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ABSTRACT

There has been continuous progress in neurotherapeutics and neuropsychopharmacology in the past year. Notable are the reports of successful preliminary disease-modifying trials in Niemann-Pick disease and Friedreich’s ataxia. Progress also has been made in treatment of migraine, stroke, epilepsy, multiple sclerosis, traumatic brain injury, and pain. Biomarkers are increasingly used to establish proof of pharmacology including measures of cerebrospinal fluid constituents and brain changes on magnetic resonance imaging. There is an increasing diversity of patient populations participating in clinical trials, including pediatric migraine and traumatic brain injury.

Key words: argatroban, atorvastatin, biomarkers, bipolar depression, clinical trials, deep brain stimulation, depression, disease modification, duloxetine, epilepsy, fingolimod, Friedreich’s ataxia, glatiramer acetate, Huntington’s disease, idebenone, methylphenidate, Miglustat, migraine, modafinil, multiple sclerosis, neuropathic pain, nicardipine, Niemann-Pick Type C disease, Parkinson’s disease, pharmacogenetics, pregabalin, retigabine, riluzole, rivastigmine, rizatriptan, schizophrenia, spinal cord injury pain, testosterone, tramiprosate, transcranial magnetic stimulation, traumatic brain injury, zolmitriptan, zonisamide.

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Neurologic and psychiatric disorders are among the most common afflictions of human kind and continue to produce enormous disability globally. It is incumbent on the scientific community to search for means to relieve of neurologic and psychiatric disorders, to improve understanding of disease mechanisms, and to enhance neuropsychopharmacology. There continue to be advances in neurotherapeutics based on an improved understanding of disease mechanisms and improved access to tractable therapeutic targets. Progress in neurotherapeutics in neuropsychopharmacology 2008 captures some of the recent advances in the treatment of neurologic and psychiatric illnesses.

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Disease-Modifying Therapies

Niemann-Pick Type C disease is an inherited neurodegenerative disorder with an intracellular lipid trafficking defect leading to accumulation of glycosphingolipids. It heretofore has been an untreatable progressive neurodegenerative disorder. Based on understanding of glycosphingolipid synthesis, a new agent capable of ameliorating the synthetic process was tested in a clinical trial. Miglustat was tested in 29 patients randomly assigned to receive active treatment or standard care for 12 months in a phase IIa proof-of-concept (CPOC) trial. The primary outcome measure was horizontal saccadic eye movement velocity, chosen because of its correlation with disease progression. At study termination patients receiving miglustat had improved eye movement velocity as well as improved swallowing, stabilization of auditory function, and slower deterioration in ambulation. Adverse events included diarrhea, flatulence, weight loss, and abdominal pain. This study represents one of the first successful interventions in a neurodegenerative disease with a disease-modifying therapy (Patterson et al., 2007).

Use of Idebenone to treat patients with Friedreich’s ataxia also suggested an ability to intervene in a neurodegenerative disease. Forty-eight patients with Friedreich’s ataxia were randomized to active treatment or placebo in a 6-month double-blind trial. The primary endpoint was a biological marker indicative of oxidized DNA damage; secondary endpoint included clinical ratings. At trial termination there was no difference in the biological marker. An overall analysis showed no clinical impact. A pre-specified analysis excluding patients who required wheelchair assistance showed a significant clinical improvement with a dose–response relationship (Di Prospero et al., 2007). The results are sufficiently promising to warrant further investigation of idebenone and other potent anti-oxidants.

A neuroprotective trial of riluzole in Huntington’s disease in a 3-year randomized trial involving 379 patients found no benefit of treatment (Landwehrmeyer et al., 2007).

Cerebrovascular Disease

Recent trials have improved our understanding of optimal treatment of patients with various types of cerebrovascular disease. A comparison of oral anticoagulant therapy with aspirin showed that oral anticoagulants are not more effective than aspirin for secondary prevention after transient ischemic attacks or minor stroke of arterial origin (ESPRIT Group, 2007).

Greater benefit in stroke prevention was observed in a double-blind placebo-controlled trial of atorvastatin after stroke or transient ischemic attack in secondary stroke prevention. The reduction in stroke risk was 3.5% (statistically significant) (SPARCL, 2006).
Sugg et al. (2006) provide preliminary evidence on a small number of patients suggesting that low dose argatroban combined with intravenous rtPA may produce greater recanalization following stroke than use of rtPA alone. This trial is discussed in detail in this volume.

A double-blind trial of nicardipine prolonged release implants in patients with aneurysmal subarachnoid hemorrhage suggests that the incidence of vasospasm and delayed ischemic deficit was reduced with treatment (Barth et al., 2007).

**Parkinson’s Disease**

There has been substantial activity in the development of new symptomatic therapies for Parkinson’s disease. There has been particular interest in the testing of a transdermal therapy, rotigotine. Two studies (Giladi et al., 2007; Jankovic et al., 2007) assessed the efficacy of transdermal rotigotine in early Parkinson’s disease. In both double-blind placebo-controlled trials, patients on rotigotine had improved motor performance compared to patients receiving placebo. The most common adverse events observed were site reactions, nausea, and somnolence. In a third study, rotigotine was compared with pramipexole to assess the impact on motor fluctuations in patients with advanced Parkinson’s disease and wearing-off type motor functions. Rotigotine was shown to be non-inferior to pramipexole (Poewe et al., 2007). These studies demonstrate that transdermal rotigotine offers a viable alternative to oral medications for patients with both early and advanced Parkinson’s disease.

A prolonged release form of ropinirole was assessed in a double-blind placebo-controlled trial. Compared to patients receiving placebo, those on prolonged release ropinirole were able to reduce their daily dosage of levodopa and had reductions in daily “off” time. There was improvement of a variety of secondary outcome measures including time “on”, dyskinesias, activities of daily living, depression, and sleep quality (Pahwa et al., 2007). A similar study compared “on” time in patients receiving entacapone to those receiving placebo (Mizuno et al., 2007). Both entacapone doses (100 mg or 200 mg administered with levodopa) were equally efficacious and superior to placebo. The most common adverse event observed was an increase in dyskinesias. These two strategies are alternatives for reducing “off” time and improving “on” time for patients with advanced Parkinson’s disease.

Murata et al. (2007) explored the utility of zonisamide in improving motor function in patients with Parkinson’s disease. Improved motor function and diminished “off” time was observed with both zonisamide dosage groups (50 mg and 100 mg) compared to placebo. Dyskinesia was not higher in the zonisamide treated patients. The authors concluded that zonisamide is a useful adjunctive therapy to levodopa in Parkinson’s disease patients with suboptimal therapeutic responses.

Deuschl et al. (2006) conducted a randomized trial of deep brain stimulation for Parkinson’s disease. They showed that compared with medication management
alone, those with deep brain stimulation had improvement on measures of mobility, activities of daily living, emotional well being, stigma, and bodily discomfort. There were more serious adverse events in the neurostimulation group including one fatal intracerebral hemorrhage. Deep brain stimulation offers an alternative to medication-resistant patients, but patient selection must be scrupulous and installation of stimulation devices should be confined to highly experienced centers and neurosurgeons.

Another study investigated the utility of deep brain stimulation in patients with early Parkinson’s disease (Schupbach et al., 2007). In an unblinded comparison study where matched pairs of patients were randomly assigned to either deep brain stimulation or medication management; improvement in quality of life was shown in those receiving surgical management; and there was no improvement in motor function after 18 months of therapy. This provocative study suggests that consideration of deep brain stimulation earlier in the course of Parkinson’s disease is warranted.

**Epilepsy**

In a study comparing early versus delayed anti-convulsant therapy in patients whose physicians were uncertain as to whether or not to intervene with anti-epileptic drugs, carbamazepine as monotherapy was strongly associated with a delay of seizure recurrence; there was mixed evidence for an effect of valproate (Marson et al., 2007).

Three doses of retigabin were compared to placebo in a multiarm double-blind placebo-controlled trial of patients with partial seizures. Doses compared to placebo were 600, 900, and 1200 mg/day. Median percent change in seizure frequency from baseline was −23%, −29%, and −35%, respectively compared to −13% for placebo. Treatment-emergent adverse events included somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia. The study suggests that retigabin is an effective adjunctive therapy and reduces the frequency of partial onset seizures. Side effects must be carefully monitored (Porter et al., 2007).

Hessen et al. (2007) executed a double-blind placebo-controlled withdrawal study of patients who had been seizure free for at least 2 years and were on monotherapy with an anti-convulsant. Those in the discontinuation group improved on tests that require complex cognitive processing under time pressure. Simple tasks of attention and reaction time revealed no significant differences between the discontinuation group and the non-discontinuation group. The results suggest that patients who had been seizure free for at least 2 years and are on monotherapy may experience cognitive benefits with anti-convulsant withdrawal.

Transcranial magnetic stimulation is gaining in popularity as a treatment for epilepsy. Fregni et al. (2006) treated 21 patients with malformations of cortical development and refractory epilepsy with five consecutive sessions of low frequency repetitive transcranial magnetic stimulation. This was a randomized
double-blind sham-controlled trial. Those receiving active transcranial magnetic stimulation experienced a significant decrease in the number of seizures compared to those receiving sham therapy. The effect persisted for 2 months. Adverse events were limited. This preliminary study suggests that repetitive transcranial magnetic stimulation may represent an important alternative to medication management in certain classes of epilepsy patients.

**Multiple Sclerosis**

Glatiramer acetate was studied in both primary progressive multiple sclerosis and relapsing remitting multiple sclerosis in recent double-blind placebo-controlled trials. Cohen et al. (2007) found a trend favoring the 40-mg group over placebo on the primary endpoint of gadolinium-enhancing lesions on magnetic resonance imaging (MRI) at months 7, 8, and 9. There was also a trend favoring the 40-mg group for relapse rate and proportion of relapse-free subjects. Overall tolerability was acceptable with higher injection site reactions and immediate post-injection reactions with 40 mg compared to 20 mg. The results suggest but do not prove that the 40-mg dose will be more beneficial compared to the 20-mg dose for patients with relapsing remitting disease.

The study group led by Wolinsky et al. (2007) failed to demonstrate a significant treatment effect of glatiramer acetate on primary progressive multiple sclerosis. The low event rate and premature discontinuation of study medication decreased the power to detect a treatment effect.

A phase II study of intravenous synthetic peptide MBP8298 in a 24-month double-blind placebo-controlled trial showed no drug-placebo difference on the expanded disability status scale in the analysis of all patients. A contingency analysis in an HLA class 2 sub-group showed a statistically significant benefit of therapy compared to placebo in those with HLA haplotypes BR2 or DR4. The apparent benefit was sustained in long term (5 year) follow up. The study suggests that it may be possible to define responsive sub-groups of patients with progressive multiple sclerosis who benefit from treatment with this intravenous synthetic peptide.

Oral fingolimod (FTY720) was tested in a proof-of-concept (POC) study in relapsing remitting multiple sclerosis (Warren et al., 2006). In the 6-month double-blind placebo-controlled portion of the trial there was a benefit to fingolimod in terms of gadolinium-enhancing MRI lesions and annualized relapse rate for both doses of the active agent (0.125 and 5 mg/day). The benefit continued to be evidenced in the open label extension portion of the study. Adverse events included nasopharyngitis, dyspea headache, diarrhea, and nausea; 10% of patients had asymptomatic elevations of liver enzyme levels. The authors concluded that the results were sufficiently promising that the agent warrants further study.
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Sicotte et al. (2007) tested the hypothesis that men with multiple sclerosis might benefit from treatment with testosterone supplementation. They showed in a crossover design with a 6-month treatment period that men receiving testosterone gel evidenced improved cognitive performance and slowing of brain atrophy. There was no effect of testosterone treatment on gadolinium-enhancing lesions or lesion volume. Testosterone was well tolerated.

**Traumatic Brain Injury**

Rivastigmine, a cholinesterase inhibitor commonly used in Alzheimer disease, was assessed in a double-blind placebo-controlled 12-week trial in patients with traumatic brain injury and persistent cognitive deficit (Silver et al., 2006). Rivastigmine did not perform better than placebo in overall analysis, but sub-group assessment suggested improved memory in those with moderate to severe memory impairment at baseline. Further investigation of the use of cholinesterase inhibitors in traumatic brain injury is needed.

Treatment with methylphenidate of patients with severe and moderate traumatic brain injury has showed that patients receiving active treatment on admission had shorter ICU and hospital lengths of stay compared to patients receiving placebo. Patients with severe traumatic brain injury had reductions in both ICU and hospital length of stay, whereas patients with moderate brain injury had reductions in ICU length of stay only (Mocin et al., 2006).

**Complications of Spinal Cord Injury**

Pregabalin was shown to be effective in relieving central neuropathic pain in patients with spinal cord injury (Siddall et al., 2006). Conclusions were based on a randomized double-blind placebo-controlled trial of flexible dose pregabalin (150–600 mg/day). Pain, disturbed sleep, and anxiety were all improved in patients receiving pregabalin therapy.

The international campaign for cures of spinal cord injury paralysis has provided recent guidance on the conduct of clinical trials in patients with spinal cord injury (Steeves et al., 2007; Fawcett et al., 2007).

**Migraine and Cluster Headaches**

There has been increased attention to treating neurological disorders in children. Rizatriptan was shown in a double-blind placebo-controlled trial to relieve migraine attacks in children ages 6–17 years (Ahonen et al., 2006). Rizatriptan was well tolerated and no serious adverse events were observed in the trial.

A randomized trial of intranasal zolmitriptan was shown to relieve acute cluster headache within 30 minutes of intranasal administration (Cittadini et al., 2006). Ninety-two patients were included in the randomized trial. No serious
adverse events were observed; shortness of breath, vomiting, and rheumatic pain occurred in the group receiving intranasal zolmitriptan.

**Neuropathic Pain**

Duloxetine is a selective serotonin reuptake inhibitor of serotonin and norepinephrine. It has been shown to reduce depression. Wernicke et al. (2006) performed a randomized placebo-controlled trial of patients with diabetic peripheral neuropathic pain. Duloxetine was shown to be superior to placebo and had a rapid onset of action. Reductions in pain were approximately 15% in the placebo group and approximately 50% in the duloxetine-treated group.

**Schizophrenia**

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study sponsored by the National Institute of Mental Health continues to provide interesting and provocative observations into the real-world management of schizophrenia. Swartz et al. (2007) measured quality of life as an outcome for treatment with first- and second-generation antipsychotics – olanzapine, perphenazine, quetiapine, risperdone, ziprasdone, for up to 18 months. All antipsychotic treatment groups in all phases of the trial made modest improvements in psychosocial functioning as measured with the quality of life scale analysis. There were no differences among the pharmacologic agents in producing this response.

In another trial addressing possible treatment differences among therapeutic approaches, Lindenmayer et al. (2007) found a significant improvement in negative symptoms in patients treated with olanzapine compared to those treated with haloperidol. There were no treatment differences in positive symptoms, general psychopathology, or depressive symptoms.

A randomized double-blind placebo-controlled trial of modafinil for negative symptoms of schizophrenia (Pierre et al., 2007) failed to establish a benefit of modafinil for negative symptoms.

**Depression**

Two recent double-blind placebo-controlled trials addressed means of reducing relapse in patients with major depressive disorder. In both studies patients were treated for 1 year following a recovery from an acute depressive episode. Amsterdam & Bodkin (2006) showed that transdermal selegiline was significantly better than placebo in preventing depression relapse. Similarly, Kornstein et al. (2006) demonstrated that escitalopram maintenance treatment also was significantly better than placebo in reducing recurrent depression.
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Corya et al. (2006) compared an olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in patients with treatment-resistant depression. All interventions were similarly effective at study endpoint. The olanzapine/fluoxetine combination showed a more rapid onset of anti-depressant action.

Bipolar depression was also the subject of investigation. Sachs et al. (2007) showed that the use of anti-depressant medication as compared to the use of mood stabilizers was not associated with increased efficacy or with increased risk of treatment-emergent affective switching. Patients receiving a mood stabilizer plus adjunctive anti-depressant therapy had similar outcomes to patients receiving a mood stabilizer only.

The anti-depressant venlafaxine also was shown to be effective in reducing symptoms of post-traumatic stress disorder in a 24-week double-blind placebo-controlled trial (Miller et al., 2007).

**Incorporation of Biomarkers into Clinical Trials**

MRI was used in a 2-year placebo-controlled trial of natalizumab. Nine hundred and forty-two patients with relapsing remitting multiple sclerosis were included in the trial. Relapse rates were reduced by 68% and progression of disability by 42%. MRI showed a 92% decrease in enhancing lesions, an 83% decrease in new or enlarging hyperintense lesions, and a 76% decrease in new hypointense lesions over 2 years (Miller et al., 2007). This study shows a utility of including MRI monitoring in multiple sclerosis trials.

Cerebrospinal fluid amyloid beta protein was used as the primary outcome in a phase II tramiprosate trial (Aisen et al., 2006). Tramiprosate reduced cerebrospinal fluid a beta 42 level in a dose-dependent level over 3 months of treatment. No clinical treatment differences were seen among the treatment groups.

**Pharmacogenetics**

Genetic profiles may come to play an increasingly important role in prediction of treatment response and adverse event occurrence. In a preliminary study of this type Denys et al. (2007) analyzed responders in a trial of paroxetine and venlafaxine for obsessive-compulsive disorder. They found genotype specificity for the responder group for each medication. Larger samples and replication studies would be required to confirm such an effect, but the study is a forward-looking application of pharmacogenetics.

**Summary**

Patients with neurologic and psychiatric illness require new disease-modifying and symptom relieving medications to improve target indications and quality of life.
Advances in neuroscience are providing consistent improvements in understanding of the basic mechanisms in neurologic and psychiatric illnesses. Mechanistic understanding provides the opportunity for identification of critically vulnerable and exploitable steps in the pathogenic cascade that may surrender to therapeutic intervention. In addition to an urgent need to improve therapeutics, biomarkers that support POC studies are also required to advance clinical trials and to enhance the opportunity for success for developing new therapeutics. As shown in this and the following chapters, success is evolving in the development of new treatments for disabling neurologic and psychiatric disorders.

Disclosures

Dr. Cummings has provided consultation to the following pharmaceutical companies: Avanir, Eisai, EnVivo, Forest, Janssen, Lilly, Lundbeck, Medivation, Merck, Novartis, Ono Pharma, Pfizer, Sanofi-Aventis, and Takeda Pharmaceuticals.

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