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Neurotherapeutics

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The fifth issue of *Neuropsychopharmacology Reviews* focuses on Neurotherapeutics. The publication of the issue coincides with the 50th anniversary of the American College of Neuropsychopharmacology (ACNP). The issue provides us with an important opportunity to reflect on the progress in the field and to look toward promising areas for new treatments. The remarkable advances in animal models, genetics, biomarker development, and drug discovery have led to the development of novel treatment approaches. Innovative treatments include neurochemical and molecular targets, genes and epigenetic therapies, cognitive construct-based behavioral interventions, as well as neural circuitry-based therapies such as deep brain stimulation and magnetic stimulation. The papers in this issue exemplify the development of new therapies for neurological and psychiatric disorders across the lifespan. Each paper illustrates the translation from preclinical research and human mechanistic studies into a unique therapeutic approach that, in many cases, has applications beyond the initial neuropsychiatric disorders targeted. We hope that the issue communicates the promise for the development of prevention strategies, symptomatic, and neuroprotective treatments that will ultimately translate into improved patient care.

Assembling the table of contents for the issue was remarkably challenging. Many of the papers represent collaborations between basic and clinical researchers, as well as between senior and promising junior faculty. Some papers focus on a specific pharmacological mechanism in a neuropsychiatric disorder, while other papers provide an overview of therapies for a particular disorder. Some promising specific mechanisms (cognitive rehabilitation for schizophrenia, cognitive therapy for depression, inflammation for mood disorders, and deep brain stimulation for Parkinson's disease (PD)) focus on one disorder, but we hope this overview will inspire applications to other psychiatric and neurological disorders. Each paper tells an interesting translational story that we hope will inspire further cross-talk between basic and clinical researchers and promote application of therapeutic development for one neuropsychiatric to another. In many or even most cases, the most exciting recent advances have not yet yielded new therapeutic agents or approaches that have been launched for broad clinical use. As experiences over the recent decades have shown, advancing a potential new approach to a marketed therapeutic agent is a tremendous challenge. It is hoped that further highlighting experimental approaches that have the most promise will encourage further investment and innovative efforts to translate these advances to improve the standard of patient care for serious brain disorders.

The section on *schizophrenia* focuses on three of the most promising areas of treatment development. Moghaddam and Javitt (2012) present the history of the glutamate hypothesis of schizophrenia, a critical evaluation of the hypothesis and avenues for future drug development. Jones *et al* (2012) reviews the great progress on the development of sub-type selective muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of positive and negative symptoms, including cognitive disturbances, of schizophrenia. Vinogradov *et al* (2012) present the history of cognitive training applications and then focus on an innovative systems neuroscience approach for cognitive training that has been applied to patients with schizophrenia. In these three therapeutic areas, the innovative work presented has substantial applications to the treatment of mood, addictive, and cognitive disorders.

The section on *mood disorders* includes paper on pharmacotherapy and somatic treatment, as well as two focused papers on two specific, promising targets, inflammation and cognitive deficits. Li *et al* (2012) review the literature on the use of antidepressants, mood stabilizers, and antipsychotics in the treatment of mood disorders. Then, they present advances in neurochemical modulators (5-HT1B, 5-HT4, 5-HT7 receptors, glutamatergic, and cholinergic treatments), as well as new approaches including *sleep and circadian regulation* as a therapeutic target, signal transduction mechanisms (GSK3). Rosa and Lisanby (2012) review the history of somatic therapies, discuss advances in such areas as transcranial magnetic stimulation, magnetic seizure therapy, and deep brain stimulation. They discuss the remarkable technical advances in ultrasound, near infrared light therapy, and optogenetic stimulation that will lead to the development of novel future treatments. Haroon *et al* (2012) present the compelling evidence for a role of inflammation in mood disorders. They describe the new interventions that are being evaluated. Treatments that target neuroinflammatory mechanisms may also be effective in treating prodromal or secondary affective symptoms in neurodegenerative diseases, as well as in schizophrenia and addiction.

In mood disorders across the lifespan, cognitive deficits may persist despite remission of mood symptoms. Rosier *et al* (2012) present the evidence from cognitive neuroscience, neuroimaging, and antidepressant treatment

studies that have identified deficits in affective and non-affective aspects of cognition (referred to as 'hot' and cold cognition, respectively, by the authors), the underlying neural circuitry affected and the modulation by antidepressant treatment. As the authors describe, such cognitive deficits, particularly in affective processing, may be a target for prevention strategies as such deficits are observed in 'at risk' individuals. The authors illustrate how these data can be used to inform the development of cognitively based strategies to be used alone or in combination with pharmacological and circuitry-based interventions (TMS, DBS) for more effective prevention and intervention strategies.

In the section on *addiction*, Addolorato *et al* (2012) provide an overview of pharmacotherapies for drug and alcohol abuse, and focus on three areas of promising treatment development in which translation to human populations is ongoing or expected in the next decade: GABA receptors, voltage-gated ion channels, and transcranial magnetic stimulation in which human translation is expected within the next decade.

The section on *childhood disorders* focuses on two areas where there have been recent, substantial advances in therapeutics as a result of translational research approaches: fragile X syndrome and autism. Gross *et al* (2012) focus on fragile X syndrome, which is perhaps the best example of the development of an animal model and the use of the model to develop human therapeutic approaches. These therapeutic targets, some of which are already in clinical trials, include extracellular neurotransmitter receptors, intracellular central signal transduction molecules, and downstream located signaling molecules or proteins.Veenstra-VanderWeele and Blakely (2012) highlight developments in the preclinical and clinical therapeutics of autism that have been informed by animal models, as well as human genetics and biomarkers that focus on mTor pathway and serotonin signaling pathways.

The section on *neurodegenerative and neurocognitive disorders* includes papers on PD and Alzheimer's disease (AD) and a paper focused on the exciting area of epigenetic interventions (HDAC inhibitors). Smith *et al* (2012) review the neuropathology and neural circuitry of PD. The authors present the important advances in PD therapeutics, including pharmacotherapy, neurosurgical approaches (eg, DBS), stem cell, gene therapy, and neuroprotective strategies. Similar to schizophrenia and addictions, in PD, initial therapeutic approaches focused on the dopamine system. As observed in these other conditions, the dopamine system is necessary, but not sufficient to account for the diverse psychiatric/neurological and neurocognitive symptoms observed. In the field of psychiatry, there are many lessons to learn from the development of pharmacological and circuitry-based treatment, as well as new approaches for the treatment of PD, as the chapter illustrates. Savonenko and colleagues provide a critical overview and analysis of AD therapeutics (Savonenko, 2012). The authors highlight the challenges in translating from animal models to human patients, the limitations of recently developed treatments focused on the amyloid hypothesis and the important considerations in developments more effective and safe treatments in the future. The paper by Day and Sweatt (2012) captures the excitement of epigenetic therapies for cognitive disorders, including memory deficits in AD that will have applications to other neuropsychiatric disorders (including schizophrenia and addictions). The authors provided a thoughtful presentation of the complexities of developing such treatments.

The issue concludes with an outstanding series of commentaries from the leadership of the National Institute of Health institutes that have supported much of the work described in the issue. The institutes have recently developed innovative strategies that have encouraged collaborations across groups, as well as 'high risk' development and testing of new drug targets, molecular imaging agents, and treatments. Brady and Insel present the National Institute for Mental Health's (NIMH) innovative programs to identify promising molecular mechanisms, to identify novel clinical and neurocognitive treatment targets, to reorganize psychiatric diagnosis based on neurobiological mechanistic criteria (Research Domain Criteria, RDoC) and to develop public–private partnerships for biomarker and drug development. Volkow and Skolnick of the National institute on Drug Abuse (NIDA) highlight the issue that despite important discoveries in preclinical drug and alcohol abuse therapeutics, the industry support of drug and alcohol abuse relative to other medical conditions is modest. Although NIDA has focused on specific promising areas, including vaccine therapy and combination therapies, these are still barriers to drug development that relate to stigma associated with drug use, as well as misperceptions of the morbidity and mortality. Edwards from the National Center for Complementary and Alternative Medicine (NCCAM) points out that despite the substantial use of complementary (including yoga, meditation, mindfulness-based cognitive therapy, placebo) or alternative medicine as a complement or adjunct to conventional care, the evidence base for their use is limited. An institute priority is to use state of the art neurobiological approaches to understand the mechanism of such treatments. This is especially critical to areas of great public health significance in which traditional interventions are not consistently effective and may have side effects (chronic pain and depression, substance abuse/behavioral addictions). Buckholtz, Ryan, Petanceska, and Refolo from the National Institute on Aging describe their innovative programs that have revolutionized the field of biomarker development, drug discovery, and clinical trials in Alzheimer's dementia. They highlight the important point that in a disease such as AD, that involves multiple neural systems and a diverse symptom presentation, a systems biology approach is needed to develop targeted treatments. They emphasize the importance of public–private partnerships for drug discovery and testing. The Alzheimer's disease Neuroimaging Initiative (ADNI) is one example of such a

successful partnership for biomarker development. Heemskerk, Farkas, and Kaufmann from the National Institute of Neurological Disorders and Stroke highlight the importance of 'closing the gap between discovery and drugs'. Although there are many promising small molecule compounds identified by such programs as the NIH Molecular Libraries Roadmap initiatives, the process of developing these compounds into treatments for patients is complicated by limited support of early stage drug development by industry, as well as access to clinical trial infrastructure. Several unique and important preclinical and clinical initiatives are described, including a 'virtual pharma' network for preclinical translation and a phase 2 clinical trials network for neurology. The section concludes with a commentary by Potter, who has been a leader in the NIMH intramural program, as well as the pharmaceutical industry. In his inspirational commentary entitled 'New Era for Novel CNS Drug Development', he shares his vision for the future of treatment development and proposes important strategies for academic–industry partnerships in drug development and target validation in particular.

Several themes are consistently articulated by these NIH leaders. Many potentially promising agents, tested in patients based on strong preclinical data, have had negative results in clinical trials. There are issues with the generalizability of preclinical data that have informed the choice of agents used, as well as clinical diagnostic and outcome measures. Efforts across institutes are focusing on the further identification of biomarkers, the refinement of relevant clinical outcomes and the role of public–private partnerships to develop more targeted treatments that will be more effective. The discussion from the institute leaders underscores the urgent need to developed targeted treatments for individual patients (personalized medicine).

Editing this issue has been a remarkable experience to work with an outstanding group of colleagues. Peter Kalivas provided critical scientific and strategic input throughout the process. Kathryn Cunningham did an outstanding job in editing the Hot Topics section that includes many late breaking developments in Neurotherapeutics. As always, the issue reflects Diane Drexler's outstanding editorial skills, tireless efforts, and tenacity. Jim Meador-Woodruff's outstanding leadership, wisdom and strong character have made *Neuropsychopharmacology* one of the most highly respected scientific journals. The great reputation of the journal made our jobs much easier in recruiting authors and reviewers for the issue. We are extremely grateful to these individuals for making this important issue possible and helping us look toward the next 50 years of the college and the field of neurotherapeutics.

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