Commentators

John Y. Fang, MD
Department of Neurology
Vanderbilt University
Nashville, Tennessee

David J. Houghton, MD, MPH
Department of Neurology
Ochsner Health System
New Orleans, Louisiana

Joohi Jimenez-Shahed, MD
Parkinson Disease Center and Movement Disorders Clinic
Baylor University
Houston, Texas

John Morgan, MD, PhD
Department of Neurology
Georgia Health Sciences University
Augusta, Georgia

Daniel Weintraub, MD
Department of Psychiatry
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Jayne R. Wilkinson, MD
Parkinson’s Disease Research, Education, and Clinical Center
Department of Veterans Affairs
Philadelphia, Pennsylvania

From the editor...

Studies of modest size and scope are challenging. When addressing questions unlikely to be soon answered by level 1 evidence from a multicenter randomized trial, the data they generate may be influential despite reservations about their limitations. By asking our commentators to address the clinical relevance of such studies, which are particularly well represented in this issue of PD Monitor & Commentary, the primary goal is to stimulate our readers to consider why they would or would not apply the conclusions to patient care.

One example is a positive study of cognitive-behavioral therapy (CBT) for treating impulse control behaviors. Dr. Daniel Weintraub of the University of Pennsylvania explains why a small, single-center study might be relevant. Conversely, Dr. John Fang of Vanderbilt University outlines the reasons to remain circumspect about early use of neurostimulation to treat PD despite positive results from a much larger study. Dr. John Morgan of Georgia Health Sciences University discusses the practical value of a driving fitness evaluation, while Dr. Joohi Jimenez-Shahed of Baylor University considers how the high risk of hip fracture relates to care of PD patients.

We round out the commentaries section with a piece on the limited value of dopaminergic drugs in treating nonmotor PD symptoms, which is provided by Dr. Jayne Wilkinson of the Department of Veterans Affairs in Philadelphia, and my own views on a study of a selegiline-to-rasagiline switch. We hope the opinions expressed provide context for clinicians to reach their own decisions.

In the Q&A section, I address what is on the horizon for treatment of PD. Finally, in “Research News Roundup,” we offer brief summaries of some of the most interesting presentations related to PD from the 65th Annual Meeting of the American Academy of Neurology, held from March 16 to 23, 2013, in San Diego, California.

Please feel free to reach me with comments or suggestions at info@delmedgroup.com.

David J. Houghton, MD, MPH
Chief, Division of Movement and Memory Disorders
Department of Neurology
Ochsner Health System
New Orleans, Louisiana
In This Issue

Commentaries

3  CBT for impulse control behaviors in PD
4  Neurostimulation for PD with early motor complications
5  Validation of a screening battery to predict driving fitness in people with PD
6  Hip fractures in people with idiopathic PD
7  Nonmotor symptoms in early PD
8  Switch from selegiline to rasagiline in patients with PD

Q&A with David J. Houghton, MD, MPH

9  What is on the horizon for treatment of PD?

Research News Roundup

10  News briefs from the 65th Annual Meeting of the American Academy of Neurology; March 16–23, 2013; San Diego, CA
Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers.

First Author and Institution:
David Okai, MRCPsych, King’s College Hospital, London, United Kingdom.

Citation:

Objective:
Test cognitive-behavioral therapy (CBT) for impulse control behaviors in Parkinson’s disease (PD) patients.

Type of Study:
Randomized controlled trial.

Result:
Relative to standard medical care, CBT reduced mean scores of impulsive behavior from the moderate to the mild level ($P < .001$) and also significantly reduced neuropsychiatric disturbances.

Conclusion:
Although larger, multisite studies are needed to validate these results, CBT appears to be an effective way to reduce impulse control behavior problems in people with PD.

Impulse control disorders (ICDs) occur in a substantial minority of Parkinson’s disease (PD) patients and have a large number of potential manifestations, including compulsive shopping, gambling, sex, and eating. The efficacy of cognitive-behavioral therapy (CBT) for treatment of ICDs in individuals without PD suggests that it may also be beneficial in this patient group.

In this study, 44 PD patients with ICDs were randomized to receive a CBT-based intervention ($n = 27$) or to be placed on a waiting list (ie, standard medical care; $n = 17$). The CBT, provided weekly for 12 sessions, followed published protocols. The coprimary outcomes in patients, evaluated on average 6 months after completing treatment, were clinician-rated Clinical Global Impression (CGI) of symptom severity and change, and the Neuropsychiatric Inventory (NPI) conducted with a structured interview. Secondary patient outcomes included evaluation of frequency and impact of impulse control behaviors, anxiety, and depression.

A total of 75% of patients receiving CBT improved on the CGI relative to baseline versus only 29% in the waitlist group. The improvement from baseline in the active treatment group was statistically significant ($P < .001$). In those receiving CBT, the mean ICD score improved from moderate to mild. NPI scores were also significantly improved ($P = .03$) in the CBT group relative to controls.

The study provides objective evidence that CBT is superior to standard medical care for reducing impulse control behaviors in PD patients. According to the authors, longer-term studies are needed to verify these benefits and better establish how and by whom CBT is best delivered.

Commentary:
Daniel Weintraub, MD
Department of Psychiatry
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

This is a helpful study. ICDs are a clinical problem in PD. Cognitive-based interventions are attractive for their potential to avoid the side effects of the pharmacologic therapies sometimes used to manage impulse control behaviors, such as antipsychotic drugs. In this study, which was well designed and well controlled, CBT demonstrated impressive benefit. Although the number of enrolled patients was limited, the degree of improved symptom control provides a reasonable justification for considering CBT in PD patients with ICDs, particularly given the low risk of complications. However, it is important to consider potential obstacles to CBT, including the logistics of such treatment. In this study, fewer than 60% of patients attended all 12 sessions. The accessibility and cost of CBT may also be problematic. While it is unclear whether a CBT counselor needs specific experience with PD patients, expertise may be important.

There are also some study limitations in terms of generalizability. One is that only half of the patients were on a dopamine agonist, which is atypical of PD patients with an ICD. Another was that patients were younger than in a representative PD population. It is also unclear why the active treatment group in a 1:1 randomized trial was 50% larger than the control group. Still, a nonpharmacologic approach for ICDs in PD patients is attractive. These results support CBT as a treatment option to consider if impulse control behaviors remain poorly controlled after adjustment of dopaminergic therapies.
Neurostimulation for Parkinson’s disease with early motor complications.

First Author and Institution:
W.M.M. Schuepbach, MD, Assistance Publique–Hôpitaux de Paris, Centre d’Investigation Clinique 9503, Institut du Cerveau et de la Moelle Épinière, Département de Neurologie, Université Pierre et Marie Curie–Paris 6 and INSERM, Centre Hospitalier Universitaire Pitié–Salpêtrière, Paris, France.

Citation:

Objective:
Determine whether neurostimulation has clinical benefit early in Parkinson’s disease.

Type of Study:
Prospective, randomized trial.

Result:
For measures of quality of life, including activities of daily living, neurostimulation was superior to medical therapy alone at the end of 2 years of follow-up.

Conclusion:
Based on the clinical advantages relative to medical therapy, neurostimulation may be a therapeutic option at a much earlier stage than that at which it is currently recommended.

High-frequency stimulation of the subthalamic nucleus has been reserved for advanced stages of Parkinson’s disease (PD) when medical therapies are no longer effective. However, the improvements in quality of life (QOL) associated with this intervention may also be relevant to PD patients at a much earlier stage.

Promising results from a pilot study prompted a multicenter trial of neurostimulation in relatively early stage PD. In this trial, 251 PD patients with a recent onset of motor complications (disease severity <stage 3 Hoehn and Yahr scale) and good cognitive and psychological function were randomized to receive bilateral subthalamic neurostimulation plus medical therapy or medical therapy alone. The primary outcome was mean change in QOL as measured with the Parkinson’s Disease Questionnaire (PDQ-39) at 2 years. Secondary outcome assessments included mobility measures using the Unified Parkinson’s Disease Rating Scale (UPDRS).

At the end of 2 years, the PDQ-39 score improved by 7.8 points in the neurostimulation group and worsened by 0.2 points in the group receiving medical therapy alone (P = .002). The differences favoring neurostimulation were highly significant for motor disability (P < .001), activities of daily living (P < .001), and levodopa-induced motor complications (P < .001). UPDRS score for severity in the off-medication condition, confirmed with blinded analysis of video recordings, improved by a mean of 16.4 points more (P < .001) in the neurostimulation group. Serious adverse events were recorded in 54.8% of the neurostimulation group versus 44.1% of those on medical therapy alone, but most resolved spontaneously in both groups.

Based on the evidence from this trial that neurostimulation improves QOL in PD patients even before disabling motor complications develop, the authors concluded that this intervention may be a beneficial treatment option for relatively early stage disease.

Commentary:
John Y. Fang, MD
Department of Neurology
Vanderbilt University
Nashville, Tennessee

This study shows that deep brain stimulation (DBS) targeting bilateral subthalamic nuclei is generally well tolerated and well accepted by PD patients at a relatively early stage (4–10 years’ duration). DBS plus medical therapy was also associated with minor improvements in motor scores compared with medical therapy alone. However, this study has many limitations that weaken the utility of the results. The mean age was under 53 years, and more than 75% of the study group was male. Thus, the study patients were younger at onset than the typical PD patient and likely more risk-tolerant. Also, no sham procedure was performed in the control arm, a source of likely bias in favor of patients randomized to surgery.

Although this study does confirm the widely held belief that DBS can provide advantages over medical therapy alone in some patients, the study would have been much more helpful if it had addressed where this intervention might fit into typical clinical practice. Specifically, while these results support earlier use of DBS, more information is needed to understand its role relative to other options along the trajectory of disease progression. The study also did not address the issue of cost effectiveness, which is also an important concern about this very expensive treatment option.
Validation of a screening battery to predict driving fitness in people with Parkinson’s disease.

First Author and Institution:
Hannes Devos, PhD, Katholieke Universiteit Leuven, Leuven, Belgium.

Citation:
Movement Disorders. 2013 Feb 23 [Epub ahead of print].

Objective:
Validate screening test battery for driving fitness in patients with Parkinson’s disease (PD).

Type of Study:
Prospective, uncontrolled study.

Result:
For predicting those who passed a government driving evaluation, this battery of tests provided a high degree of sensitivity but a modest degree of specificity.

Conclusion:
This clinical test battery, which does not require driving simulators, appears to be a practical tool to identify those individuals with PD who are fit to drive and those who should be evaluated further.

In practical terms, the results suggest that the battery of tests is accurate for identifying individuals fit to drive. However, some proportion of those who fail this battery of tests may still be fit to drive. For these individuals, referral for more comprehensive testing, including an evaluation with a driving simulator, may be appropriate.

As driving requires visual, motor, and cognitive skills, there is a substantial risk of misjudging driving fitness on the basis of clinical impression alone.

Commentary:
John Morgan, MD, PhD
Department of Neurology
Georgia Health Sciences University
Augusta, Georgia

Determining driving fitness in PD patients is a common challenge for which there are as yet no uniformly accepted guidelines. Objective measures are needed for counseling both patients and family members. This was a well-done study that indicates that a battery of tests conducted in the office has a high sensitivity for identifying those likely to pass a government-administered driving examination. Although specificity was not as good, a tool with reliable negative predictive value can limit the proportion of patients who are referred to centers with more comprehensive testing equipment, such as a driving simulator.

It is important to develop accurate clinical tools to assess driving fitness. While driving restrictions in patients without impairments can impose unnecessary limitations on independence and quality of life, it is important to recognize impaired driving fitness with the potential to lead to accidents. As driving requires visual, motor, and cognitive skills, there is a substantial risk of misjudging driving fitness on the basis of clinical impression alone. Objective information may also be helpful when the priorities and opinions of patients and their family members differ. Although one can argue that clinical judgment is needed to distinguish the driving fitness required for a short journey in a rural setting from that of a more complex journey on a crowded freeway, this study draws attention to the need to formally evaluate driving skills in order to help patients and families reach an informed decision.
First Author and Institution:
Richard W. Walker, MD, North Tyneside General Hospital, North Shields, United Kingdom.

Citation:

Objective:
Establish incidence and outcomes of hip fracture in patients with Parkinson’s disease (PD).

Type of Study:
Analysis of hip fracture database.

Result:
Compared to people without PD, those with PD had a higher incidence of hip fracture and less mobility after hospital discharge.

Conclusion:
These findings from a large database suggest that clinicians should consider the risks of hip fracture in people with PD and be aware of the slower recovery when these fractures occur.

It is reasonable to presume that the motor symptoms of Parkinson’s disease (PD) increase the risk of hip fracture. However, the data assessing hip fracture risk or outcome in PD patients are limited.

In this study, data prospectively collected in the National Hip Fracture Database of the Northumbria Healthcare National Health Service Foundation Trust in the United Kingdom were used to compare hip fracture incidence in those with and without PD. The database also permitted PD and non-PD patients to be compared for 30-day outcomes after hip fracture. Comparisons were age-matched.

Over the 2-year study period, the incidence of hip fracture was several times greater for those with PD relative to those without PD. Between the ages of 60 and 74 years, for example, the annual incidence of hip fracture was approximately six times as high in people with PD. Although the in-hospital experience following hip fracture was similar, PD patients with impaired mobility prior to the fracture had a longer time to discharge and greater relative mobility impairment than those without PD.

The high risk of hip fracture in PD patients deserves greater attention, according to the authors of this study. The authors also concluded that clinicians should recognize the potential for more complications from hip fracture in those with PD relative to those without PD.

Commentary:
Joohi Jimenez-Shahed, MD
Parkinson Disease Center and Movement Disorders Clinic
Baylor University
Houston, Texas

Intuitively, a higher rate of hip fractures would be expected in PD patients compared to people who do not have symptoms that adversely influence balance and mobility. The value of this article is that it has provided objective data from a reliable source using robust methodology to confirm and quantify this risk and relate it to greater morbidity.

Although an increase in fracture risk compared to non-PD patients will not be surprising to most clinicians who treat PD, the magnitude of the increase in this study was impressively large. Although the greatest difference on an age-matched analysis was among those 60 to 64 years old, with the relative risk being more than eightfold greater in PD patients, the risk remained consistently higher among those with PD across all age stratifications. This study also documented a greater risk of complications in people with PD who had disability prior to fracture compared to those without PD. This included a longer median time to discharge, a higher propensity for pressure ulcers, and a greater likelihood of being wheelchair- or bed-bound 30 days after surgical correction of the fracture.

Although it may be helpful to caution individuals with PD about the risk of hip fractures, these data may be most useful for encouraging patients to adhere to recommendations, including medication adjustment and physical therapy, aimed at reducing falls. Compliant patients may thereby find themselves in the best position to reduce their fracture risk. The study should also serve as an important reminder to clinicians about performing regular assessments of fall risk in their PD patients and implementing measures to reduce it.
Non-motor symptoms in early Parkinson’s disease: a 2-year follow-up study on previously untreated patients.

First Author and Institution:
Roberto Erro, MD, University Federico II, Naples, Italy.

Citation:

Objective:
Evaluate nonmotor symptom progression in relation to dopaminergic replacement therapy.

Type of Study:
Prospective study in consecutive patients.

Result:
A minority of nonmotor symptoms were improved with the initiation of dopaminergic replacement therapy in Parkinson’s disease (PD) patients, but most patients remained stable over 2 years of assessment.

Conclusion:
Nonmotor symptoms are very common in early-stage PD patients, but their relationship to dopamine depletion is unclear given that few of these symptoms were improved with therapy.

There has been increasing attention to nonmotor symptoms (NMS) as a contributor to adverse quality of life in Parkinson’s disease (PD), but this attention is largely confined to patients with advanced disease, even though NMS are common at the time of diagnosis. The effect of dopaminergic therapy on NMS in early stages of disease has not been well studied.

In this trial, identified as the first prospective study to evaluate the effect of dopaminergic therapy on NMS, 116 untreated PD patients were enrolled. No patient enrolled was receiving anticholinergic therapy or other agents affecting neurologic function. All participants completed the Non-Motor Symptoms Questionnaire (NMSQuest), which is a validated tool for evaluating NMS. Motor symptoms were also evaluated at baseline prior to initiation of dopaminergic therapy. While type of dopaminergic therapy was not limited, L-dopa-equivalent daily dose was calculated for each patient once therapy was initiated.

At baseline, nearly all patients (97.8%) reported NMS, including mood disorders, sexual function disorders, pain, and altered bladder function. When patients were evaluated at least 2 years after enrollment, significant changes in NMS included reductions in depression ($P = .001$) and anxiety ($P = .038$) but increases in pain ($P = .028$), weight ($P = .004$), and sexual difficulties ($P = .039$), with a trend for a significant increase in constipation ($P = .092$). Most NMS remained unchanged.

Although presence of NMS was evaluated in a yes-no format, so changes in the severity of NMS were not captured, the authors concluded that dopaminergic therapies have very limited beneficial effects on the NMS of PD patients.

Commentary:
Jayne R. Wilkinson, MD
Parkinson’s Disease Research, Education, and Clinical Center
Department of Veterans Affairs
Philadelphia, Pennsylvania

Nonmotor symptoms are a critical area of investigation in Parkinson’s disease (PD) because of their prevalence and negative impact on patient well-being and quality of life. Given that some studies have suggested that patients rate NMS as more disabling than the more characteristic motor impairments of PD, I commend the authors for exploring this essential aspect of PD care.

This observational study is useful, as it allows us to follow the natural history of these symptoms over the first 2 years on dopaminergic therapy. While slightly more NMS worsened than improved from baseline, the vast majority were unchanged. Many clinicians will not be surprised by the weight gain and worsening of sexual function in PD patients, but it is interesting that non-motor-related pain was significantly increased despite dopaminergic therapy, and that this occurred so early in the disease course. Conversely, the improvement in mood after starting dopaminergic therapy is encouraging but requires more research to interpret possible causality.

As the first 2-year prospective study to evaluate NMS early in PD, this investigation draws attention to those complaints likely to worsen early in PD despite dopaminergic therapy. For clinicians, more information is now needed on strategies that may be useful for diminishing the adverse impact of these often under-recognized and undertreated PD symptoms.
Switch from selegiline to rasagiline is beneficial in patients with Parkinson’s disease.

First Author and Institution:
Thomas Müller, MD, St. Joseph-Hospital, Berlin, Germany.

Citation:

Objective:
Evaluate efficacy and safety of switching from selegiline to rasagiline.

Type of Study:
Prospective, nonrandomized study.

Result:
After the switch from selegiline to rasagiline, which was well tolerated, there were improvements in motor symptoms, mood, and sleep with a reduction in motor complications.

Conclusion:
There are several potential explanations for the reductions in sleep disturbances and motor symptoms observed after the switch to rasagiline; double-blind confirmatory trials are needed.

Monoamine oxidase B (MAO-B) inhibitors reduce breakdown of dopamine and are commonly employed in the treatment of Parkinson’s disease (PD). Owing to differences in effects outside the MAO-B pathway, these drugs may not be interchangeable. For example, amphetamine-like metabolites are generated in the breakdown of selegiline but not rasagiline.

In this study, 30 patients who were taking a daily 7.5-mg dose of selegiline for at least 3 months were switched to 1 mg of rasagiline. Motor behavior, motor complications, and sleep were monitored along with plasma levels of L-amphetamine and L-methamphetamine for a 4-month period after the switch.

At measurement after 4 months, the switch to rasagiline from selegiline was associated with favorable changes in the Unified Parkinson’s Disease Rating Scale (UPDRS) scores for motor behavior ($P = .0098$) and motor complications ($P < .001$). There were also significant improvements in the Parkinson’s Disease Sleep Scale (PDSS) ($P < .001$) and the Hamilton Depression Scale (HAMD) ($P = .003$).

L-amphetamine and L-methamphetamine were detected in the plasma of PD patients only during selegiline therapy.

This study suggests that there may be clinically relevant differences between selegiline and rasagiline. The presence of amphetamine metabolites during treatment with selegiline but not rasagiline may explain these differences. Double-blind studies are needed to validate the observed improvements in motor scales and sleep quality.

Commentary:
David J. Houghton, MD, MPH
Department of Neurology
Ochsner Health System
New Orleans, Louisiana

This small study of 30 patients evaluated the practical notion of converting from selegiline to rasagiline in mild Parkinson’s disease (PD) (mean Hoehn and Yahr scale 2.1). These data help support the safety and tolerability of switching MAO-B inhibitors in patients being treated concomitantly with other PD medications. The study also makes the point that a conversion from selegiline to rasagiline may favorably affect the nonmotor complications of sleep or mood disruption. After 4 months of follow-up, the authors found modest improvements in motor, sleep, and mood measures. As expected, plasma L-methamphetamine was absent once patients were switched from selegiline to rasagiline.

But there are some significant limitations to this pilot study. Ratings were performed by one physician, and the open-label status confirms that the rater was not blinded. In addition, the translation to US populations may be difficult, as the treatment dose of selegiline in this study was 7.5 mg daily rather than the 10 mg daily (divided) that remains more standard. This could account for motor improvements achieved after an “upgrade” to a more beneficial treatment dose of 1 mg of rasagiline. Similarly, the interpretation of the nonmotor benefits is more difficult with dose differences in such a small study.

Rasagiline is currently undergoing additional large-scale clinical trials to better evaluate its potential effects on mood and sleep (see www.clinicaltrials.gov), so we will have more data to help support or refute the outcomes of this small study when those trials are completed. Should we find the clinical need to make a switch for our patients, it is reassuring that the conversion from selegiline to rasagiline was easily tolerated without side effects in this ordinary group of PD patients.
Question: What is on the horizon for treatment of Parkinson’s disease?

Answer: In this issue, we pick up where we left off in the Winter 2012 issue in discussing the value of clinical trials in Parkinson’s disease (PD). Now we address the second part of the story: What is on the horizon for PD?

Complex new treatments of PD can be simply divided into two primary categories: “disease management” and “disease modification.” Disease management encompasses the use of therapeutics to help control the symptoms, while disease modification holds the promise of slowing, reversing, or even curing PD itself.

Researchers are currently looking at ways to optimize disease management for several major issues in PD. Delivery systems that provide greater continuous dopaminergic stimulation should reap benefits in limiting motor fluctuations and dyskinesia. The on-off cycling of dopaminergic tone may be helped by two significant opportunities for carbidopa/levodopa. Duodopa is a carbidopa/levodopa gel infusion that continues to be studied for the US market for its benefits in off-time reduction. It is already available in other countries in Europe. IPX066 is a new extended-release formulation that may improve upon some of the inconsistencies of the absorption and action of existing extended-release carbidopa/levodopa. This new compound is being studied head to head against immediate-release carbidopa/levodopa and the combination carbidopa/levodopa/entacapone, and promising results have already emerged. Innovative delivery systems with dermal absorption and inhalation of levodopa are also being investigated.

New formulations within existing drug categories as well as those with novel potential mechanisms of action are also being aggressively pursued for disease management. Alternative dopamine agonists (pardoprunox, aplindore), novel catechol-O-methyltransferase (COMT) inhibitors (nebicapone, opicapone), and a new mono-amine oxidase B (MAO-B) inhibitor (safinamide) are being tested at various stages of safety, tolerability, and efficacy for PD. Moreover, serotonin 5-HT\textsubscript{1A} antagonists, adenosine A\textsubscript{2A} antagonists, and AMPA antagonists are being considered for on-off fluctuations, and alpha-2-adrenergic antagonists and metabotropic glutamate receptor 5 (mGluR5) antagonists may help smooth dyskinesia after it appears.

Fresh approaches to the management of nonmotor complications in PD remain more elusive. Most of the delivery systems mentioned above do include nonmotor measures as secondary outcomes. The MAO-B inhibitor rasagiline is currently in several trials to analyze its impact on cognition, mood, sleep, and gait in PD. Dopamine agonists are being studied for their possible primary effects on depression, apathy, and pain, while transcranial magnetic stimulation is also being investigated for PD-related pain. Droxidopa has been evaluated in promising studies for its use in neurogenic orthostatic hypotension.

Disease modification remains the metaphorical “Fountain of Youth” for PD treatment. The introduction of growth factors, gene therapy, and pluripotent stem cells all have the potential for offering symptomatic relief while lessening the slope of the neurodegenerative curve. Current studies that have been built on past successes include the neurotrophic factors neurturin and PYM50028, and more trials are currently being designed to test pluripotent stem cells. To date, all other studies of therapies to slow disease progression have been inconclusive at best, but research is pushing ahead at a quickened pace. Pioglitazone, isradipine, glutathione, creatine, green tea polyphenol, iron chelators, deep brain stimulation, and exercise protocols are all under examination for possible long-term benefits to slow disease progression.

The horizon for treatment of PD may not be crystal clear, but it certainly is wide. Educating ourselves and our patients about clinical trial participation keeps the PD therapeutic pipeline flowing!
Salivary gland test may diagnose PD

Testing the submandibular salivary gland may be a feasible diagnostic approach in PD, according to results of “the first study demonstrating the value of testing a portion of the saliva gland to diagnose a living person for Parkinson’s disease,” commented lead investigator Charles Adler.

Biopsies were taken from the submandibular glands and minor salivary glands in the lower lip of 15 patients with a mean age of 68 years and mean disease duration of 12 years. Abnormal Parkinson’s protein was detected in the submandibular biopsies in 9 of 11 patients (82%) who had sufficient tissue to study. Positive findings in lower lip gland biopsies were lower, but analysis is still ongoing.

“This finding may be of great use when needing tissue proof of Parkinson’s disease, especially when considering performing invasive procedures such as deep brain stimulation surgery or gene therapy,” the investigators concluded.


Tozadenant reduces “off-time” without promoting dyskinesias

Tozadenant, an oral selective adenosine A<sub>2A</sub> receptor antagonist, reduced levodopa-related end-of-dose off-time without significantly increasing dyskinesias in a phase 2 trial in 420 patients, reported C. Warren Olanow and colleagues.

Patients on stable doses of levodopa were randomized to 60, 120, 180, or 240 mg tozadenant or matching placebo twice daily for 12 weeks. Patients had at least 2.5 hours of off-time daily, with the mean off-time at about 6 hours.

At week 12, the 120- and 180-mg doses showed the greatest decreases from baseline in off-time (−1.1 and −1.2 hours, respectively; both P = .004) and significantly improved Unified Parkinson’s Disease Rating Scale (UPDRS) part III scores. UPDRS part I scores were improved with all tozadenant doses, whereas dyskinesias during “on-time” did not increase from baseline with any of the tozadenant doses.

The most common adverse events (AEs) with tozadenant were dyskinesia, nausea, dizziness, constipation, worsening PD symptoms, insomnia, and falls.


Droxidopa relieves orthostatic hypotension symptoms

In patients with neurogenic orthostatic hypotension, symptoms of dizziness/light-headedness and standing systolic blood pressure were improved with the norepinephrine pro-drug droxidopa compared with placebo, reported Stuart Isaacson and colleagues.

Patients were randomized to placebo or titrated droxidopa ranging from 100 to 600 mg three times daily for 8 weeks. After 1 week, dizziness/light-headedness and mean standing systolic blood pressure were improved (P = .008 and P = .014, respectively) relative to placebo. By week 8, these differences had lessened, showing a trend toward improvement (P = .077 and P = .414, respectively).

Fewer falls and fall-related injuries occurred in droxidopa-treated patients compared with placebo, but the difference between groups did not reach statistical significance.

The most common adverse events (AEs) with droxidopa were headache, dizziness, nausea, fatigue, and hypertension.


Pimavanserin improves several measures of PD psychosis

Pimavanserin, an inverse agonist of the serotonin 5-HT<sub>2A</sub> receptor, demonstrated efficacy across several outcome measures in PD psychosis in the phase 3-020 study, presented by lead investigator Jeffrey Cummings.

There were 199 patients randomized to 40 mg pimavanserin or placebo once daily for 6 weeks. Patients taking pimavanserin experienced significant improvement (P = .001) on the 9-item Scale for Assessment of Positive
Symptoms for Parkinson’s Disease (SAPS-PD); good motoric tolerability as measured by UPDRS parts II and III; and significant improvements in all secondary efficacy outcomes using CGI scales for Severity (P < .001), Improvement (P = .001), and Improvement responder analysis (P = .002).

Adverse events were mild to moderate, the most common being urinary tract infection (UTI) and falls. Serious AEs in pimavanserin patients included UTI (3 versus 1 with placebo) and psychotic disorder (2 versus 0 with placebo).

More than 90% of patients who completed this phase opted to continue in the ongoing open-label safety extension phase.

**Stem cell engraftment encouraging in animal model**

Engraftment of stem cell–derived neuronal cells implanted in rat and primate models was safe and showed a disease-modifying effect, according to preliminary results of a placebo-controlled in vivo study presented by study coauthor Evan Y. Snyder.

Highly pure populations of neuronal cells derived from human parthenogenetic stem cells (hpSCs) can differentiate into dopamine-producing neurons after they are implanted in the brain. In the current study of rodent and monkey models of PD, after implantation of hpSC-derived neuronal cells, dopamine levels were higher in the treated monkeys compared with the controls, and the treated rats showed improved motor symptoms indicative of cell survival, engraftment, and dopamine release. There were no dyskinesias, deformations, or tumor growth in either treated group.

“The results of our preclinical animal studies indicate that neuronal cells derived from human parthenogenetic stem cells can be a viable alternative for the treatment of Parkinson’s disease,” the investigators concluded.

**Tango dancing as treatment is effective and fun**

Learning how to the tango significantly improved disease severity, balance, and spatial ability compared with participation in a patient-centered health education program on PD management, reported lead investigator Kathleen McGee.

Over a 12-week period, 24 patients took 20 tango dancing lessons, each lasting 90 minutes and adapted for moderately impaired mobility. The 9 patients in the control group worked in pairs to parallel the partner aspect of the tango group. All patients had disease duration of 7 years and similar UPDRS motor scores (27 in controls, 28 in tango patients). Mean age was 74 years in controls and 68 years in tango patients.

UPDRS motor scores improved significantly in the tango group (P < .006) but worsened significantly in the control group (P = .03), with a difference of nearly 5 points between groups that was maintained during the follow-up period. The tango group also experienced significant improvements in balance (P = .008) and spatial cognition (P = .04). There were three noninjurious falls in tango patients out of a total of 48 classes.

Both groups strongly agreed that they enjoyed the program and would continue. Most tango patients also felt they had improved balance, coordination, walking ability, endurance, and mood, whereas control patients noted only improved mental abilities.

**Tai chi improves balance and sensory organization**

PD patients who took tai chi training two times weekly for 24 weeks had better balance and sensory organization compared with patients who participated in a stretching exercise program, according to results of a randomized trial presented by Fuzhong Li and colleagues.

While prior studies have demonstrated a correlation between tai chi and improved sensory organization, the current study examined whether tai chi could “improve sensory integration of balance responses . . . and whether improvement could be partially explained by change in limits of stability,” the investigators noted.

Patients’ performance on the Sensory Organization Test and changes in limits of stability were measured at baseline, 3 months, and 6 months. Tai chi patients had significant improvement in both measures (P < .001). Enhanced limits of stability were partly responsible for the effect of tai chi training on improving sensory organization. Tai chi participants also had modest gains in lower-body strength.
Spring 2013

Parkinson’s Disease
Monitor & Commentary

www.MonitorAndCommentary.com

Practical Analysis on Today’s Findings in Parkinson’s Disease

In This Issue:

Commentaries
• CBT for impulse control behaviors in PD
• Neurostimulation for PD with early motor complications
• Validation of a screening battery to predict driving fitness in people with PD
• Hip fractures in people with idiopathic PD
• Nonmotor symptoms in early PD
• Switch from selegiline to rasagiline in patients with PD

Q&A with David J. Houghton, MD, MPH
• What is on the horizon for treatment of PD?

Research News Roundup
• News briefs from the 65th Annual Meeting of the American Academy of Neurology; March 16–23, 2013; San Diego, CA

PD Monitor & Commentary is now available on the web at www.MonitorAndCommentary.com