

# ‘CNS Drug Discovery and Development: When Will We Rescue Tantalus?’ *Neuropsychopharmacology Reviews* Volume 2 on CNS Drug Discovery and Development: Challenges and Opportunities

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The muses sang about Tantalus, condemned to suffer forever in the underworld. He stood in water up to his neck, but could never quench his thirst, for whenever he bent to drink, the water receded. Above his head hung branches loaded with fruits, but whenever he tried to pick one, the branch bent out of his reach.

—D'Aulaire's *Book of Greek Myths*, p. 112

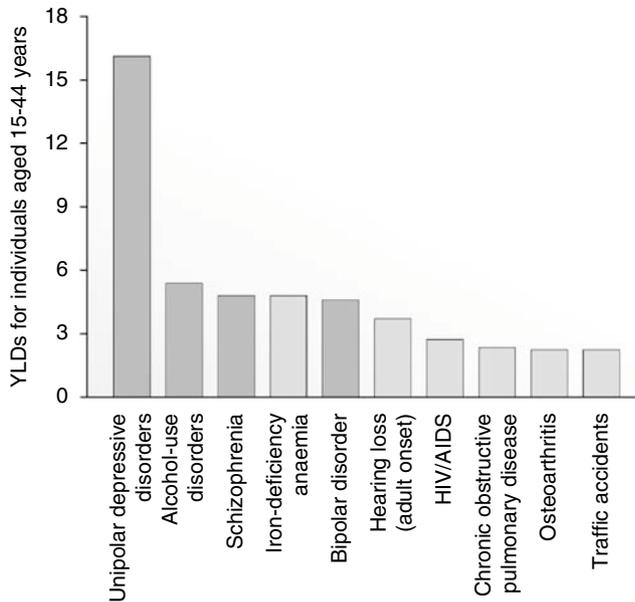
Disorders of the central nervous system (CNS) continue to be among mankind's most devastating illnesses. Worldwide, they cause enormous suffering for those affected, impeding the ability of children to grow and learn, of adults to work and live productively, and of the elderly to age with dignity. Despite the enormous strides made over the last quarter century in understanding the possible causes of various CNS disorders, and the development of novel therapeutics to treat these disorders, those of us who work in this field have often felt like the mythical Tantalus. The past decade, in particular, has seen enormous excitement but equally enormous frustration. Like Tantalus who saw the water and fruit before him, so too do we clearly see our goals: understanding the etiology and mechanisms of CNS disorders and developing more effective therapeutics to treat them. And yet, our ability to put our knowledge into practice has remained elusively out of reach. We believe the time has come, however, to make a concerted effort to rescue Tantalus. The outstanding articles in this special issue make us realize we are getting closer to achieving our goals. What we need now is a concerted, cooperative effort between leaders in the fields of academia, government, and industry; with such an integrated effort, real, tangible progress can be made.

CNS disorders have a relatively high prevalence and are characterized by many facets that make them particularly challenging to treat, including early onset (for example, autism in childhood or schizophrenia in young adulthood), a relapsing–remitting course (as with mood and anxiety disorders and OCD), and, often, disabling symptoms. CNS disorders, and the loose terms ‘neuropsychiatric’ and ‘neurodegenerative’ diseases, encompass a vast spectrum of devastating conditions that affect individuals at every stage of development, including Parkinson's disease, Alzheimer's disease, schizophrenia, mood disorders,

addiction, and autism. These illnesses exert, in aggregate, a disproportionate burden on public health. To measure the burden of any given disease, the World Health Organization (WHO) developed the disability-adjusted life year (DALY) measure, which sums the years of life lost to premature mortality in a population, and the years lived with disability (YLD). Despite the significant link between psychiatric disorders and suicide, Figure 1 (below) reflects that worldwide, the major impact of these illnesses is the disability they create. In 2000, the WHO estimated that 12% of all DALYs and 31% of YLDs worldwide were because of neuropsychiatric disorders. In developing countries such as North America and Europe, which have fewer cases of infectious diseases or malnutrition than the developing world, neuropsychiatric disorders alone were responsible for a staggering 43% of all YLDs. Others have estimated that disabilities because of neurodegenerative and psychiatric diseases now represent the second most frequent cause of morbidity and premature mortality in the United States.

The inordinately high personal, familial, societal, and financial burden of these disorders underscores the urgent need to develop novel drugs to treat them. For instance, Alzheimer's disease affects approximately 4.5 million Americans, with costs estimated at roughly \$100 billion annually. Notably, if current incidence rates hold, and no preventive treatments become available, it is estimated that by the year 2050 over 13 million Americans will be affected. Given the growing elderly population, and the slow pace of innovations in CNS therapeutics, identifying the specific disease mechanisms involved in Alzheimer's disease is tremendously important, as is developing drugs capable of addressing both its causes and symptoms (see article by Roses).

In some ways, however, our field has reached an impasse. That is, though we are acquiring more and more knowledge about the etiology and mechanisms of CNS disorders, and about putative therapeutics for these disorders, we have been unable to mount a concerted effort to put our knowledge into practice. In addition to the sheer complexity of the CNS, other obstacles include (for many of our disorders) lack of a defined pathology, no direct tissue accessibility, and the daunting fact that the complexity of



**Figure 1.** Top 10 causes of disability worldwide for individuals aged 15–44, as estimated for the year 2000. The contribution of each condition is quantified as years lived with disability (YLDs; data from the World Health Organization (2000). *World Health Report 2001*. WHO: Geneva).

behavior is not simply the sum of its parts. Further complicating the treatment of these diseases is our lack of understanding of the many varied causes of these diseases, as well as our difficulties in understanding the precise molecular and cellular mechanisms by which extant therapies actually exert their therapeutic effects.

In our field, there is wide consensus that better treatments are urgently needed. Better treatments means treatments that are more effective for more patients, that act faster, and that have fewer side effects. Although useful drugs for CNS disorders do exist, most are refinements and reformulations of drugs discovered decades ago. Real CNS disease targets are fewer in number, and proof-of-concept studies are rare in practice. Arguably, no new drug targets or therapeutic mechanisms of real significance for psychiatric disorders have been identified for more than four decades, and it is startling to consider that the number of psychotherapeutic agents with a unique mechanism of action is actually quite small and has not grown appreciably in the past two decades. Fortunately, this is finally beginning to improve, in part through the application of new genomic technologies coupled to advances in neuroscience. In practice, available medications can reduce the severity of specific symptoms for some individuals with various CNS disorders, but a substantial proportion of individuals either do not respond at all to existing therapies or the degree of improvement does not substantially improve their quality of life. Furthermore, we are also presently unable to predict who will respond to which treatment, which means that otherwise effective therapies are given to patients who will not respond to them, thus creating a lengthy and frustrating

trial and error process for many patients. These difficulties are undoubtedly because of the shortcomings associated with available medications. Because of heightened safety concerns, the challenge of developing safer, more effective pharmacological treatments is even greater for mental disorders in children and adolescents (see article by Pine and colleagues).

In recent years, the pharmaceutical industry has developed important new agents to treat a variety of diseases; however, the progress made in the treatment of CNS disorders has been less impressive. Reasons for the substantially fewer new drug approvals for CNS disorders compared to other treatment areas include extended development times, increased drug development costs, higher risk of clinical failure, changing regulatory hurdles, and an incomplete understanding of both disease biology and requirements for delivery to the CNS. As noted above, some of this is because of the complexity of CNS diseases, in combination with the biological logistics of drug delivery; unfortunately there is a dearth of new mechanism of action therapeutics in the drug discovery pipeline. The high cost of developing novel drugs, the high attrition rate of candidate therapeutics during development and clinical testing, and adverse effects contribute to the high failure rate of new compounds in clinical trials. In 2007, the number of novel drugs approved by the US Food and Drug Administration for all diseases was at its lowest point since 1983. In their article, Markou and colleagues soberly note that toxicological problems have led to concerns or even the discontinued development of a number of putative CNS medications that used our recently acquired knowledge of brain function and disease mechanisms (including corticotropin-releasing factor 1 receptor antagonists, glutamate receptor antagonists, phosphodiesterase 4 inhibitors, cannabinoid CB<sub>1</sub> receptor antagonists, and  $\beta$ -amyloid vaccine).

So, the notion that better treatments are compellingly needed is not in question. The question is: what can we do to develop these novel and more effective therapeutics? As noted above, the past few years have seen tremendous advances in neuroscience knowledge, as well as the development of new research tools that help us address these questions in ways that, just 25 years ago, would have seemed like the purest science fiction. Unfortunately, however, these scientific advancements have not yet led to the introduction of truly novel pharmacological agents for the treatment of CNS disorders. Like Tantalus, who saw before him the fruit and the water that he wanted so desperately, so too do we see our goal of developing truly novel and more effective agents clearly before us. Many possibilities have been proposed for this mismatch between our understanding of basic neuroscience and our ability to develop novel medications for CNS disorders. These include our inability to delineate the neurobiology of higher cognition, emotion regulation, and executive function; our inability to produce convincing and useful animal models to study these disorders; our inability to access the living human brain, which is protected by both the skull and the

blood–brain barrier; our inability to understand the complex genetic risk factors at play; and our inability to develop well-validated objective biological markers to delimit precise phenotypes for use in genetics or other research. Other reasons for our lack of success in developing new drugs include our antiquated diagnostic and classification system, which, at least for psychiatric disorders, is based not on etiology, neurobiology, epidemiology, genetics, or response to medications, but on a constellation of both signs and symptoms. As a field, one of our primary goals should be to develop a diagnostic system based on etiology. In addition, target validation represents one of the main barriers for CNS drug discovery and development in general, and psychiatric disorders in particular.

In the past few years, we have learned much about postreceptor signaling mechanisms, regulation of gene expression, epigenetic mechanisms, integrated mechanisms of synaptic plasticity, and we have identified valuable new biomarkers for vulnerability and drug response and resistance. What is lacking, however, are sufficient translational efforts applying new basic research findings and technology to molecular pharmacology and biological psychiatry, target discovery and validation, and clinical research. The National Institutes of Health (NIH) broadly defines translational research as ‘the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.’ Translational research, which so many of us are now engaged in, is the key to transforming scientific laboratory research into applications that benefit patient health and medical care and, in this context, the discovery of novel therapeutic agents. To understand brain function and its complexity, new ideas, new approaches, and new technologies are much needed. The articles in this special issue clearly show how much has already been carried out, but also how much is still left to do.

Despite the shortcomings discussed above, the situation is hardly bleak. As the papers highlighted in this special issue show, the field of neuroscience is growing at a feverish pace, with many different disciplines contributing various pieces of this extraordinary puzzle. In the past decade, these illnesses have increasingly come to be conceptualized as genetically influenced disorders of synapses and circuits rather than simply as deficits or excesses in individual neurotransmitters. Notably, our evolving knowledge of neuroplasticity is revolutionizing our understanding of disease etiology, as well as creating the possibility of novel pharmacological and behavioral therapies. Toward this end, the CNS disorders are treated first as diseases with molecular underpinnings that are susceptible to environmental and genetic regulation. These molecular underpinnings provide potential targets for the development of novel pharmacotherapeutics. Cellular signaling cascades regulate the multiple neurotransmitter and neuropeptide systems implicated in CNS disorders, and are targets for the most effective treatments. The next level of integration is

through brain circuitry, particularly how molecular events and adaptations to genetic or environmental vulnerabilities result in maladaptive communication within and between regions of the brain that regulate behavior. In this issue for instance, Blazer and Neubig discuss protein–protein interactions and their importance in intracellular signaling pathways, as well as their ability to lead to insights into novel potential downstream drug targets.

In the field of genetics, the past year has seen significant progress in finding common variants that might contribute to bipolar disorder and schizophrenia, as well as finding rare, highly penetrant mutations that might contribute to schizophrenia and autism. Genomics, including comparative genomics, gene expression atlases, and the organization of genome-scale projects, gene microarrays, and proteomics have all provided exciting new data. In addition, the study of gene expression changes and gene responses has provided valuable new ways to identify CNS targets for drug discovery (see Altar and colleagues).

Furthermore, as the article by Wong and colleagues so thoughtfully reviews, neuroimaging continues to be a tremendously useful tool for the clinical evaluation of new drug candidates. Continued development of imaging techniques and technologies is useful in preclinical models, but also extends to drug discovery and development. Translational imaging has been particularly valuable in the neurosciences where, because of the inaccessibility of the human brain, the use of radioisotopes (PET and SPECT) and magnetic resonance imaging is central to the assessment of brain penetration, target engagement, brain function, and neuropathology.

Many other powerful new research tools have also greatly accelerated the research process, spurred progress, and spawned new hypotheses and discoveries in all areas of biomedical research. These include high-throughput DNA sequencing, protein identification, expression arrays, and imaging technologies. New cellular tools and animal models have, in recent years, also generated a tremendous number of screening assays for use in the search for new drugs (see the articles by Wang and colleagues and Merrill).

The relatively new field of pharmacogenetics and pharmacogenomics (see article by de Leon) has also revolutionized our thinking about CNS disorders. Although the terms are largely interchangeable, pharmacogenetics has been defined as the study of variability in drug response because of heredity, and is largely used in relation to genes determining drug metabolism. Pharmacogenomics is a broader term, encompassing all genes in the genome that may determine drug response. This area of study will be key to ensuring that patients receive drugs that are both safer and more effective for them as individuals. Similarly, Kaddorah-Douak and Krishnan discuss the field of metabolomics and its importance in understanding how metabolic pathways and networks are regulated, with enormous implications for drug discovery. Grigoriadis and colleagues also explore the notion of ‘drugability,’ loosely defined as the ability of a xenobiotic or small molecule to modulate the

function of an endogenous protein and beneficially affect the organism. More specifically, this term relates to drug discovery and the ability to modify a disease state through a specific protein interaction or mechanism in the body, a concept that is increasingly key to drug development. Small molecule drugs are relatively effective in working on ‘drugable’ targets such as GPCRs, ion channels, kinases, proteases, etc but ineffective at blocking protein–protein interactions that represent an emerging class of nondrugable CNS targets. In this context, the timely article by De Souza and colleagues provides an overview of novel therapeutic modalities such as biologics (in particular antibodies) and emerging oligonucleotide therapeutics such as antisense, small-interfering RNA, and aptamers. As the field moves beyond traditional GPCRs as targets for the treatment of CNS disorders, such novel therapeutic strategies are going to become increasingly more important. De Souza and colleagues provide salient examples of their application as therapeutics for the treatment of pain and selected neurological disorders including Alzheimer’s disease, multiple sclerosis, Huntington’s disease, and Parkinson’s disease.

Notably, some of the articles in this special issue specifically address the challenges associated with achieving the promise and benefits of these innovations—namely, translating them into improved treatments and clinical outcomes for patients. For instance, one issue that has to date severely impeded our progress in this area is the lack of truly physiologically representative animal models to study these diseases. In their thoughtful and comprehensive reviews of the integral importance of animal models, Markou and colleagues and Nelson and Winslow describe the overwhelming agreement among scientists in both industry and academia regarding the function of animal models in drug discovery, what is currently lacking, and what is needed to ensure that the information that animal models can provide is used most effectively. Although no perfect animal model exists for any aspect of any CNS disorder, the limitations and strengths of most models have been extensively empirically investigated, and these issues are particularly important now, given the rapid growth of genomic and proteomic technologies.

As mentioned above, the broad concept of translational research is key to our progress, because it gives us the tools to integrate disparate findings, and make sense of them. Translational research essentially helps us to create a bridge between basic science and clinical developments and between clinical development and practice. Right now there is a gap between what we know and what we can do with it. Despite this shortcoming, that gap in our knowledge is considerably smaller than it used to be, and it is shrinking rapidly. For instance, Brady and colleagues describe how the NIH has established a number of translational research and public–private partnership programs to bridge these discrepancies by providing a way for industry and academic

scientists to pool intellectual and material resources and eventually accelerate the discovery and testing of novel putative therapeutics.

In the past decade, one of the enormous shifts in our thinking about psychiatry has been the growing appreciation that many, if not all, major psychiatric disorders have their antecedents in childhood. It is now clear that the major psychiatric disorders are serious, debilitating, life-shortening illnesses that affect millions of people worldwide. The major psychiatric disorders are clearly ‘chronic illnesses of the young,’ characterized by multiple episodes of symptom exacerbation, residual symptoms between episodes, and functional impairment. These illnesses arise from the complex, developmentally determined interaction of multiple genes and environmental factors, and the phenotypic expression of the disease includes not only affective disturbance, but also a constellation of cognitive, motor, autonomic, endocrine, and sleep/wake abnormalities. Alterations in brain development may contribute to chronic mental disorders. Pine and colleagues address the many challenges inherent in developing novel treatments targeted toward the early childhood manifestations of such chronic disorders. They further summarize data on developmental conceptualizations of anxiety from both basic neuroscience and clinical perspectives, and present a pathway to develop potential novel treatments, illustrating the manner in which basic neuroscience informs therapeutics.

When taken as a whole, much is still missing. But as the articles in this issue of *Neuropsychopharmacology Reviews* highlight, if we look carefully at individual discoveries, we see that many of our answers are there; what is needed is the integration of this knowledge into practice, especially as regards the development of novel medications. Impressive strides have been made recently toward understanding the basis of CNS disorders. Impressive strides have also been made in thinking about what these discoveries mean for practical drug development. While there is still much to be done, all of the authors whose articles are compiled here endeavor to envision a future in which this knowledge has been used to develop successful therapies. They, like us, envision a future where Tantalus can assuage his hunger and his thirst.

## DISCLOSURE/CONFLICT OF INTEREST

This work had begun while Dr Hussein K Manji was at the NIMH Intramural Program; Dr Hussein K Manji is now vice president, CNS and Pain, Johnson & Johnson Pharmaceutical Research and Development, Titusville, NJ. Errol B DeSouza is president and CEO, Archemix Corporation, Cambridge, MA.

Hussein K Manji and Errol B DeSouza