# Progress in Neurotherapeutics and Neuropsychopharmacology

Published annually, volumes in this series provide readers with updates of recent clinical trial results, impacts of trials on guidelines and evidence-based practice, advances in trial methodologies, and the evolution of biomarkers in trials. The series focuses on trials in neurotherapeutics, including disease-modifying and symptomatic agents for neurological diseases, psychopharmacological management of neurological and psychiatric illnesses, and non-drug treatments. Each article is authored by a leader in the area of neurotherapeutics and clinical trials, and the series is guided by an Editor-in-Chief and Editorial Board with broad experience in drug development and neuropsychopharmacology. *Progress in Neurotherapeutics and Neuropsychopharmacology* is an essential update of recent trials in all aspects of the management of neurological and neuropsychiatric disorders, and will be an invaluable resource for practising neurologists as well as clinical and translational neuroscientists. Articles also available at http: www.cambridge.org/jid_PNN

# Progress in Neurotherapeutics and Neuropsychopharmacology

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Jeffrey L. Cummings

Kate (Xue) Zhong
For all you are, for all you do

# Contents

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# Preface

*Progress in Neurotherapeutics and Neuropsychopharmacology* (PNN) represents a new concept in content and in publishing. From a publishing point of view, PNN is a unique combination of print and electronic processing to maximize availability of information. Chapters are solicited continuously and placed online after editing. Online, these chapters are in the complete published and citable format. Annually, chapters are collected into a single volume and published in book form. The chapters are available on the shelf or electronically according to the reader's preference. Moreover, there is minimal delay in conveying the information from the author to the reader. The growing archive of on-line chapters will allow readers to review all of the recent information available for specific diseases, biomarkers, or methodologies.

From the content point of view, PNN has a single focus on therapeutic advances through clinical trials. Clinical trials provide information for evidence-based medicine to advance care of patients. PNN will emphasize double-blind, randomized, controlled trials that provide the highest quality data to guide clinical practice. Each chapter will focus on a single trial or a few related trials and will include an interpretation of how the trial results influence contemporary approaches to practice. Articles relevant to advancing trial methodology will be included. Progress in trial design or trial analyses are an important part of the growing literature on clinical trials. In addition, the integration of biomarkers as surrogate outcome measures in clinical trials is a critically important research area, particularly as disease-modifying agents enter the clinical trials arena. PNN will include publications on these methodologic advances. Similarly, improved understanding in the informed consent process, the ethics of clinical trials, and regulatory issues relevant to drug development in clinical trials will be included among PNN contributions.

## Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, migraine, schizophrenia

This first issue of the hard bound edition of PNN includes an exiting array of new trial results. The introductory chapter by the Editor-in-Chief, sets the stage

for the progress being made with new therapeutic advances emerging for Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, migraine, schizophrenia, headache, substance use disorders and many other central nervous system conditions. The phases of drug discovery and development are outlined with Phases II, III, and IV emphasized in PNN covered in greater detail. Contributions in this volume include treatment approaches on neurologic diseases including Parkinson's disease, multiple sclerosis, brain tumors, migraine, amyotrophic lateral sclerosis, and pseudobulbar affect. Idiopathic psychiatric disorders with neuropsychopharmacologic treatments tested in new trials described in the current volume of PNN include schizophrenia and autism.

Discussions of clinical trial methods, development of new treatment approaches, and use of approved medications for new purposes are included in this volume of PNN. Tekin and Lane describe a trial in which rivastigmine – currently approved for treatment of Alzheimer's disease – is used for the treatment of the dementia of Parkinson's disease. Effect sizes may be larger in this condition than in Alzheimer's disease. Stankoff and co-workers investigated the potential utility of modafinil for fatigure in multiple sclerosis and found not benefit using the dose and regimen of this trial. Mason and colleagues present an important trial that contributed to Food and Drug Administration (FDA) approval of temozolomide for treatment of glioblastoma multiforme. Dr. Wiendels and Dr. Ferrari review the evolving types of clinical trials used to assess triptans in acute migraine and note that early treatment is not necessarily the optimal way to conduct a trial. Gordon *et al.* and Jeremy Schefner contribute chapters on minocycline and creatine as potential treatments for amyotrophic lateral sclerosis. Gordon and coworkers provide safety, tolerability, and dosing data critical to construction of a Phase III trial of minocycline. Using a futility type analysis, Schefner showed the effects of creatine were not sufficient to warrant further investigation. This outcome was somewhat surprising given the robust effects of creatine in animal models. Dosing issues will have to be reconsidered before a next step is taken with this agent. Another interesting observation in this trial concerns what patients will choose to do when they are enlisted in a clinical trial that they know is testing a medication that is already available on the market. Urine studies showed that six out of thirty-one patients in the placebo group had creatine levels in their urine suggesting that they had decided to take creatine outside of the context of the trial. Pope contributes an interesting chapter on an experimental agent (AVP-923) consisting of a fixed combination of dextromethorphan and quinidine for the treatment of pseudobulbar affect.

Autism has proven to be treatment resistant but the chapter by Hollander and colleagues suggests that fluoxetine may be beneficial for control of at least some symptom complexes. Several new therapeutic approaches to schizophrenia are included in this volume of PNN. Using a unique clinical trial methodology, Meltzer and colleagues, tested a neurokinin antagonist, a serotonin 2a/2c antagonist,

a central cannabinoid antagonist, and a neurotensin antagonist. This strategy allowed optimal use of a common placebo group to facilitate multiple proof-of-concept observations. Negative and cognitive symptoms have become an important focus of treatment research in schizophrenia. Lin and Bodkin (testing selegiline) and Turner and Sahakian (testing modafinil) provide preliminary data that these symptoms complexes may have treatable components. Simpson and coworkers report one of a small number of head-to-head comparisons of atypical antipsychotic agents. Possible earlier onset of effect of ziprasidone and greater cardiovascular morbidity of olanzapine are suggested by this trial.

Several themes emerge from an overview of the clinical trials in this volume of PNN. An exciting observation reported in the study Mason *et al*. is that genetic subtype appeared to have a great effect on treatment responsiveness. This type of information may help to guide treatment choice for individual patients in the future. Another theme concerns disease-modifying agents for treatment of neurodegenerative disorders. Clinical trials of minocycline and creatine in amyotrophic lateral sclerosis (ALS) are reported. The two trials included in the current volume do not show marked benefit but they set the stage for the next step in the development of disease-modifying and neuroprotective therapies. Another emergent theme is the use of symptomatic agents across disease states with common characteristics. Trials using modafanil to treat cognition and attentional shifting in patients with schizophrenia in one trial and to treat fatigue in multiple sclerosis in another are reported. Improvements were seen in schizophrenia but no relief of fatigue was evident on patients with multiple sclerosis. These trials begin to refine our understanding of agents such as modafanil that may have broad application in diseases with cognitive manifestations including the cognitive symptoms of schizophrenia and dementing disorders. Similarly, the use of selegiline as augmentation therapy for antipsychotic medications to treat negative symptoms in patients with schizophrenia is a further example of a medication with uses across multiple neurologic and psychiatric illnesses. Selegiline is used to treat the motor symptoms of Parkinson's disease, to slow the rate of loss of activities of daily living in Alzheimer's disease, and to have antidepressant qualities. The new trial suggests that it may be useful to treat negative symptoms in patients of schizophrenia.

Several barriers to drug development can be identified in the information provided in the clinical trials reviewed in this volume of PNN. Particularly striking is a failure of the ALS mouse model to predict a clinically significant response to creatine in patients with ALS (Jeremy Schefner). Effective drug development strategies will depend on highly predicative animal models and determining the reasons for failures in predictive success can lead to important improvements in drug development.

PNN provides an overview of emerging themes in neurotherapeutics and NPP, and guides insight into treatment advances relevant to the management of patients with a variety of neurologic and psychiatric disorders.

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