Introduction to Neurotherapeutics and Neuropsychopharmacology

Jeffrey L. Cummings
Department of Neurology and Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; Email: jcummings@mednet.ucla.edu

Key words: Neurotherapeutics; psychotropics; clinical trials; drug development; Phase II, Phase III.

Introduction

In recent years there has been tremendous progress in advancing new treatments for neurologic and psychiatric illnesses. New agents have emerged for the treatment of Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, epilepsy, migraine, schizophrenia, bipolar illness, depression, and substance abuse disorders. Advances in understanding of basic pathophysiology and molecular biology of brain disorders have led to increasingly sophisticated target identification that guides drug development. Advances in the basic neuroscience and disease mechanisms have been particularly obvious in the neurologic disorders where there is an ever improving understanding of the underlying mechanisms of brain function and brain disease.

Progress in neurotherapeutics has occurred in concert with progress in basic science methodologies, neuroimaging, clinical trial design, and trial analysis. There is an increasing enthusiasm for clinical trials that provide highly credible data with which to guide evidence-based medicine. The United States Food and Drug Administration (US FDA) requires a close link between the clinical trial population tested and the specific indication for which the agent will be approved. This contributes to the proliferation of clinical trials, as industry sponsors of trials seek to expand the populations for which their products are indicated. An increasing number of patients and physicians are involved in clinical trials. Advancing clinical trial methodology has itself become a major endeavor.

Correspondence should be addressed to: Jeffrey L. Cummings, MD, Department of Neurology, Reed Neurological Research Center, UCLA, 710 Westwood Plaza, Los Angeles, CA 90095 1769, USA; Email: jcummings@mednet.ucla.edu.
Progress in Neurotherapeutics and Neuropsychopharmacology has two objectives:

1. to provide a continuous update of the clinical trials that can be used to inform and improve the care of patients with neurologic and psychiatric illnesses
2. to provide an update on clinical trial methodologies, designs, and outcome assessments.

This article provides an overview of the themes emerging in current neuropsychopharmacology and the associated clinical trials.

**Drug Discovery and Development**

The process of drug discovery and development begins with the identification of a human disease or condition, and an unmet need in the form of inadequate treatment (Figure 1). The objective of neurotherapeutic drug discovery and development is to identify new treatments that will improve the quality of life (QOL) of patients suffering from neurologic and psychiatric disorders. Advances in molecular genetics, basic cell biology, brain connectivity, neurologic chemistry, and brain

![Fig. 1.](image) Cycle of drug discovery and development.
imaging have continued to an improved understanding of the neurobiologic basis of normal brain function, and of major neurologic disorders.

Characterization of basic disease processes facilitates a focused search for pharmacologically manipulable targets around which a drug development program can be built. Once a neurochemical deficit or alteration in enzymatic activity, transmitter receptor or transporter physiology, gene product abnormality, or protein production or folding disturbance is identified compounds can be sought that ameliorate the consequences of these abnormal mechanisms. For example, the current concepts of Alzheimer’s disease suggest that the aggregation of amyloid beta protein in the brain is the principal cause of the disorder. Many current drug development programs are aimed at modifying this process (Cummings, 2004). After a target has been identified and compounds that may potentially modify the basic processes have been found, the “druggability” of these chemical entities must be determined. Factors such as whether they can cross the blood–brain barrier, are likely to have a half-life that will support clinical application, have biochemical features commonly associated with side-effects, or have properties that interfere with establishing clinically useful formulations are reviewed to determine if the chemical entity is plausible as a drug candidate. In some cases the molecular structure of the candidate entity can be modified in the process of lead optimization to produce a compound or a series of compounds that can be advanced in the drug development process.

Candidate compounds can come from a wide variety of sources. Pharmaceutical companies, biotechnology companies, and some federal agencies maintain compound libraries that may be screened for the properties sought to intervene in an identified pathophysiologic process. Modern techniques of high-throughput screening allow thousands or tens of thousands of compounds to be screened rapidly. In silico design of new molecular entities using advanced computerized modeling techniques is also advancing. Designer drugs with the desired chemical characteristics can then be produced by medicinal chemists. Herbal medicine and folk treatments, such as Chinese traditional medicine, are another source of compounds. Empirical observations often made over thousands of years have suggested specific activities of compounds to be tested. The variable occurrence of neurologic and psychiatric disorders among world populations may suggest environmental or dietary substances that may be tested for potential pharmaceutical development. Many drugs are developed not through an improved understanding of basic pathophysiologic mechanisms but on the basis of empirical observations of drugs used for one clinical condition and re-purposed for another. For example, the ability of propranolol to reduce essential tremor was discovered when this agent was used in patients with cardiovascular disease who incidentally suffered from a tremor disorder. Another common pathway for drug development is to refine an existing compound to increase efficacy or decrease
side-effects. This pathway is particularly common as a mechanism for developing new psychotropic compounds where relatively minor modifications in molecular structure have led to the new antipsychotics, antidepressants, anxiolytics and hypnotics. Finally, biologic agents such as antibodies are increasingly being investigated for their potential utility in treating neuropsychiatric illnesses.

Once lead optimization has occurred, further pre-clinical testing of the chemical entity in laboratory animals is indicated (Figure 1) (Ng, 2004; Lee et al., 2003). Absorption, distribution, metabolism, and excretion (ADME) are investigated to determine the effects of the body on the drug. Toxicologic investigations are also pursued to determine the effect of the drug on the body. Assessments are typically made in at least three species to allow for interspecies variability in drug metabolism and toxicity. Only those agents with pharmacokinetic characteristics suggestive of a compound that can be used successfully in human beings are advanced to the next stage.

Simultaneously with the testing of pharmacokinetic properties, pharmacodynamic characteristics are also typically investigated in models of the disease the agent is intended to treat. Effects on prepulse inhibition or learned helplessness assist in predicting antipsychotic and antidepressant qualities, respectively. Lesioning of the nucleus basalis creates a cholinergic deficit and allows testing of compounds for their potential beneficial cholinergic effects in this model. Medical proficiency training program (MPTP) is used to create models for some aspects of parkinsonism. There is increasing enthusiasm for the use of transgenic animals created by the introduction of human mutations into the experimental animal (usually a mouse, but other species also may be used) genome. These animals are fated to develop aspects of the human disease against which the effects of candidate compounds can be tested.

Agents with promising pharmacokinetic and pharmacodynamic profiles are advanced to first-in-human studies in Phase I clinical trials (Figure 1). Normal healthy volunteers are typically used in these trials in an attempt to determine if candidate agents have safety effects or limited tolerability that would make further human testing impractical. Single-dose studies of increasing doses of the drug are typically followed by longer multiple-dose studies. Pharmacokinetic data are collected to determine the half-life, the maximum concentration area under-the-curve, and other parameters. Vital signs, blood and serum measures, electrocardiograms and cognitive functions, are carefully followed to detect any adverse effects. Computerized neuropsychologic assessments and electroencephalography may assist in determining which compounds pass the blood–brain barrier and have either adverse or beneficial central nervous system (CNS) effects. In some cases, Phase I studies called “bridging” studies may be conducted with the intended patient population.

After the completion of Phase I, compounds are advanced to Phase II if they have acceptable tolerability, safety, and pharmacokinetic properties (Ng, 2004; Lee et al., 2003). Phase II studies involve a specific patient population and are intended
to garner additional safety and tolerability information in this specific patient group as well as to determine the doses and formulations that will be used in Phase III clinical trials. Phase II studies also generate preliminary efficacy information that may assist in determining whether a compound is advanced to Phase III. Carefully executed Phase II studies are critical since inadequate testing of a variety of doses and optimal formulations may lead to inappropriate abandonment of a compound or choice of sub-optimal doses for Phase III.

Phase III is the final phase of drug development prior to presenting a new chemical entity to the FDA for review and potential approval for marketing (Ng, 2004; Lee et al., 2003) (Figure 1). These trials are “pivotal” trials in which the doses and formulations to be marketing are tested for efficacy. Standardized disease or syndrome definitions, well-established outcomes with valid and reliable instruments, and sophisticated data management and pre-specified data analytic strategies are required for FDA presentation. Drug safety and tolerability are comprehensively assessed.

Once the FDA receives and reviews the documentation, it may choose to approve the compound and will base the language of the package insert that describes the specific indications for the approved drug on the data presented from the Phase III clinical trials. This language is critically important to industry sponsors since marketing can occur only for approved indications of the drug. So-called “off label” use of drugs is common but observations derived from “off label” use cannot be incorporated as part of a drug marketing program. The FDA may also view the submitted data as inadequate and choose not to approve the drug or additional data may be requested.

After marketing, the drug is widely used by physicians to treat many patients including individuals not suffering from the disorder the medication was intended to treat. New side-effects commonly emerge and these are occasionally sufficiently severe that the FDA must change the labeling, append warnings to the package insert, or rarely withdraw the compound from the market. Phase IV trials or post-marketing studies provide an important opportunity to identify additional indications for use of the drug. These may be based on “off label” observations of the successful use of a compound in disorders related to the population testing in pivotal Phase III trials. For example, atypical antipsychotics were first developed for treatment of schizophrenia and have been tested in Phase IV programs to extend their indication to include bipolar mania (both acute and chronic phases) and bipolar depression. These expanded indications form an important part of the life-cycle management of a compound.

At the end of Phases III and IV, advances have been made in meeting the unmet need of the inadequately treated human disorder that stimulated the search for improved therapy (Figure 1). Progress in Neurotherapeutics and Neuropsychopharmacology will emphasize Phase II, III, and IV clinical trials and advances in
clinical trial methodology. These are key translational research endeavors that link basic science observations of disease pathophysiology and mechanism of drug action to testing and establishment of efficacy in human clinical populations.

**Neurologic and Psychiatric Therapeutics**

*Progress in Neurotherapeutics and Neuropsychopharmacology* will include clinical trials and advances in clinical methodology involving compounds for the treatment of both primarily neurologic illnesses and psychotropic agents used for the treatment of idiopathic psychiatric disorders. Both neurologic and psychiatric conditions are included since it is obvious that successful intervention in a psychiatric disorder depends on modifying brain activity to minimize psychiatric symptoms. There is a spectrum of neuropsychopharmacologic intervention from purely symptomatic management of idiopathic psychiatric syndromes, to treatment of psychiatric disorders in patients who have neurologic disorders, to investigation and intervention in the emerging neurobiology of psychiatric conditions to treatment of identified pathophysiologic pathways in patients with neurologic disease (Figure 2).

There is increasing intellectual commerce between concepts of treatment of neurologic and psychiatric illnesses. For example, antidementia agents exhibit psychotropic properties and have beneficial effects on psychiatric aspects of Alzheimer’s disease and other disorders (Emre et al., 2004; Cummings, 2000). Similarly psychiatric compounds are increasingly recognized to exert neurologic effects. For example, the antidepressant properties of selective serotonin reuptake inhibitors correlate with their ability to produce neurogenesis in the hippocampus (Jacobs et al., 2000). *Progress in Neurotherapeutics and Neuropsychopharmacology* will promote understanding of neurobiologic mechanisms and neuropsychotropic interventions by including clinical trials devoted to both neurologic and psychiatric syndromes.

**Emerging Themes in Clinical Trials**

Several major themes are emerging across clinical trials in neurologic and psychiatric disorders.

![Fig. 2.](image_url) Relationship of neurotherapeutics and neuropsychopharmacology.
Informed Consent

Appropriate informed consent is difficult to achieve particularly in patients with neuropsychiatric illnesses that often alter judgment. Patients are desperate to have new treatments and clinicians are eager to advance therapeutic trials. Financial incentives involved in drug development further complicate the informed consent process. Means of insuring fully informed patient participants is an objective across clinical trials in all diseases.

Recruitment

Recruitment of appropriate patients in a timely manner falls short in many trials involving neurologic diseases. Despite a high prevalence of neurologic illnesses in the population, efficient screening, identification of patients that have all inclusion criteria and no exclusion criteria, and obtaining informed consent increasingly narrows the recruited population, delays trial completion, and impedes the emergence of new therapeutics. Establishment of community-based networks and community-based trial sites, reducing exclusionary criteria to allow the clinical trial population to more clearly mirror “real world” populations, and media campaigns to increase public awareness of neuropsychiatric illness and the need for clinical trials are methodologies that may improve recruitment. Increasing use of trial sites in Asia and India are anticipated.

Generalizability of Clinical Trial Results

Patients participating in clinical trials tend to be largely of Caucasian ethnicity and to be more highly educated, have better general physical health, have lower levels of psychopathology and are generally younger than unselected patient populations. These selection biases may influence the results of clinical trials and limit their generalizability. There are ethnic differences in drug metabolism which may go undetected using current clinical trial approaches.

There is an increased interest in conducting effectiveness trials in which the results of the current efficacy trials are extended into more typical patient populations using common clinical outcomes and trials conducted in community practices rather than specialized trial sites. Resource utilisations are an important outcome in effectiveness trials. These trials may provide new information on the performance of drugs when used in more “real world” settings.

Biomarkers

There is an increasing need for biomarkers that can be used as surrogate outcomes in clinical trials of disease-modifying agents. Clinical trial outcomes by themselves are unlikely to produce sufficient evidence of disease-modifying activity since it is difficult to distinguish symptomatic from disease-modifying effects on the basis
of trial outcomes alone. Establishment of a drug as disease-modifying will require demonstration of a plausible mechanism of action in a basic science model, results from a clinical trial that are consistent with disease-modification, and effects on a surrogate biologic marker related to disease activity (Figure 3).

Progress is being made in the use of biologic markers in neurologic disorders. Positron emission tomography scans with amyloid ligands have evolved and promise to identify patients with Alzheimer’s disease who have elevated levels of brain amyloid. These scans may function to monitor reduction of amyloid burden with effective therapeutic compounds (Klunk et al., 2004).

Similarly measures of temporal lobe structures on magnetic resonance imaging (MRI) reflect progressive cerebral atrophy in neurodegenerative disorders such as Alzheimer’s disease and slowing this rate of atrophy may function as a surrogate marker for the activity of a disease-modifying compound. Biologic markers relevant to other neurologic and psychiatric diseases are needed.

**Treatment of Prodromal States**

Identification and treatment of the earliest manifestations of neurologic and psychiatric illness is increasingly valued. Disease course is more difficult to modify and QOL more resistant to rescue when treatment is initiated after the brain disease is well established. For example, treatment of mild cognitive impairment with the aim of slowing the progression from this prodromal state to Alzheimer's disease is an increasingly important clinical trial strategy. Similarly, identification and treatment of the earliest phases of Parkinson’s disease is a valuable clinical trial approach. The trial is terminated for the individual patient when treatment with initiation of levaodopa has become necessary and time to levaodopa therapy is the critical clinical trial measure. Treatment of prodromal phases of psychiatric illnesses, such as schizophrenia, are also of interest.
Disease Prevention

Primary prevention trials aimed at asymptomatic populations also deserve consideration. Prevention of stroke through control of stroke risk factors and amelioration of the progression from normal aging to mild cognitive impairment and Alzheimer’s disease are important clinical trial paradigms. Identification of risk factors, some of which are modifiable, for neurologic and psychiatric illnesses will facilitate primary prevention trials.

Cross-Disease Treatment Approaches

Many neurologic disorders share common pathophysiologic mechanisms. Thus, inflammation is present in multiple sclerosis, stroke, and in neurodegenerative disorders, including Alzheimer’s disease. Anti-inflammatory agents can possibly play a role in each of these conditions. Oxidative damage also is a common final pathway for cellular injury in many neurologic diseases. Excitotoxicity appears to play a role in both neurodegenerative and cerebrovascular diseases.

Neurodegenerative disorders are increasingly linked to protein misfolding and protein metabolism abnormalities (Cummings, 2003). Overproduction or accumulation of amyloid beta protein is regarded as the central even in Alzheimer’s disease. Alpha synuclein is misfolded in idiopathic Parkinson’s disease, tau and ubiquitin abnormalities are present in the frontotemporal lobar degeneration syndromes, huntingtin is abnormal in Huntington’s disease, prion protein is accumulated abnormally in Creutzfeldt–Jakob disease, and other rare neurodegenerative disorders have their corresponding misfolded proteins. Information about how best to intervene in protein-misfolding disorders may result in principles applicable across many neurodegenerative disorders.

Pharmacogenomics

Both pharmacokinetic and pharmacodynamic responses have important genetic determinants. Increasing precision in pharmacogenomic studies may allow improved prediction of both efficacy and adverse responses to pharmacologic interventions. Pharmacogenomics may eventually provide a platform for developing highly individualized therapies that are best suited for the person’s specific genetic constitution.

Pharmacoeconomics

Drug development occurs in a complex economic setting. Shareholders expect returns on investments in pharmaceutical and biotechnologic companies. New drugs must recoup the research costs of both successful and unsuccessful agents. Patients and drug purchasing organizations wish to minimize costs. Resource utilization is affected by effective drug treatment and these savings must be considered.
when calculating costs. Pharmacoeconomic outcomes are now more regularly included in clinical trials.

Quality of Life
There is greater interest in patient-centered outcomes that bear directly on the life of the patient and caregiver. The QOL measures of patient and caregiver are evolving and are included in some clinical trials as outcome assessments. QOL, health-related QOL, cost/benefit analyses, and quality-adjusted life years represent alternative current approaches to collecting patient-centered data. Those in a dearth of QOL instruments specifically useful in clinical trials that may be sensitive to drug–placebo differences.

Summary

*Progress in Neurotherapeutics and Neuropsychopharmacology* will bring together contributions from leading academic and industry investigators to provide a continuous update on pharmaceutic advances based on controlled clinical trials as well as advances in clinical trial methodology, including design, analysis, and use of biomarkers.

Disclosures

Dr. Cummings has served as a Consultant or performed research for AstraZeneca, Avanir, Eisai, Janssen, Lilly, Lundbeck, Memory, Merz, Neurochem, Novartis, Ono, Pfizer, *Takeda, Sanofi-Aventis, and Sepracor.

Acknowledgments

Dr. Cummings is supported by the National Institute on Aging (P50 AG 16570), the Alzheimer’s Disease Research Centers of California and the Sidell-Kagan Foundation.

References


