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## Progress in Neurotherapeutics and Neuropsychopharmacology 2007

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### ABSTRACT

There continues to be progress in neurotherapeutics and neuropsychopharmacology with each advancing year. Production of new molecular entities (NME's) remains small, but advances are being made in repurposing agents and extending their indications, obtaining more safety and tolerability data in long term and extension studies, introducing novel trial methodologies that provide insight into how to best to conduct trials and how best to treat diseases, and developing new formulations that improve adherence and decrease the barriers to patient compliance. Advances in how to test potential disease-modifying agents in patients with progressive neurological illnesses is advancing. Promising biomarkers have been identified in some neurological diseases.

**Key words:** Clinical trials, drug development, futility trials, Parkinson's disease, Amyotrophic Lateral Sclerosis, Schizophrenia

### Progress in Neurotherapeutics and Neuropsychopharmacology 2006

Progress continues to be made in advancing our understanding of how best to treat neuropsychiatric illnesses and how best to conduct clinical trials to establish the worthiness of potential therapies. This introduction reviews major advances that have occurred in the past year emphasizing novel trial methodologies and approaches to establishing therapeutic efficacy.

The low level of discovery of new molecular entities (NME's) with therapeutic potential continues to be a notable observation despite increasing investment from the industry and NIH funding for clinical trials (Johnston, 2006). New drug discovery methodologies, including *in silico* drug discovery approaches, high throughput screening and constructing large molecular libraries have failed to produce a wave of new NME's that are making their way into advanced clinical trials and clinical

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care. There continues to be optimism that these technologies will identify new therapeutic candidates that will succeed in preclinical assessments and enter advanced developmental phases.

The following chapter is organized by disease state to facilitate discussion of advances in treatment relevant to specific classes of patients. This organization is not meant to suggest that all therapeutic advances must be disease-specific; there is increasing evidence of cross-disease syndromic and phenotypic responses to therapeutic interventions independent of disease etiology.

### **Amyotrophic Lateral Sclerosis**

The Northeast Amyotrophic Lateral Sclerosis (ALS) Consortium reported the results of a large trial of celecoxib, a cyclooxygenase-2 inhibitor, in the treatment of this progressive motor neuron disease (Cudkowicz *et al.*, 2006). Patients were randomized to receive either 800 mg of celecoxib per day or placebo for 12 months. This dosage of celecoxib had no evident beneficial effect on any measurable aspect of the disease. There was no effect on decline in muscle strength, vital capacity, motor unit number estimates, ALS functional rating scales/revised, or survival. Celecoxib was well tolerated without an elevated frequency of adverse events compared to placebo. The results of this study are a disappointment to ALS victims and to researchers alike. Investigators were striving to translate basic science observations of the presence of inflammatory changes in the central nervous system (CNS) of ALS on patients at autopsy into a potential for benefit from anti-inflammatory agents such as celecoxib.

This study demonstrates several aspects of the evolution of clinical trial methodologies to assess potentially disease-modifying agents in patients with neurodegenerative disorders. The design was a parallel group design with change in rate of decline of maximal voluntary isometric contraction strength as the primary outcome measure. Such parallel designs, emphasizing rate of change, have been adopted in studies of other neurodegenerative disorders, such as Alzheimer's disease (AD). Ninety of the 300 subjects had a lumbar puncture at baseline visit; 63 had a second lumbar puncture at month 2. No effect on prostaglandin levels were identified with treatment, but inclusion of this measure illustrates the desire to integrate biomarkers into clinical trials of neurodegenerative diseases. This trial had all of the three elements deemed necessary to establish disease-modifying effects of a candidate therapy: (1) evidence of efficacy in a validated animal model of ALS; (2) incorporation of a biomarker into the clinical trial, and (3) clinical trial design with measures relevant to disease progression (e.g. change in rate). Despite these well-motivated choices, the therapeutic intervention appears not to provide therapeutic benefit. One challenge with studies of this type, is the choice to study a single dose. At the end of the study, one is left with uncertainty regarding whether the lack of efficacy

was related to choice of dose below the therapeutic level or due to the lack of a meaningful impact on the disease process regardless of dose. How best to conduct dose-finding in slowly progressing diseases where trial duration is likely to be 12–18 months is an unresolved challenge in the development of drugs for neurodegenerative diseases.

De Carvalho & Swash (2006) suggest one potential strategy for shortening the duration of preliminary testing for potential therapeutic agents in ALS. They showed that a subgroup of patients with rapid progression of ALS could be identified; clinical trials of such patients would require a shorter duration of time to demonstrate drug-placebo differences. This strategy might be particularly applicable in Phase II proof-of-concept and dosing studies. A repetition of the results in a more unselected representative population would then follow in Phase III.

## Parkinson's Disease

Investigators and patients are eager to identify disease-modifying agents in Parkinson's disease (PD) as well as other neurodegenerative disorders. Palhagen *et al.* (2006) reported the results of a 7 year double blind placebo control trial of patients with new onset PD. There was an initial period of monotherapy with selegiline and a later phase of combination treatment with levodopa. Patients on selegiline had a better therapeutic outcome in both phases of the study. Selegiline may have symptomatic effects in PD that could explain some of these findings but the benefits seen in the long-duration portion of this study make it less likely that the benefits observed are strictly symptomatic in nature. This study was of unusually long duration (7 years); it used a straightforward drug-placebo comparison at end-point to determine therapeutic benefit of selegiline. No biomarker was incorporated into the study to help validate the disease-modifying effect.

There is enthusiasm for neurorestorative approaches in the treatment of PD with either fetal-nigral transplantation or use of nerve growth factor to maintain dopaminergic cell viability. A recently reported trial of cell line derived neurotrophic factor (GDNF) found no benefit after 6 months of therapy. There was a significant difference in favor of GDNF in  $^{18}\text{F}$ -dopa influx as measured on positron emission tomography (PET). This biological difference was not reflected in any clinical benefit (Lang *et al.*, 2006).

Two trials attempted to treat cognitive aspects of PD. Modafinil (Ondo *et al.*, 2006) was used in a double blind placebo controlled trial of daytime somnolence in PD, and the nicotinic agonist SIB-1508Y was tested for its possible cognitive-enhancing potential. Neither study identified a treatment benefit. A double blind placebo control trial of melatonin found only a 10-minute improvement in sleep time with 50 mg of melatonin, although there was an improvement in subjective sleep disturbance (Dowling *et al.*, 2005).

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There has been progress in developing new formulations for the administration of dopaminergic therapy in PD. A transdermal delivery system has been developed for the dopamine receptor agonist rotigotine (Babic *et al.*, 2006). Transdermal delivery systems are becoming increasingly popular with emerging applications in AD and PD dementia, along with established indications in pain, hormonal therapy, smoking cessation, motion sickness, and delivery of cardiac agents.

A critical aspect of conducting randomized clinical trials is to understand better the patient population that is willing to engage in these critical experiments. Kim *et al.* (2006) studied patients with PD who either would or would not participate in a hypothetical Phase I gene transfer study. The investigators concluded that the decision to participate in this type of controlled trial would depend mostly on patient attitudes regarding risk, optimism about science, and action orientation rather than on functional, clinical or demographic characteristics. This study provides insight into patient motivations to participate in clinical trials.

### Stroke

In the past year, advances in both the medical and surgical management of stroke have been reported (Lees *et al.*, 2006). As in other neurological disorders, there is a great desire to find neuroprotective compounds that would reduce permanent injury following ischemic stroke. In a large randomized double blind placebo control trial (1722 patients with acute stroke), intravenous NYX-059 produced significant benefit compared to placebo on the modified Rankin score of post-stroke disability. There was no concomitant improvement in the National Institutes of Health Stroke Scale. There was a lower incidence of hemorrhagic transformation and intracranial hemorrhage in patients receiving NXY-059. This was a promising beginning for a potential neuroprotective compound although further studies failed to establish a drug-placebo difference. Further studies of related agents are warranted.

In a large study of patients with greater than 50% carotid stenosis and symptoms of cerebrovascular disease, clopidogrel plus aspirin, was found to be significantly more effective than aspirin alone in reducing asymptomatic microemboli detected by transcranial doppler (Markus *et al.*, 2005). There were an insufficient number of cerebrovascular events to allow statistical analysis of this outcome. This trial is interesting in several ways. First, it is a trial of two active therapies without a placebo control group – a strategy that is necessary where placebo interventions might place patients at substantial risk. Second, transcranial doppler was used as a surrogate marker to evaluate anti-platelet therapy and provided preliminary evidence of differential benefit in patient populations too small to have enough clinical events to demonstrate therapeutic superiority of one intervention over the other.

Intracerebral hemorrhage has been the most treatment resistant of all forms of stroke. In a double blind placebo controlled trial of three doses of recombinant

activated factor VII (40 µg/kl, 80 µg/kl or 160 mg/kl) administered within 1 hour of a baseline computed tomogram, all treatment groups had less growth of the hematoma compared to those receiving placebo. Reduced mortality and improved functional outcomes at 90 days were evident despite a small increase in the frequency of thromboembolic events (Mayer *et al.*, 2005). This study suggests that acute intervention in intracerebral hemorrhage can result in limiting the growth of the intracranial clot and limit mortality and morbidity. It is notable that only 12% of candidate patients with intracerebral hemorrhage (199 of 1636) were enrolled at the 38 study sites that collected complete screening data. These figures show the difficulty of conducting this type of research where acute intervention is required.

There have been relatively few studies comparing neurosurgical approaches to the treatment of neurological and neurovascular disorders. In one such study, 2143 patients with ruptured intracranial aneurysms were randomly assigned to neurosurgical clipping or endovascular coiling. There was a greater likelihood of independent survival in year one, continuing for at least 7 years after endovascular coiling compared to neurosurgical clipping (Molyneux *et al.*, 2005). The risk of late re-bleeding was low but more common after coiling.

A problem that challenges investigators determined to find neuroprotective therapies for stroke patients is how best to identify the most promising therapeutic candidates given the large number of potential therapies that emerge from pre-clinical studies. Futility studies offer one potential mechanism for identifying such candidate therapies (Palesch *et al.*, 2005). In this approach, the proportion of positive outcomes in a single treated group is compared with a minimally worthwhile success rate sufficient to warrant additional testing of the agent. Using this strategic design, agents can more quickly be tested and those likely to be futile eliminated from undergoing future trials. The purpose of futility trials is to identify agents not likely to be of therapeutic benefit when tested in larger more conventional Phase II and Phase III clinical trials. Retrospective application of the methodology to agents which had progressed to Phase III showed a good fit between the predictive capacity of futility trials and actual Phase III results. Futility trials are being applied in other therapeutic situations including attempts to find treatments for PD (see Ravina, this volume).

## Multiple Sclerosis

Multiple sclerosis (MS) is an active area of therapeutic research in neurological disorders. Magnetic resonance imaging (MRI) has been integrated into MS clinical trials. More successfully than into trials for treatment of other disease states. Use of this imaging approach provides insight into how biomarkers might be used in other clinical settings. Examining data from seventeen clinical trials, Barkhof *et al.* (2005) showed that T2 burden of disease added to the predictive value offered by

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clinical factors for gadolinium enhancement of MS lesions. Gadolinium enhancement is often used in trials to assist in the evaluation of efficacy of new drugs. This study imposes understanding of the predictors of gadolinium enhancement.

Massacesi *et al.* (2005) used measures of gadolinium enhancing brain lesions to show that azathioprine is effective in reducing new brain inflammatory lesions in MS.

Most immuno-modulatory agents currently available for treatment of MS involve subcutaneous or intramuscular injections that challenge compliance. A double blind placebo controlled trial of two doses of oral teriflunomide reduced gadolinium enhancing lesions on MRI, as well as T2 lesions per scan and new T2 lesions. There was a trend toward lower annualized relapse rates and lower relapsing rate in the treatment group. Significantly fewer patients receiving high dose of teriflunomide demonstrated an increase in disability. This Phase II trial represents a preliminary step in establishing an effective oral therapy for immuno-modulatory treatment of MS.

There have been few studies of the effect of ethnicity on therapeutic results. Cree *et al.* (2005) observed that African American subjects experience more exacerbations and are less likely to remain exacerbation free after initiation of treatment with interferon beta 1-a. It is not clear if this represents a difference in disease activity or therapeutic response, but the observation warrants further investigation. Ethnicity might be considered as an outcome- influencing variable in other studies.

Another oral therapy for MS that has undergone testing in a recent double blind placebo controlled trial is fingolimod (FTY72) (Kappos *et al.*, 2006). Two hundred fifty-five patients received either placebo or oral fingolimod at a dose of 1.25 mg or 5 mg daily. Those receiving fingolimod evidenced fewer gadolinium-enhancing lesions on MRI and a lower annualized relapse rate. Clinically asymptomatic elevations of alanine aminotransferase levels were more frequent in those receiving active therapy. One case of reversible encephalopathy occurred in the highdose fingolimod treatment group. This and related compounds deserve further investigation as potential oral therapy is for MS.

### Alzheimer's Disease and Related Dementias

Current therapy for AD involves use of cholinesterase inhibitors and memantine. Cholinesterase inhibitors have traditionally been indicated for use of patients in mild to moderate AD – those who's Mini Mental State Examination (MMSE) scores are 10 and above. Recently, donepezil, was shown to be effective in patients with severe AD (Winblad *et al.*, 2006). The US Food and Drug Administration (FDA) reviewed this and additional documentation and has approved donepezil for treatment in severe AD as well as for patient with mild to moderate dementia with AD.

An investigation of the efficacy of rivastigmine in patients with PD dementia showed that this agent improved global function, cognition, activities of daily living,



and behavior compared to placebo. Rivastigmine received FDA approval for treatment of PD dementia (Emre *et al.*, 2004).

Memantine was relatively recently introduced to the therapeutic armamentarium for AD. Reisberg *et al.* (2006) reported an open label extension of a 28-week randomized double blind, placebo controlled trial of memantine in patients with moderate to severe AD. Compared to their baseline, patients switched from placebo to active treatment evidenced functional, global and cognitive improvement relative to the decline had they experienced on placebo. The completion rate for the extension study was 78% with a favorable adverse event profile. This study suggests that patients delayed in treatment onset will experience improvement when treated with memantine and that patients on long-term therapy continue to benefit from treatment. The additional safety and tolerability safety information suggest that this agent has a benign safety and side-effect profile. The limitations of open label studies must be borne in mind when interpreting these results. Open label extensions involve patients who are tolerant of the agent and may include a disproportion number who have benefited from treatment. In addition, the open label nature of the study makes it difficult to draw efficacy conclusions (Cummings, 2006).

A treatment goal in dementia is to identify and concentrate on outcomes that are meaningful to individual patients. This individualization of therapeutic outcomes may be difficult to achieve but has been codified in the methodology known as “goal attainment scaling”. Rockwood *et al.* (2006) applied this technique in a study of galantamine for the treatment of AD. In a randomized placebo controlled trial, clinician-rated goal attainment scaling significantly distinguished the treated from the placebo group. The patient-caregiver goal attainment scaling did not distinguish the two treatment groups. Traditional outcome measures, including the Alzheimer’s Disease Assessment Scale Cognitive portion and the Clinician Interviewed-Based Impression of Change with caregiver input were significantly better in those receiving galantamine than in those receiving placebo at the end of the trial. This study presents an interesting new approach to attempting to expand the range of treatment outcomes relevant to dementia therapeutics.

## Epilepsy

A clinical trial question that crosses many therapeutic interventions regards whether to use fixed or flexible dose approaches. In a unique trial, Elger *et al.* (2005), assigned patients to either placebo, fixed dose of pregabalin, or a flexible dose of pregabalin for twelve weeks. In the flexible dose arm, dosage could be adjusted based on tolerability. Both pregabalin regimens significantly reduced seizure frequency compared to placebo and the reduction was greatest in the fixed dose groups. Discontinuation rates also were higher in the fixed dose group. This

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suggests that there may be an efficacy–tolerability trade-off. Patients in the fixed dose arm received higher doses and achieved better seizure control, however they had significantly more side-effects and more discontinuations associated with adverse effects. These data may help structure future clinical trials particularly with agents where side-effects are common.

**Searching for New Indications for Old Agents**

An often effective strategy for developing new treatments is to use compounds approved for other therapeutic indications. This approach has advantages in that the tolerability and safety of the agent is established prior to clinical trials, and in many cases dosing decisions also can be based on existing information. Thus developing new indications for from existing therapies entails less risk and expense than developing novel therapeutic approaches. In the recent past, these have been several studies of existing agents in new therapeutic settings. Levetiracetam, an antiepileptic agent, was found in a short-term open label trial to reduce chorea in patients with Huntington's disease (de Tommaso *et al.*, 2005). Similarly, an open label trial of riluzole, an antiglutamatergic agent, used for the treatment of ALS, led to lower anxiety levels in patients with generalized anxiety (Mathew *et al.*, 2005). These preliminary open label studies warrant follow-up with double blind placebo controlled trials.

A blinded controlled trial of pregabalin for generalized anxiety disorder showed that two doses of pregabalin (400 mg per day and 600 mg per day), as well as venlafaxine, produced significant improvement in Hamilton Anxiety Scale scores compared to placebo (Montgomery *et al.*, 2006). Patients on pregabalin 400 mg per day experienced significant improvement in all primary and secondary outcomes included in the trial. Discontinuation rates were lower in the placebo group and highest in the venlafaxine group.

A randomized placebo controlled trial of sertraline showed that this selective serotonin reuptake inhibitor typically used for the treatment of depression and anxiety was effective for reducing symptoms of night eating syndrome (O'Reardon *et al.*, 2006). Measures showing significant improvement included clinical global severity ratings, quality of life ratings, frequency of nocturnal eating and awakenings, and caloric intake after the evening meal.

**Schizophrenia**

Attrition rates have been a consistent challenge to data generalization in studies of antipsychotic drugs; discontinuation rates frequently approach 50% in placebo controlled trials. Kemmler *et al.* (2005), compared attritions in active control trials where the agent of interest is compared with an existing antipsychotic treatment



to attrition in placebo-controlled trials. Discontinuation in placebo-controlled trials was significantly more common than in active controlled trials (48.1% versus 28.3%). The interaction between placebo control and attrition should be borne in mind when constructing antipsychotic drug trials.

The cognitive component of schizophrenia is an increasingly important object of study (see Kern chapter on MATRICS, this volume). Bender *et al.* (2006) examined the cognitive effects of olanzapine compared to clozapine in a randomized active controlled trial using executive function as the principal cognitive outcome measure. Improvements were seen in all measures of executive function, including the Stroop Color-Word Test, Tower of London, and Wisconsin Card Sorting Test. Improvement was independent of effects on positive symptoms and extrapyramidal side-effects. This suggests that atypical antipsychotics may benefit executive function.

The role of *N*-methyl-D-aspartate (NMDA) function in schizophrenia has been a source of consistent interest. Agents that enhance NMDA receptor function through the glycine modulatory site (e.g. D-serine) or through the glycine transporter (e.g. sarcosine) have been shown in previous studies to improve the symptoms of patients with chronic stable schizophrenia. In a randomized double blind placebo controlled trial of D-serine, sarcosine and placebo, Lane *et al.* (2005) found that sarcosine produced greater reduction in the Positive and Negative Syndrome Scale (PANSS) than placebo or D-serine. Similar results were found for the Scale for the Assessment of Negative Symptoms (SANS). This study was unique in involving patients in an acute exacerbation of schizophrenia rather than patients with stable chronic disease. The findings suggest that sarcosine may be superior to D-serine in patients with acute relapses. The study further supports the growing body of evidence suggesting a role for NMDA receptors in schizophrenia.

### **Obsessive–Compulsive Disorder**

Simpson *et al.* (2006) studied clomipramine, exposure/ritual prevention plus clomipramine, and exposure/ritual prevention placebo and placebo in patients with obsessive-compulsive disorder. In this trial, exposure/ritual prevention led to a superior treatment outcome compared to clomipramine alone or placebo. An important aspect of this study is that the authors studied four separate definitions of response to treatment and three definitions of remission in the course of examining their treatment outcomes. They proposed a standard definition of response (at least 25% decrease on the Yale–Brown Obsessive–Compulsive Scale) and remission (a total score of  $\leq 12$  for at least 1 week on the Yale–Brown Obsessive–Compulsive Scale). Standardization of response and remission definitions will assist future studies of obsessive–compulsive disorder.

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**Summary**

Advances in pharmacotherapy and clinical trial design promise to improve drug development strategies and therapeutic outcomes in patients with a variety of neurologic and psychiatric illnesses.

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