VOLUME 4, NUMBER 4
WINTER 2011

Parkinson's Disease Monitor & Commentary

www.MonitorAndCommentary.com

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

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This publication has been supported by an educational grant from Teva Neuroscience.

From the editor...

ANDREW D. SIDEROWF, MD

Among the studies reviewed in this issue that look at relatively hard endpoints, such as off time and bradykinesia, we have also included a study that has placed its focus on quality of life (QOL). The main point of this study, reviewed by Dr. Lisa Shulman of the University of Maryland, is that early-onset Parkinson's disease (PD) is associated with a poorer QOL than typical onset. However, the more interesting finding is perhaps that the poor QOL is largely driven by depression rather than disability and therefore is modifiable.

Also in this issue, a phase 2 study of preladenant, an adenosine A2A receptor antagonist, allows our reviewer, Dr. Daniel Kremens of Thomas Jefferson University, to speculate about the future of the non-dopaminergic therapies in PD. Separately, a post-hoc summary of the effect of rasagiline on bradykinesia permits Dr. Lawrence Elmer of the University of Toledo to express his opinion about bradykinesia as an isolated endpoint. Dr. Kevin Biglan of the University of Rochester School of Medicine and Dentistry also weighs in on a Spanish study that indicates an elevated risk of mortality among elderly patients with PD, information that may be helpful when counseling patients about the risks of PD.

We did not ignore readers who like basic science. Dr. Michael Okun of the University of Florida reviews new evidence that the physical properties of α-synuclein have been previously mischaracterized. It may mean new targets of therapy. Finally, in reviewing a body of work in which functional dopaminergic neurons are created by reprogramming fibroblasts, Dr. Claire Henchcliffe of Weill Cornell Medical Center in New York suggests that this direction of research may well prove to be as exciting as it sounds.

In the Q&A column, Dr. Matthew Brodsky of Oregon Health & Science University discusses exercise recommendations for people with PD, while the controversy section focuses on whether placebo-controlled trials are a necessity for surgical treatments of PD. Dr. Lauren Schrock of the University of Utah says yes, while I say no. It makes for a lively discussion.

The issue offers a mix of practical and experimental work that we try to include in each issue to provide readers with a taste of current research. As always, comments and suggestions are welcome. Please feel free to reach me at info@delmedgroup.com.

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NEW: CONTROVERSIES IN PD AND Q&A WITH MATTHEW A. BRODSKY, MD

PD Monitor & Commentary

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Faculty Disclosures

Dr. Kevin M. Biglan, Dr. Matthew A. Brodsky, Dr. Michael S. Okun, and Dr. Lauren E. Schrock have nothing to disclose.

Dr. Lawrence Elmer has received honoraria for consulting and serving on Speakers' Bureaus for GlaxoSmithKline, Novartis, Teva Neuroscience, and UCB. He has received research or unrestricted educational grant support from GlaxoSmithKline and Teva Neuroscience.

Dr. Claire Henchcliffe has served on Advisory Boards for Allergan, GE Healthcare, and Teva Neuroscience, and Speakers' Bureaus for Allergan, Avanir, GlaxoSmithKline, Novartis, and Teva Neuroscience.

Dr. Daniel Kremens has received consulting fees from GE Healthcare, Merz, and Teva Neuroscience, and has served on Speakers' Bureaus for Allergan, Merz, Novartis, and Teva Neuroscience.

Dr. Lisa Shulman has received research grants from Teva Neuroscience.

Dr. Andrew D. Siderowf has received honoraria from Teva Neuroscience and consulted for General Electric and Synosia Therapeutics, Inc.

Publishing Information
Delaware Media Group, LLC
66 S. Maple Avenue, 3rd Floor,
Ridgewood, NJ 07450
Tel: 201-612-7676, Fax: 201-612-8282
Websites: www.delmedgroup.com
www.MonitorandCommentary.com

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In This Issue

Commentaries

Q&A with Matthew A. Brodsky, MD

Controversies in PD

Determining the efficacy of rasagiline in reducing bradykinesia among Parkinson's disease patients: A review.

First Author and Institution:
Dee E. Silver, MD, Coastal Neurological Medical Group, Inc., La Jolla, California.

Citation:
Int J Neurosci. 2011;121:485-489.

Objective:
Summarize findings from studies that evaluated the effect of rasagiline on bradykinesia in patients with Parkinson's disease (PD).

Type of Study:
Review of previously conducted studies.

Result:
Of three studies identified that evaluated the effect of rasagiline on bradykinesia, all three associated this therapy with significant improvements as measured with the Unified Parkinson's Disease Rating Scale (UPDRS) motor examination.

Conclusion:
The benefit of rasagiline in the control of bradykinesia, a defining symptom of PD, is reassuring. Prospective studies are needed to evaluate the benefit on patient functioning.

As a manifestation of diminished dopamine activity in the central nervous system (CNS), bradykinesia is among the characteristic symptoms of PD. It is likely but unproven that the monoamine oxidase-B (MAO-B) inhibitor rasagiline has a favorable influence on bradykinesia.

In this review, the goal was to reevaluate clinical trials with the MAO-B inhibitor rasagiline to determine its efficacy against bradykinesia. These investigators reviewed 124 abstracts, isolating three studies that evaluated the effect of rasagiline using the UPDRS movement symptoms bradykinesia subscale.

Two of the three studies evaluated, all of which were double-blind, compared 1 mg per day of rasagiline to placebo. In the third study, there were two active treatment arms—1 mg of rasagiline and 200 mg of entacapone—plus a placebo arm. In the first of the two studies with a placebo control, called TEMPO, there was a 1.51 unit reduction in bradykinesia over the course of 26 weeks for rasagiline versus placebo. In the second, called PRESTO, the UPDRS reduction was 0.89 units. In the third, called LARGO, rasagiline was associated with a 1.36 unit reduction and entacapone was associated with a 1.25 unit reduction. All differences were statistically significant relevant to placebo.

The controlled trials provide consistent evidence of statistically significant benefit from rasagiline against bradykinesia.

Commentary:

Lawrence Elmer, MD, PhD
Director, Parkinson's Disease and Movement Disorders Program
University of Toledo
Toledo, Ohio

This descriptive review emphasizes the impact of rasagiline in treating one of the cardinal features of PD—bradykinesia. Unfortunately, the authors were only able to identify three manuscripts that documented the effects of this treatment on bradykinesia, the pivotal studies known as TEMPO, PRESTO, and LARGO. Of the three, perhaps only the TEMPO study is the most relevant, as this was a comparison of rasagiline versus placebo. It is unfortunate that the much larger ADAGIO study, comparing rasagiline to placebo in early PD, did not publish the individual scores for subscales of the UPDRS in their pivotal trial report of September 2009.

The summary stresses the authors' finding that bradykinesia does indeed respond to intervention with rasagiline. The process followed for identifying potential contributing data was standard, but without unexpected conclusions. Given the sense of poor "precision" intrinsic to the UPDRS, a conclusion that rasagiline impacts bradykinesia in a statistically significant manner seems unlikely to influence or alter a treating clinician's algorithm.

Nevertheless, in our current culture resolving to "treat based on randomized clinical trial data and randomized clinical trial data alone," this consistent evidence that rasagiline is beneficial for PD symptom control should encourage physicians to consider this agent as a potentially helpful tool in their Parkinson's armamentarium. If history and studies demonstrate further that this compound has disease-modifying effects, patients will enjoy the double jackpot of slower progression along with symptom relief. Time will tell. Unfortunately, time remains the one entity that few of our patients possess in abundance. ■

Quality of life in young- compared with late-onset Parkinson's disease.

First Author and Institution:
M. Duleeka W. Knipe, MPH, Cardiff University, Cardiff, Wales, United Kingdom.

Citation:
Movement Disorders. 2011;26:2011-2018.

Objective:
Compare quality of life (QOL) in young-onset versus older-onset patients with Parkinson's disease (PD).

Type of Study:
Prospective, controlled study with questionnaires.

Result:
Onset of PD at a young age was associated with a poorer QOL than onset at an older age. The adverse effect on QOL appears to be largely mediated by a depressed mood.

Conclusion:
Based on evidence that younger patients have a poor QOL associated with depressed mood, more emphasis may be needed on diagnosis of mood disorders in this group.

There has been relatively little data about the impact of PD on QOL in patients with early onset, defined in this study as age less than 45 years at diagnosis. Previous studies have suggested a poorer QOL but have not always been well controlled for confounders, such as disease severity.

In this study, data on QOL using the 39-item Parkinson's Disease Quality of Life questionnaire (PDQ-39) was collected from 426 patients and 402 controls without PD who were recruited from the community. Patients were also assessed with a number of other tests relevant to QOL, including the Beck Depression Inventory (BDI) and the Epworth Sleepiness Scale (ESS).

When compared with patients with later-onset PD, early-onset PD was associated with a 2-fold increase (P=0.003) in the odds ratio of a worse QOL. In particular, early-onset PD was associated with worse emotional well-being even after adjusting for depression. However, depression remained an important predictor of poor QOL.

While QOL is worse in patients with early- relative to later-onset PD, the burden of early onset of PD appears to be largely experienced by its emotional impact, according to the authors of this study, who conclude that these results emphasize a need to diagnose and effectively treat depression in young-onset patients.

Commentary:
Lisa M. Shulman, MD
Professor of Neurology
University of Maryland School of Medicine
Baltimore, Maryland

Ever since health-related QOL appeared on our radar screen as a legitimate and highly desirable outcome of health care, studies of the determinants of QOL have mushroomed. And it is easy to understand why—isn't our primary objective as clinicians to use our tools wisely in order to optimize our patients' QOL?

This well-conducted study examined QOL in a large community-based sample and found that a younger age of onset of PD was associated with worse QOL ratings. The authors propose a causal pathway between age of onset and QOL, and identify depression as an important intermediary factor. Daytime sleepiness was elevated in PD but did not differ among those with early- and late-onset disease.

When compared with patients with later-onset PD, early-onset PD was associated with a 2-fold increase (P=0.003) in the odds ratio of a worse QOL.

Like all studies, the limitations should be recognized. There are many plausible intermediary factors that are likely to correlate with QOL and no study can include them all. Consider the potential influence of the following factors: apathy, anxiety, sexual dysfunction, fatigue, resilience, self-efficacy, income, and social support. In general, investigations of QOL continue to focus on a relatively limited panel of factors, so there is likely to still be a lot to learn about QOL in PD.

Nonetheless, not all determinants of QOL are modifiable. Fortunately, depression is a modifiable factor and, based on these findings, we should be especially vigilant in recognizing and treating depression in early-onset PD. ■

Mortality from Parkinson's disease: A population-based prospective study (NEDICES).

First Author and Institution:
Ignacio J. Posada, MD, PhD, University Hospital 12 de Octubre, Madrid, Spain.

Citation:
Movement Disorders. 2011[Epub ahead of print].

Objective:
Assess the causes of death in patients with Parkinson's disease (PD).

Type of Study:
Prospective, population-based, cohort study.

Result:
In a cohort of elderly subjects, PD was an independent predictor of mortality after adjusting for confounders. Dementia with PD increased the odds ratio for mortality.

Conclusion:
After controlling for a variety of confounders, such as co-morbidities, PD is associated with a high rate of death even though the most common causes, such as cardiovascular disease, are similar.

Numerous studies have indicated that patients with PD have a higher rate of mortality than those without PD. However, many of these studies did not necessarily include representative patient samples.

In this prospective, population-based study, a cohort of 5,262 elderly patients was followed over a median period of 12 years. Of these patients, 81 had PD at baseline. The rates of death were compared in those with and without PD when controlling for a variety of confounding factors, such as demographics and co-morbidities.

Of the 81 patients with PD, 66 (81.5%) died over the course of follow-up. Of the 5,181 without PD at baseline, 2,635 (50.8%) died, producing an unadjusted hazard ratio (HR) of 2.29 (P<0.001) for the patients with PD. After adjusting for confounders, the HR was 1.75 (P<0.001) in the PD group. In PD and non-PD subjects, the leading cause of death was cardiovascular disease. Patients with PD and dementia had a 2.62 HR of mortality relative to 2.0 for patients without dementia. Patients with PD managed by neurologists had a slightly lower HR for mortality.

The results of this study confirm previous evidence that mortality rates are greater in patients with PD than in those without PD. These data may be useful in counseling patients.

Commentary:

Kevin M. Biglan, MD, MPH
Associate Professor of Neurology
Clinical Director, Movement and Inherited Neurological Disorders Unit
University of Rochester School of Medicine and Dentistry
Rochester, New York

The information generated by this study is not unexpected, but it is useful because there have been very few population-based studies looking at this issue. A study design that captures a complete population and follows them prospectively is one of the best ways to address the question of relative mortality risk. The authors report that the major causes of death, such as cardiovascular disease, were similar in those subjects with PD when compared to those without PD, but they report that 18% of the patients with PD died of PD. A more specific cause of death in these cases would be useful for understanding and addressing risks, particularly because other studies have suggested that indirect complications from the consequences of PD, such as pulmonary emboli stemming from limited mobility or pneumonia from impaired swallowing function, may be more common in the PD population.

The authors emphasize that patients with PD and dementia are at the highest risk of early mortality relative to individuals without PD, but the increased risk for this population was actually rather modest, and dementia increased mortality risk in the non-PD population as well. Although the authors found that the unadjusted hazard ratio for mortality was 2-fold higher in patients with PD, this was concentrated in those with PD at baseline. The increased risk was more modest for those who developed PD during follow-up.

When I counsel patients about PD risks, I note that there is a slightly increased rate of death, but a normal lifespan is common with appropriate care. ■

α-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation.

First Author and Institution:
Tim Bartels, MD, Harvard Medical School, Boston, Massachusetts.

Citation:
Nature. 2011;477:107-110.

Objective:
Characterize the native state of the protein α-synuclein.

Type of Study:
Analysis of cell-line experiments in the context of previously published observations.

Result:
The helically folded tetramer that characterizes normal α-synuclein appears to be misfolded in pathophysiological conditions, leading to α-synucleinopathies such as Parkinson's disease (PD).

Conclusion:
If destabilization of the α-synuclein tetramer is a critical pathogenic event, therapies designed to improve stabilization might prevent the α-synuclein aggregation that drives PD.

The characterization of α-synuclein in its native state relative to the changes it undergoes under pathologic conditions is important because of the insight it might provide about disease pathogenesis, as well as the potential to yield new targets for therapy. Previously, native α-synuclein protein has been characterized as an unfolded monomer of 14 kDa, but the techniques used to isolate native α-synuclein may have denatured this protein and provided an inaccurate description of its form and size.

In an initial series of experiments designed to avoid denaturation and conducted in cell lines and cells from a normal mouse brain, the findings suggested that α-synuclein exists in a stable, helically folded oligometric form and is larger than that described previously. A subsequent set of experiments conducted in freshly collected human red blood cells, including tests employing scanning transmission electron microscopy, corroborated these findings. In addition to showing a folded rather than unfolded native state, the main α-synuclein species in the red blood cells and other human cell populations appeared to range in size from about 55 kDa to 60 kDa.

Overall, this series of studies provides several independent lines of evidence that α-synuclein exists in its native stage as an α-helically folded ~58 kDa tetramer rather than the unfolded ~14 kDa monomer described previously. Although other α-synuclein types, including monomer forms, may exist, the authors believe that the ~58 kDa tetramer is the dominant form of α-synuclein.

If this new characterization of native α-synuclein is correct, the steps involved in pathogenic changes may prove potentially "targetable" to prevent or control PD and other synucleinopathies.

Commentary:

Michael S. Okun, MD
Administrative Director and Co-Director Center for Movement Disorders & Neurorestoration
University of Florida
Gainesville, Florida

Much research on the underlying causes of PD has focused on α-synuclein misfolding, which is thought to be followed by protein aggregation and eventual formation of a Lewy body within the brain. Bartels and colleagues report potentially important new information on the shape of α-synuclein. Rather than a natively "unfolded" protein that becomes a helically shaped structure when it binds to lipids, α-synuclein under more careful analysis appears to be a folded tetramer (a structure made up of four small subunits). The authors hypothesize that the order of events leading to PD may thus include: 1) destabilization of this helically folded tetramer; 2) misfolding of α-synuclein; and, finally, 3) formation of the Lewy body. The investigators discuss the provocative idea of stabilizing the tetramer as a way to prevent or treat PD.

This recent study adds important information to our understanding of PD, but the findings will require replication by other groups. In particular, it will be important to demonstrate a crystallized structure of α-synuclein across many species, as well as to better understand how much of α-synuclein exists as a tetramer shape versus an unfolded one. Our broadening of the understanding of the shape of α-synuclein, both before and after it misfolds, may assist scientists and clinicians in better shaping the future of PD therapeutics. ■

Direct generation of functional dopaminergic neurons from mouse and human fibroblasts.

First Author and Institution:
Massimiliano Caiazzo, MD, San Raffaele Scientific Institute, Milan, Italy.

Citation:
Nature. 2011;476:224-227.

Objective:
Identify critical transcription factors for transforming fibroblasts into dopaminergic cells.

Type of Study:
Series of animal and cell-line analyses.

Result:
Three transcription factors were able to elicit dopaminergic transformation in a variety of fibroblasts.

Conclusion:
These studies suggest functional dopaminergic cells may be created from fibroblasts by direct programming with transcription factors, thus avoiding the need for stem cells.

Transplantation of embryonic stem cells to generate dopamine-producing neurons in patients with PD has been shown to be feasible, but the potential risks from this approach include the generation of tumors. Success converting fibroblasts into neuronal cells by forced expression of three transcription factors, Mash1, Brn2, and Myt1l, has suggested an alternative strategy, but this produces a mix of neuronal cell subtypes, such as glutamatergic and GABAergic cells. Dopaminergic-specific cells are the goal of ongoing studies.

In this study, mouse embryonic fibroblasts were transduced with a series of lentiviruses transporting various combinations of transcription factors. The result of this series of experiments was the confirmation that Mash1, Nurr1, and Lmx1a provide a gene cocktail proficient in reprogramming mouse fibroblasts to neurons producing dopamine. A variety of subsequent experiments were performed, such as determining whether these reprogrammed cells were capable of forming synaptic contacts in culture, before transferring the experiments to human fetal fibroblasts.

The most advanced set of experiments involved reprogramming of human fibroblasts taken from two healthy adult donors and two patients with genetic forms of PD. In culture, these experiments, like those with mouse fibroblasts, demonstrated that dopaminergic and electrophysiological functions, including depolarization and spiking events, could be elicited.

Reprogrammed cells using the techniques described in this study produce gene expression, dopaminergic release, and pacemaker activity modulated by D2 receptors that are similar to human brain dopaminergic cells, according to the authors. This approach may have advantages over the use of reprogramming pluripotent stem cells, including a more easily generated population of cells suitable for autologous cell replacement therapies.

Commentary:
Claire Henchcliffe, MD, DPhil
Director, Parkinson's Institute
New York-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Initial attempts to treat PD by cell transplantation, using fetal tissue grafts, have thus far met with limited success. There remain critical yet unanswered questions, including what the best donor cells will be. The present experiments are important in that they could represent a new source of dopaminergic neurons for cell-replacement therapy. The investigators convincingly demonstrate that from both mouse and human adult fibroblasts they are able to generate dopaminergic neurons that recapitulate many characteristics of "normal" adult dopamine neurons, including molecular markers and electrophysiological properties. Close inspection of their data reveals a number of differences between induced cells and native A9 and A10 mesencephalic dopaminergic cells (for example, in differential gene transcription). Exactly what these differences mean is unclear, but they possibly signify that the induced dopaminergic cells have an "abnormal" or perhaps "in-between" phenotype, and this needs to be further understood.

If we are to test cell-replacement therapy for PD, developing a well-characterized, sustainable, available, and standardized donor-cell population is imperative. This study is a step towards that goal, and one important consideration is that avoiding use of stem cells could address the safety concern of potential tumor development from grafted cells.

For the clinician, this is a new and fascinating technology as yet in early development, and we are still some years from its potential application in PD clinical practice. ■

Preladenant in patients with Parkinson's disease and motor fluctuations: A phase 2, double-blind, randomised trial.

First Author and Institution:
Robert A. Hauser, MD, University of South Florida, Tampa, Florida.

Citation:
Lancet Neurol. 2011;10:221-229.

Objective:
Assess safety and efficacy of the adenosine 2A (A_{2A}) receptor antagonist preladenant in Parkinson's disease (PD).

Type of Study:
Phase 2, dose-finding, multicenter, double-blind, placebo-controlled trial.

Result:
For the two highest doses of preladenant tested, there were significant reductions in off time relative to placebo. The rate of adverse events was comparable to those in the placebo group.

Conclusion:
The efficacy and safety of this agent is sufficiently encouraging to warrant a definitive phase 3 study to evaluate its potential in routine PD care.

Dopaminergic therapies are the mainstay of treatment for PD, but these are associated with numerous adverse effects, including motor complications, nausea, postural hypotension, and hallucinations. Preladenant is an A_{2A} antagonist with the potential to reduce PD symptoms by a non-dopaminergic pathway. Blockade of A_{2A} receptors, which are located on GABAergic neurons, is associated with relief of motor symptoms through an indirect improvement in dopamine transmission.

In this multicenter, double-blind, placebo-controlled, dose-finding study, 253 patients were randomized to 1 mg, 2 mg, 5 mg, or 10 mg of preladenant or placebo. All medications were administered twice daily. The primary outcome was change in mean daily off time at week 12 when compared to baseline.

Relative to baseline and to placebo, the reductions in mean daily off time over the 12 week study were significant for both the 5-mg (-1 hr; P=0.0486) and the 10-mg (-1.2 hr; P=0.019) doses. On the basis of safety analyses that compared all preladenant doses to placebo, the most common adverse events were worsening of PD (11% versus 9%), somnolence (10% versus 6%), constipation (8% versus 2%), dyskinesia (9% versus 13%), and nausea (9% versus 11%). Unified Parkinson Disease Rating Scale (UPDRS) motor scores were not significantly improved with any dose of preladenant relative to baseline or placebo, but there were small improvements in part 1 scores (motivation/initiative) in the 5- and 10-mg groups compared with the placebo group.

The results of this study suggest that preladenant may be useful in reducing off time in PD patients taking a dopaminergic agent such as levodopa. A phase 3 trial is underway.

Commentary:

Daniel Kremens, MD, JD
Co-Director, Parkinson's Disease and Movement Disorders Center
Thomas Jefferson University
Philadelphia, Pennsylvania

This is an interesting study, and a potentially important one. It provides more evidence that a non-dopaminergic approach to PD with an A_{2A} receptor blocker may be useful clinically. However, this was only a phase 2 study and the patients were randomized to one of five treatment groups, so each group was relatively small. The study did not attempt to evaluate whether the reductions in off time were clinically relevant. Due to a high discontinuation rate, 23% of the final numbers used to compare the groups were based on a last-observation-carried-forward (LOCF). However, most adverse events were due to worsening PD and did not appear to be related to the active treatment, which did appear to be safe and well tolerated.

There is an important need for non-dopaminergic therapies in PD, and the A_{2A} antagonists look promising. The results with another A_{2A} antagonist, istradefylline, have been mixed, so it is probably too soon to determine whether these drugs will have an important role in treatment. The fact that preladenant is now going to be evaluated in a phase 3 trial suggests that there is confidence that this agent will be clinically useful, but we need to see those results to understand better where it will fit in if the agent reaches regulatory approval. ■

Q&A

WITH

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Associate Professor of Neurology
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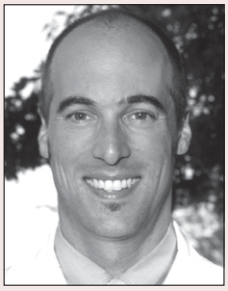

Question: What type of exercise should I recommend to my patients with Parkinson's disease (PD)?

Answer: There is a growing body of evidence that aerobic exercise may provide a neuroprotective and/or neurorestorative effect on the brain in animal models of PD, something that, to date, no treatment definitively provides. In one recent study in a mouse model of PD, exercise on a treadmill promoted partial recovery of motor function and partial restoration of dopamine cells in the substantia nigra.[1] In a partially and progressively lesioned mouse model that better approximates PD, treadmill exercise slowed the loss of dopamine nerve terminals and improved motor function, demonstrating a slowing of the degenerative process. In a follow-up study, when the rodents were exercised *first* and *then* lesioned with MPTP, a protective effect was seen in terms of recovery of motor function and modest recovery of dopamine nerve terminals.[2] There is further evidence that exercise induces neuroplasticity, improving function of the dopaminergic pathways affected in PD, ultimately improving motor function.[3]

Another important unmet need as PD progresses is gait and balance impairment, which is not very responsive to current therapies. This motor aspect of PD invariably becomes more disabling than the tremor or slowed dexterity that is typical in the early years. Recent studies demonstrate that particular exercise programs may be helpful in this regard. A sensorimotor agility exercise program for people with PD, for example, may prevent or delay mobility disability. Mobility depends upon dynamic balance, dual tasking, negotiating complex environments, quick changes in movement direction, and other sensorimotor skills affected by PD.[4] One version of agility training includes tai chi, kayaking/rowing movements, boxing, lunges, Pilates, and an agility course. When such a program was compared to exercising in a more traditional format on a treadmill, both regimens improved gait, but only the agility program improved balance and activities of daily living.[5] Tai chi alone has also been studied in PD, and demonstrated to improve gait and balance in a number of small controlled trials.[6,7] Another intensive standardized exercise approach, the LSVT®BIG, re-trains the planning of amplitude while attending to the sensory feedback that it generates, and this method was superior to alternative programs (Nordic walking and unassisted home exercises) in improving motor function in PD.[8]

With the goal of achieving regular aerobic exercise, and in a format that might be useful, the advice I give my patients is to work an exercise routine into their lifestyle, ideally 4 to 5 days a week, for a minimum of 45 minutes at a time. They should exercise vigorously enough to elevate their resting heart rate by 150%. For example, if their resting heart rate is 70 beats per minute, they should reach a heart rate above 105 beats per minute while exercising. If a patient has the time and resources to commit to a more involved program, I work with our rehabilitation team to develop a more targeted agility program to recover and maintain balance and gait.

Aside from working with a trainer, combining aerobic exercise with an activity that challenges the patient's sense of balance is a good combination. It's important to advise patients to exercise appropriate caution, taking care to avoid falls, especially if their balance is already impaired. For example, going for a brisk walk, on varied terrain when safe, is ideal. I've started a local hiking group for people with PD to put this idea into practice, and I implore my patients—to quote a famous motto from the Pacific Northwest—"Just do it!"

References

1. Smith BA, Goldberg NRS, Meshul CK. Effects of treadmill exercise on behavioral recovery and neural changes in the substantia nigra and striatum of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse. *Brain Research*. 2011;1369:70-80.
2. Meshul CK (personal communication).
3. Petzinger GM, Fisher BE, Van Leeuwen JE, et al. Enhancing neuroplasticity in the basal ganglia: The role of exercise in Parkinson's disease. *Mov Disord*. 2010;25(Supp 1)S141-S145.
4. King LA, Horak FB. Delaying mobility disability in people with Parkinson disease using a sensorimotor agility exercise program. *Phys Ther*. 2009;89:384-393.
5. King LA (personal communication).
6. Hackney ME, Earhart GM. Tai chi improves balance and mobility in people with Parkinson disease. *Gait Posture*. 2008;28:456-460.
7. Marjama-Lyons J, Smith L, Mylar B et al. Tai chi and reduced rate of falling in Parkinson's disease: A single-blinded pilot study. *Mov Disord*. 2002;17(Suppl 5) S70-71.
8. Ebersbach G, Ebersbach A, Edler D, et al. Comparing exercise in Parkinson's disease—The Berlin LSVT®BIG study. *Mov Disord*. 2010;25:1902-1908.

Controversies in PD

PRO Opinion

Lauren E. Schrock, MD

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The past decade has witnessed a changing dynamic in biomedical science, with an increasing emphasis on cell-based and gene therapies that have quasi-drug classifications. In PD, delivery of these "biologics" requires a neurosurgical procedure. The FDA, long in the business of overseeing drug trials, holds as its gold standard the randomized, placebo-controlled trial. Now that the FDA's jurisdiction has expanded to include biologics, it is requiring that these potential new therapies be held to the same standard. However, this flies in the face of surgical tradition, wherein procedures have commonly been introduced into practice based on uncontrolled studies, in part due to the ethical issues raised by surgical placebos. Although bureaucratic momentum may have been a factor in the emergence of placebo-controlled surgical trials, important questions remain: (1) are "sham" surgery controls methodologically necessary, and (2) are they ethically permissible?

First, to assess methodology, we must determine whether PD surgical treatments are vulnerable to placebo effects. A meta-analysis found that significant placebo effects have been noted in two important situations: (1) studies of pain interventions, and (2) studies where the primary outcome variable was a subjective and continuous measure.[1] In the case of PD, where valid objective biomarkers of disease progression remain elusive, routinely used outcome measures (eg, the Unified Parkinson's Disease Rating Scale [UPDRS]), are subjective and continuous variables. Additionally, substantial placebo effects have been demonstrated in PD clinical trials; in fact, surgical placebo effects are more robust than those of medical placebos.[2,3] The risk of placebo effects has been borne out by six negative, randomized, placebo-controlled PD trials of surgical interventions that had shown promise in open-label studies.[5] PD surgical studies have also been shown to be vulnerable to investigator bias.[5]

Next, there are many ways in which sham-surgery controls challenge ethical norms. Controls in surgical trials have no chance of gaining additional benefit, but are exposed to risks associated with a "sham" procedure. Macklin argues that this creates a tension between the highest standards of research design and the highest standards of ethics.[6] However, this charge is derived from a misconceived dichotomy that betrays a very narrow view of research ethics. Research ethics take into account *not only* the interests of research subjects, but also the interests of biomedical science, and encompass a fiduciary relationship with the larger patient cohort and with society at large.[7] In this view, a flawed study design is an ethically important fact—by its very nature, it breaks this fiduciary relationship. The actual problem is tension between obligations to individual research subjects and obligations to the larger patient cohort and society.[8] The real danger is that false-positive trial results may admit into routine clinical practice procedures with little or no benefit and significant risks to patients, and significant societal costs. The critical point is that false-positive results represent an *existing* harm, and by their continued acceptance, a *future harm* to individual patients and to society at large.

Placebo-controlled surgical trials should not be the default design for clinical trials involving surgical interventions. However, until we have valid objective biomarkers or reasonable alternative trial designs, sham-surgery controls are necessary in PD trials to prevent the dissemination of useless and risky procedures into the general population.

References

1. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001;344:1594-1602.
2. Goetz CG, Wuu J, McDermott MP, et al. Placebo response in Parkinson's disease: Comparisons among 11 trials covering medical and surgical interventions. *Mov Disord.* 2008;23:690-699.
3. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: Randomised controlled trial of two placebo treatments. *BMJ.* 2006;332:391-397.
4. de la Fuente-Fernandez R, Ruth TJ, Sossi V, et al. Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science.* 2001;293:1164-1166.
5. Alterman RL, Tagliati M, Olanow CW. Open-label surgical trials for Parkinson disease: Time for reconsideration. *Ann Neurol.* 2011;70:5-8.
6. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med.* 1999;341:992-996.
7. Dekkers W, Boer G. Sham neurosurgery in patients with Parkinson's disease: Is it morally acceptable? *J Med Ethics.* 2001;27:151-156.
8. Albin RL. Sham surgery controls: Intracerebral grafting of fetal tissue for Parkinson's disease and proposed criteria for use of sham surgery controls. *J Med Ethics.* 2002;28:322-325.

The Question: Are placebo-controlled trials of surgical treatments for Parkinson's disease (PD) necessary?

CON Opinion

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Surgical treatments are increasingly used in PD, either as standard therapy or in research. However, unlike medical treatments, surgical interventions are not necessarily tested in randomized, placebo-controlled trials before they are adopted by treating physicians. Deep-brain stimulation (DBS) was widely adopted by neurologists and neurosurgeons based on results from uncontrolled case series. Only after many patients had been implanted were randomized trials conducted that confirmed prior, open-trial results.[1-3] In the case of DBS, placebo control was not needed to appropriately change clinical practice.

By contrast, open trials of fetal cell transplantation, which showed large treatment effects, were not confirmed by subsequent randomized trials.[4,5] This experience has been used as evidence to argue that placebo controls are always needed in surgical trials in PD. The arguments in favor of the need for placebo focus on the susceptibility of clinical rating scales or patient-reported outcomes to a placebo effect and the tendency of intensive therapies like surgery to induce particularly large placebo responses. In reality, these arguments are relevant to only a narrow segment of proof-of-principle clinical trials of surgical treatments, and many trials of surgical treatments for PD would either expose participants to unnecessary harm or provide less clinically relevant data than studies that do not include a placebo.

Randomization is almost always a feature of a well-designed trial, but a placebo group may not always be necessary or even desirable, particularly in surgical trials in PD. Because placebo-controlled surgical studies generally require a "sham" surgical procedure to ensure masking to treatment assignment, the control group is subjected to risk, which needs to be carefully justified.[6] The use of a placebo may not be justified when the advantages of placebos are less obvious, such as trials using objective biomarker outcomes or studies intended to identify the best dose to bring to a subsequent, definitive trial.

In other cases, an active control may be more appropriate than a placebo. Current studies of gene therapy or stem-cell transplantation are aimed at showing that these surgically delivered treatments can have any effect at all on PD. Ultimately, however, these treatments need to be much more than minimally effective to justify their costs and risks. To identify their place in clinical practice, they should be compared to active treatments such as levodopa or DBS.

The issue of effect size is relevant not only to the use of a placebo control, but to the general question of how trials of surgical treatments will be designed to lead to changes in practice. DBS was widely adopted because it had a large treatment effect in a group of patients who lacked adequate treatment alternatives. Current gene-therapy studies have shown treatment effects that are the same or smaller than existing treatments.[7] Although proof-of-concept trials designed to demonstrate small treatment effects are appropriate for testing biological treatments at this phase of their evolution, these treatments will need to have much larger effects to be widely adopted in clinical practice. The implication for trials for these interventions is that definitive studies should identify treatment effects that are clearly evident to patients and physicians and that are superior to available alternatives. A treatment that is only better than a placebo will not be good enough.

References

1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2006; 355:896-908.
2. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled trial. *JAMA.* 2009;301:63-73.
3. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* 2003; 349:1925-1934.
4. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embrionic dopamine neurons for severe Parkinson's disease. *N Engl J Med.* 2000;344:710-719.
5. Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol.* 2003;54:403-414.
6. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med.* 1999;341:992-996.
7. LeWitt PA, Rezai AR, Leehey MA, et al. AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol.* 2011; 10:309-319.

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Winter 2011

Parkinson's Disease Monitor & Commentary

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