, e.g., LY487379 (Galici *et al.* 2005), and the mGluR5 receptor, e.g. VU0360172 (Rodriguez *et al.* 2010), represent additional approaches to potentiating the effects of glutamate.

Genome-wide association studies in populations of patients with schizophrenia have identified more than 30 disease-associated genes (Marino *et al.* 2008) that include neuregulin, reelin, *DTNBP*, *RGS4*, *DISC1*, *CMYA5*, and the alpha 7 *NNR*, the role(s) of which in disease causality has yet to be established in the context of the existing dopamine/glutamate hyper/hypofunction hypotheses. The most recent gene association for schizophrenia, *CMYA5* (cardiomyopathy associated 5 gene or *myospryn*), was identified in 20 independent samples involving more than 33 000 participants (Chen *et al.* 2011). *Myospryn* binds to dysbindin (Benson *et al.* 2004), the protein product of the *DTNBP1* (dystrobrevin binding protein 1) gene, a major schizophrenia susceptibility factor (Kendler 2004). Like other genome-wide association studies candidate genes, the function of *myospryn* in schizophrenia is unclear. Its reported association with left ventricular hypertrophy (Nakagami *et al.* 2007) questions a specific role in the etiology of schizophrenia.

Anxiolytics

Since the 1960s, many NCEs have been identified that interact with the BZ receptor. The majority were iterations on the basic BZ pharmacophore, itself a privileged pharmacophore (Evans *et al.* 1988). Other ligands were identified by screening chemical libraries using radioligand binding assays, e.g., β-carbolines. The characterization of such compounds has become increasingly nuanced with the cloning and identification of the component α, β, and γ subunits of this pentameric ligand gated-ion channel receptor (Olsen and Sieghart 2009). The discovery of partial agonists that act at various subunit-containing complexes has been an active research area focused on the possibility to differentially and selectively modulate the many different effects of benzodiazepines that include anxiolytic, sedative, anticonvulsant, and cognitive activities (Rudolph and Möhler 2006). Unfortunately, the translational path from an "atypical" BZ ligand with superior anxiolytic efficacy and reduced side effects in various animal models of anxiety to an efficacious new drug remains a major challenge and has, thus far, been elusive (D'Hulst *et al.* 2009; see Chapter 2). Unlike the antipsychotic field, the clinical shortcomings of anxiolytics, while inherently present, are less of an issue in driving research efforts in the area.

Antidepressants

Following the discovery of the MAO inhibitor, iproniazid, as an antidepressant (Crane 1956), newer antidepressants were also discovered, one of which was the tricyclic antidepressant (TCA) imipramine, a product of medicinal chemistry efforts at CIBA-Geigy to develop a successor to the antipsychotic, chlorpromazine (Maxwell and Eckhardt 1990; Pletscher 1991). Since TCAs enhance extrasynaptic levels of the monoamines, 5-HT and norepinephrine (NE), by blocking the transporters for NE and 5-HT (SERT), this led to the biogenic amine hypothesis that depression was the

result of a chronic decrease in the extrasynaptic levels of these monoamines (Schildkraut *et al.* 1965). As with the antipsychotics, the original TCA imipramine was joined by second- and third-generation compounds including desipramine, amitriptyline, and clomipramine. Due to a multitude of direct receptor interactions including serotonergic, muscarinic, histaminic, and α-adrenergic, the TCAs have multiple side effects that include sedation, orthostatic hypotension, and dry mouth that can limit their clinical use (Lieberman 2003). One of the TCAs, clomipramine, unlike imipramine, desipramine, and amitriptyline, proved to be more selective in its effects on 5-HT uptake than on NE uptake and led to the evolution of the 5-HT hypothesis of depression (Coppen 1967) and to the development of the selective serotonin reuptake inhibitors (SSRIs) that include fluoxetine (Wong *et al.* 2005), sertraline, and citalopram. The SSRIs have been highly successful drugs for the treatment of depression and led to various iterations on the TCAs that include the serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., venlaflaxine and duloxetine), the norepinephrine-dopamine reuptake inhibitors (NDRIs, e.g., buproprion), the selective serotonin reuptake enhancers (e.g., tianeptine), and the norepinephrine-dopamine disinhibitors (e.g., agomelatine) (de Bodinat *et al.* 2010) that, in antagonizing the 5-HT_{2C} receptor, can modulate NE and DA release. A UK meta-analysis of antidepressant treatment (Baldwin *et al.* 2011) concluded that fluoxetine and sertraline appeared to have some advantages over other monoamine-based drug treatments and that duloxetine and escitalopram might be superior to venlafaxine and paroxetine.

The triple reuptake inhibitors that block the reuptake of all three monoamines, NE, DA, and 5-HT, such as DOV 21,947 and NS-2359/GSK-37247, while effective in animal models of depression, have failed to date to show robust clinical efficacy in depression. JZAD-IV-22 (Caldarone *et al.* 2010) is a newer triple reuptake inhibitor, the preclinical data for which suggest it may lack some of the side effects seen with other members of this class of potential antidepressants.

The search for new classes of antidepressants that are distinct from those acting via monoamines had, until recently, limited success. A major challenge was that the majority of antidepressants, in addition to various side effects related to their effects on monoamine function (Lieberman 2003), all have a delayed onset to action. This delay is of concern in that depressed patients do not undergo any beneficial effects from their medication for some 2–6 weeks or more after treatment is initiated, leading to rapid treatment dropouts (Pigott *et al.* 2010) and to suicide.

A major breakthrough in time to onset was the recent finding, albeit still controversial, that the NMDA receptor antagonist, ketamine, can rapidly (within 2 h) attenuate depression in patients, an effect that lasted up to a week (Zarate *et al.* 2006). These findings were extended (Diazgranados *et al.* 2010) to subjects with treatment-resistant bipolar depression in whom antidepressant effects were observed as soon as 40 minutes after they received ketamine (0.5 mg/kg). The use of ketamine is limited by the potential for the development of symptoms of mania, the necessity for its intravenous administration, and the short-lived nature of its antidepressant effects. Additional research in preclinical models showed that the rapid antidepressant effects of ketamine could be associated with increases in synaptic signaling proteins and synapse formation in the prefrontal cortex mediated via the mTOR pathway (Li *et al.* 2010). In these studies, the antidepressant actions of ketamine were mimicked to a degree by the NR2B antagonist, Ro25-6981, suggesting that a glutamate-associated brain mTOR pathway may represent a novel target for the development of improved antidepressant agents, provided that the psychotomimetic effects of ketamine can be "tuned out" in NCEs. This latter task was the major challenge in developing effective therapeutic treatments for ischemic stroke based on the glutamate excitotoxicity hypothesis and eventually proved to be insurmountable based on the pharmacodynamic properties of the pharmacophores evaluated (Hall 2007; Pangalos *et al.* 2007).

After some 60 years of research based almost exclusively on the monoamine hypothesis, the ketamine/glutamate approach to NMDA function may represent the first of several paradigm shifts in antidepressant research that may result in new medications for depression with the potential for a more rapid onset. The latter include growth factors, specifically BDNF (Chen *et al.* 2010), that affect neuronal survival and synaptic plasticity; the central melatonin system, where agomelatine produces its antidepressant effects in addition to its $5HT_{2C}$ antagonist activities (de Bodinot *et al.* 2010); various members of the phosphodiesterase family (Halene and Siegel 2007); the 5-HT_7 receptor (Sarkisyan *et al.* 2010); neuropeptide receptor antagonists (e.g., CRF-1 and NK

receptors); protein kinases as reflected in the mTOR findings discussed above (Li *et al.* 2010); protein phosphatases, e.g., MAPK kinase phosphatase-1 (Duric *et al.* 2010); GSK-3 inhibitors (Li and Jope 2010); and *bcl-2* proteins (Mathew *et al.* 2008). The finding that an endogenous microRNA, miR-16, complimentary to the 3'-untranslated region of SERT mRNA, mediates the effects of the SSRI fluoxetine on SERT expression via a pathway involving GSK-3 beta and *Wnt* (Baudry *et al.* 2010) further reinforces a potential role for GSK-3 in depression. Additionally, in line with an involvement of a glutamate axis in mood disorders as evidenced by the effects of the NR2B antagonist, Ro25-6981 in the mTOR model (Li *et al.* 2010), the PPARγ agonist rosiglitazone has been reported to have antidepressant-like actions (Eissa *et al.* 2009).

The translational research paradigm in CNS drug discovery

The key challenge in the search for a new generation of improved psychoactive drugs has focused on: (1) enhanced validation of the animal models used to characterize NCEs as bona fide models of the human disease and the use of these models to effectively translate NCEs to the human disease state (Day *et al.* 2008; Markou *et al.* 2009; Millan 2008; Nestler and Hyman 2010; Spedding *et al.* 2005; van der Greef and McBurney 2005); (2) ensuring that NCEs intended to produce their effects in the CNS actually reach their site of action at sufficient concentrations to produce efficacy (Frank and Hargreaves 2003; Sakoğlu *et al.* 2011); and (3) robust biomarkers for disease diagnosis and the assessment of disease progression and drug effects on progression (Flood *et al.* 2011; Ryten *et al.* 2009). As noted, efforts in CNS translational research have been confounded by (1) a focus on target-based approaches (Enna and Williams 2009; Lindner 2007; Sams-Dodd 2005) to the almost complete exclusion of more systems-based approaches to CNS function that include neuronal circuitry, signaling pathways, and database integration and interrogation (Akil *et al.* 2010; Haber and Rauch 2009; van der Greef and McBurney 2005); (2) shortcomings in the predictive value of animal models (Day *et al.* 2008; Markou *et al.* 2009; McArthur and Borsini 2008; Nestler and Hyman 2010; Pangalos *et al.* 2007) together with concerns related to the intrinsic pathophysiology of these models as they relate to the chronic nature of the majority of human CNS disease states (Spedding *et al.* 2005); and (3) by a lack of systematic effort in translational approaches to CNS disorders (Dawson *et al.* 2011; Wang *et al.* 2008; Williams and Enna 2011). The latter is also related to the issues surrounding patient diagnosis and the heterogeneous, overlapping nature of psychiatric disorders (Hyman 2010), clinical trial design, and analysis. The multifactorial causality of CNS diseases, genetic, developmental, and epigenetic, may be considered to be in marked contrast to the current "targephilic" (Enna and Williams 2009) approach that dominates current CNS drug discovery in both academia and industry (Conn and Roth 2008) and may also be considered as an impediment to the effective translation of preclinical findings to the clinic setting.

The translational research paradigm is generally viewed as a series of multidisciplinary steps that transition an optimized NCE from the preclinical setting to a phase II proof-of-concept outcome, the latter of which is a logical extension of the original research hypothesis (Duyk 2003; LoRusso 2009; Wehling 2009). For psychotropic drugs, this process generally involves the examination of uniquely selective and potent NCEs in animal models to predict potential human efficacy and dosing and ideally involves a bidirectional flow of data from the clinic to the research laboratory and vice versa (Sung *et al.* 2003). Despite the obvious logic in such an approach and the ample historical evidence that a close interface between preclinical scientists and clinicians can greatly facilitate clinical design paradigms, the translational interface in the CNS space has been described as an "unbridged gap" (Klein 2008) or a "valley of death" (Brady *et al.* 2009) that is greatly in need of reinvention to ensure that heuristically promising new approaches to the treatment of CNS disease states are not dismissed after evaluation of a single compound (Bloom 2009). The "unbridged gap" reflects the dependence on a history of clinical serendipity where NCEs had already made their way into the clinic, eliminating any requirement for a translational focus but instead requiring the funding of multiple trials in different CNS disorders to identify a match between the molecular, pharmacodynamic, and pharmacokinetic properties of the NCE and the human disease state. The "valley of death" refers to the chasm where drugs have failed during the transition from preclinical evaluation to clinical validation. More

effective translational approaches are clearly needed that include a deeper understanding of the pathophysiology, a more reliable early predictors of clinical relevance, and the development of suitable biomarkers, to name just a few.

Animal models of human diseases

As noted, the majority of current preclinical animal models of CNS disease states reflect models in which drugs known to effectively treat CNS diseases have provided robust phenotypic signals (Day *et al.* 2008; Markou *et al.* 2009; McArthur and Borsini 2008; Nestler and Hyman 2010; Pangalos *et al.* 2007; Spedding *et al.* 2005). The use of these models, to a major extent, limits any additional hypothesis testing to the mechanistic approach to the disease state that underlies the mechanism of action(s), known or unknown, for the drugs used to define the model. A major cause of NCE attrition in the clinic occurs as the result of false positives from the present generation of animal assays or from the appearance of side effects that were not and could not be detected preclinically.

Although there has been considerable interest in the potential utility of transgenic models (Cryan and Holmes 2005; Zambrowicz and Sands 2003), few if any transgenic models fully recapitulate the disease symptoms. The use of gene ablation or gene knockins still reduces the experimental paradigm to the evaluation of the behavioral phenotype of the animal in the presence (wild-type), absence (knockout), or overexpression (knockin) of the proposed disease target. Although transgenic models have value in target identification and validation, they may contribute confounds, e.g., unknown and unknowable systems and target redundancies and abnormal CNS development, that can further complicate data interpretation.

Among the several recent reviews and monographs on the adequacy and current status of animal models of CNS diseases, Nestler and Hyman (2010) provide a challenge to the CNS research community to provide more rigor and insight – "clearly stated rationales and sober discussions of validity" – into the use and development of animal models for drug discovery rather than being "phenomenological." The authors take issue with the use of transgenic models with generic modifications that are not highly penetrant, that are dependent on rare or familial genetic mutations, or that focus on genes that have been associated with more than one CNS disease phenotype.

More recently, for schizophrenia, it has been suggested (Ibrahim and Tamminga 2011) that animal models should focus on individual components of the disease complex rather than model the disease as a single entity. This *component symptom complex* approach focuses on individual models for psychosis, cognitive dysfunction, and negative symptoms. Newer models reflecting the cognitive and negative symptom domains are under development (Neill *et al.* 2010). The potential difficulty here is that cognitive dysfunction in schizophrenia may be different than that in dementia or in other disorders, requiring a careful delineation and deeper understanding of the pathophysiological underpinnings of the phenotype that, on the surface, might appear to be similar.

Concerns related to animal model validity are not unique to the CNS area; numerous NCEs displaying target efficacy and safety (to the extent tested or testable) in animal models for multiple human disease states have failed in the clinic (Hackam and Redelmeier 2006), a result attributed to poor preclinical methods (Hackam 2007; Perel *et al.* 2007). These include a lack of blinding, randomization, and adequate powering/size of experiments; failure to conduct full dose–response curves; an "optimization bias" that can result in only positive data being reported (Lindner 2007; Pigott *et al.* 2010); genetic homogeneity in animals that contrasts with the heterogeneity present in the human population; and the absence of the chronic features of the human disease state in animals.

The CNS clinical translation disconnect?

Added to the concerns regarding the use of animal models in predicting clinical efficacy are concerns related to the clinical trials. Those for depression have undergone extensive post hoc assessment (Blier 2008; Kirsch 2009; Kramer 2005; Leventhal and Martell 2005; Pigott *et al.* 2010) and remain highly controversial, with major concerns regarding the contribution of placebo responses to reported efficacy (Klein 2008). A meta-analysis of data from 47 clinical trials covering the six most widely prescribed antidepressants approved between 1987 and 1999, fluoxetine, paroxetine, sertraline, venlafaxine, nefazodone, and citalopram, concluded that approximately 80% of the efficacy ascribed to an antidepressant was also seen in placebo controls, leading to the widely disseminated view that four out of six clinical trials for now-approved antidepressants failed to meet their

stated end points. A subsequent analysis of fluoxetine, paroxetine, venlafaxine, and nefazodone (Kirsch *et al.* 2008) established that baseline severity was critical for antidepressant-related responses, with decreased responses to placebo rather than drug effects being responsible for positive clinical outcomes. Additional concerns, generic to most clinical trials, were that the patients recruited into clinical trials were not representative of the average depressed patient treated in practice (Fleischhaker and Goodwin 2009; Wisniewski *et al.* 2009) and the selective reporting of data in the literature (Eyding *et al.* 2010; Mathew and Charney 2009; Pigott *et al.* 2010; Turner and Rosenthal 2008; Turner *et al.* 2008). Thus, published data from 37 of 74 antidepressant trials registered with the FDA indicated that 94% of these trials yielded positive results. However, an analysis of the full 74 trials showed that only 51% of these were actually positive, indicating that the data selected for publication provided an overly optimistic view of compound efficacy. Additional analyses (Pigott *et al.* 2010) of published trials that included the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial (Wisniewski *et al.* 2009) concluded that current antidepressant drugs were only "marginally efficacious" with "effectiveness ... probably even lower than ... reported ... with an apparent progressively increasing dropout rate across each study phase." The placebo effect issue in clinical trials for psychiatric medications, especially antidepressants, remains controversial (Silberman 2009), not only in terms of those compounds approved but also from the ability to effectively translate an NCE to an NDA approval. An additional factor that is of concern is the confounding of outcomes by the underreporting of negative trial results (Eyding *et al.* 2010; Mathew and Charney 2009; Pigott *et al.* 2010; Ramsey and Scoggins 2008; Turner *et al.* 2008).

Questioning the value of the *Diagnostic and Statistical Manual of Mental Disorders*

An additional challenge in developing new approaches to and treatments of mental disorders has been increasing concerns as to the intrinsic value of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in defining psychiatric disorders and their diagnosis (Hyman 2010; Insel 2010). DSM diagnosis is based on the phenomenology of symptoms rather than objective causes. As a result, the DSM has been viewed as "hampering research" (Miller 2010*b*) and as being "arbitrary or hazy" (Hyman 2010) in the "targephilic"-based research environment that reflects current approaches to drug discovery (Enna and Williams 2009; Sams-Dodd 2005). The National Institute of Mental Health has recently undertaken a new initiative to classify psychiatric disorders in the context of Research Domain Criteria (RDoC) that are based on a neural circuitry approach (Insel *et al.* 2010) that involves five distinct domains: negative emotionality, positive emotionality, cognitive processes, social processes, and arousal/regulatory symptoms, with the expectation that this will provide greater clarity and differentiation for psychiatric disorders.

Conclusions

Arguably, the learning curve for CNS research over the past two decades that has relied so heavily on discrete drug targets and gene associations has come full circle as it again focuses on the unique complexity of the brain rather than treating it as an organ indistinguishable in composition and complexity and function from the heart or liver (Akil *et al.* 2010). Additional facets of this shift include a focus on database development and mining for specific CNS drug classes (Geerts 2009), information processing networks (Bassett *et al.* 2010), and a re-emergence of observational CNS pharmacology (the "pharmacometric screen" (Enna and Williams 2009) as embodied in both the classical Irwin test (Irwin 1968) and more recent automated versions (Kafkafi *et al.* 2009; Tecott and Nestler 2004).

With the productivity void in new CNS drugs after more than half a century of effort and the abandonment of efforts in pharma in the area of neuropsychiatric disorders (Miller 2010*a*; Nierenberg 2010; Stovall 2011), the position of a "the best we can do" approach, given the complex challenges of CNS function, is now giving way to a long-needed paradigm shift based on valid concerns. These concerns include animal models, diagnosis of psychiatric disorders, and the challenges of clinical trial design and analysis that can no longer be ignored. In addition to the controversial comparative effectiveness initiatives, other federally funded activities are designed to bridge the translational gap. These projects are presently in the area of schizophrenia (Brady *et al.* 2009) and include MATRICS (Measurement and Treatment Research to

Improve Cognition in Schizophrenia) (Marder and Fenton 2004) to delineate guidelines for the approval of NCEs to treat the cognitive aspects of schizophrenia; NCDDDGs (National Cooperative Drug Discovery and Development Groups) (Brady *et al.* 2009), and RDoC (Insel *et al.* 2010), major science-based initiatives that will hopefully aid in driving CNS research forward in more productive directions. Against the potential backdrop of a new world of CNS drug discovery, it is noteworthy that the present challenges are in many respects reminiscent of those faced by neuroscientists and psychiatrists over half a century ago. *Plus ça change, plus c'est la même chose.*

Given the complexity of CNS disease states and the equally complex path from concept to approval of NCEs in the CNS area, one can only be amazed that the discoveries made over 60 years ago as a result of clinical serendipity have proven to be so useful to so many patients. For translational neuroscience initiatives to be truly informative and *transformational* will require a concerted, data-driven effort toward a better understanding of the fundamental pathophysiological mechanisms in CNS disease causality that is directed by basic research and coupled in real time to clinical science and the drug discovery and development process.

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