VOLUME 4, NUMBER 1
SPRING 2011

Parkinson's Disease Monitor & Commentary

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

Commentators

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

From the editor...

ANDREW D. SIDEROWF, MD

In this, our first issue in 2011, I am pleased to announce that we have expanded from eight to 12 pages and added two new features: A "Question and Answer" column (the topic: impulse control disorders), and a "Controversies in PD" column. Our first controversial topic concerns the value of early diagnosis of Parkinson's disease (PD), with the pro opinion being taken by David Russell, MD, PhD, of the Institute for Neurodegenerative Disorders, and the con opinion by Kevin Biglan, MD, MPH, of the University of Rochester School of Medicine and Dentistry. Both offer cogent arguments for their sides of the issue.

We continue to include six commentaries on recent articles. One study, for which we have commentary from Dr. Connie Marras of the University of Toronto, concerns the question of what predicts mortality in PD. Dr. Marras notes that two risk factors, dementia and psychosis, may well be amenable to better management. Next, evaluating new quality measures for PD care that were issued by the American Academy of Neurology, our commentator Dr. Mark Guttman supports the principle, but urges one more step in the process: demonstrating an impact on outcome.

Gene therapy shows promise in the laboratory, but the first double-blind trial in humans was negative. Dr. John Morgan of the Medical College of Georgia evaluates whether the fatal flaw was in the delivery, the dose, or the concept. We also hear from Dr. Kelvin Chou from the University of Michigan about a study that suggests deep brain stimulation (DBS), despite its benefits against cardinal symptoms of PD such as bradykinesia, appears to offer only transient benefits against postural instability and gait disability. He suggests that there may be a difference between the two major techniques of DBS.

A study that looks into a large prescribing database with the intent of comparing relative compliance and persistence rates of PD therapies leads our commentator, Dr. Lawrence Elmer of the University of Toledo, to express dismay at the low rates overall. He suggests that once-daily therapy may explain why rasagiline produced the best overall compliance and persistence rates but indicates that patients may need specific instruction about why daily compliance is important in order to change behavior. Finally, Dr. Laura Marsh of Baylor College of Medicine comments on a study of memantine, an N-methyl D-aspartate (NMDA) antagonist that demonstrates efficacy in Alzheimer's disease, and suggests it may be appropriate for patients with Lewy Body dementia, but more study is needed to determine the benefit of the agent in PD-related dementia.

We match our selection of articles with commentators who have an interest in the given area in order to provide an independent point of view. Our commentators do not necessarily provide the final word, just a second opinion. 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 ANDREW SIDEROWF, MD

PD Monitor & Commentary

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Faculty Disclosures

Dr. Kevin Biglan has received grants from Excellus Blue Cross, Google Inc., Lundbeck, Marvell Inc., Michael J. Fox Foundation, National Institute of Neurological Disorders and Stroke, and National Parkinson Foundation. He serves on the Tourette's Syndrome Association Scientific Advisory Board and consults to Theravance Inc.

Dr. Kelvin Chou has received royalties from publishing chapters in UpToDate; has served as a consultant for Medtronic Inc.; has served on Speakers' Bureaus for Allergan, Inc. and Teva Pharmaceutical Industries Ltd.; and has received research support from the National Institutes of Health.

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

Dr. Mark Guttman has received research funding from CHDI Foundation, Inc., Chelsea Therapeutics, Merck, Merck Serono, National Parkinson Foundation, NeuroResearch, National Institutes of Health, and Teva Neuroscience. He has received speakers' fees from Novartis and Teva Neurosicence.

Dr. Connie Marras has received an honorarium from EMD Serono for being an examiner for neurology residents in a practice examination.

Dr. Laura Marsh has received funds from the Department of Veterans Affairs as her employer. She has also research grants from Boehringer Ingelheim, Eli Lilly, Forest Research Institute, Merck Serono, Michael J. Fox Foundation, and National Institutes of Health, and royalties from Taylor and Francis/Informa.

Dr. John Morgan has received grants/research funding from Abbott, Acadia Pharmaceuticals, Boehringer Ingelheim, GlaxoSmithKline, Huntington Study Group, Impax Laboratories, Inc., Merck Serono, National Institutes of Health, National Parkinson Foundation, and Teva Neuroscience. He has received honoraria for consulting and serving on advisory boards for National Parkinson Foundation and Teva Neuroscience. He has received speaking honoraria from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva Neuroscience.

Dr. Andrew 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
Website: www.delmedgroup.com

Publishers: Joseph D'Onofrio, Frank M. Marino

Editorial Director: Nancy Monson

Senior Writer: Theodore Bosworth

Art Director: James Ticchio

In This Issue

Commentaries

Q&A with Andrew D. Siderowf, MD

Controversies in PD

Drug therapies for Parkinson's disease: A database analysis of patient compliance and persistence.

First Author and Institution:
Marcy L. Tarrants, PhD, Teva Neuroscience, Inc., Kansas City, Missouri.

Citation:
American Journal of Geriatric Pharmacotherapy. 2010;8:374-383.

Objective:
Evaluate patient adherence and persistence with various Parkinson's disease (PD) therapies.

Type of Study:
Retrospective analysis of longitudinal prescription database.

Result:
The highest compliance and persistence rates overall were generated by prescriptions for rasagiline followed by the levodopa/carbidopa/entacapone combination.

Conclusion:
The highly statistically significant differences in compliance and persistence rates for medications for PD, particularly among those receiving their first prescription, may be relevant to clinical choices.

The available drug therapies for PD act by one of four mechanisms: monoamine oxidase (MAO)-B inhibition, dopamine replacement, catechol-O-methyltransferase (COMT) inhibition, or postsynaptic D2 receptor stimulation.

This novel study compared compliance and persistence among the treatment options for PD, recognizing that they may be influenced by a wide variety of factors including convenience of dosing, adverse effects, and cost. The retrospective analysis was conducted via a 12-month look-back at a longitudinal prescription database encompassing approximately 50% of all retail prescriptions written in the United States and >150 million unique individuals. A 3-month drug selection period during which patients received their first prescription and a 12-month observation period were also analyzed.

Of the 29,682 patients who received a prescription for a new PD drug, 66.3% were receiving a first prescription and 33.7% had previously been treated. Compliance with the MAO-B inhibitor rasagiline was greater than for any other drug (P<0.001). Persistence was greater with rasagiline and levodopa/carbidopa/entacapone compared with the other agents. Compliance was slightly greater among previously treated patients compared to treatment-naïve subjects (75.9% versus 73.0%, respectively); persistence was significantly greater among the former group (150.5 days versus 122.7 days, respectively, P<0.001).

In this PD population, compliance was ≤80% in 46.5% and nonpersistence was noted within the first 5 months of the data analysis among 67.8%. The authors speculate that once-daily dosing is one possible explanation for the greater rates of compliance and persistence seen with rasagiline treatment.

Commentary:

Lawrence Elmer, MD, PhD
Professor, Department of Neurology
University of Toledo
Toledo, Ohio

PD is one of the most treatable diseases in neurology, so the high rates of noncompliance and nonpersistence, especially in patients naïve to therapy, are disconcerting. These findings suggest that either physicians need to provide more education or that the patients themselves are not sufficiently convinced regarding the need to take medication every day to control PD symptoms.

The results were somewhat difficult to interpret because of the high proportion of treatment-naïve patients, while the vast majority of medication in routine clinical practice is prescribed to patients with PD who are already on therapy. The greater compliance rates on rasagiline relative to the other drugs may be related to once-daily treatment or its tolerability, as the authors speculate, but it is interesting to note that there were large differences in persistence rates between the treatment-naïve and treatment-experienced patients for most medications. This makes sense to the degree that a more convenient therapy might have a big advantage in patients with minimal symptoms, but compliance would improve with all medications when the need increases to control a growing symptom burden. It was somewhat surprising that the next greatest level of compliance after rasagiline was obtained with the combination of levodopa/carbidopa/entacapone, considering that this therapy typically requires three or more doses per day, but others could argue that this treatment provides the additional convenience of "two pills in one."

While this study presents disproportionately more data regarding treatment-naïve patients, there is clearly still room for improvement in the realm of patients complying with medication prescriptions at all stages of PD. ■

Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: A randomised, double-blind, placebo-controlled trial.

First Author and Institution:
Murat Emre, MD, Istanbul University, Istanbul, Turkey.

Citation:
Lancet Neurology. 2010;9:969-977.

Objective:
Evaluate efficacy and safety of memantine for dementia in Parkinson's disease (PD) and Lewy body disease (LBD).

Type of Study:
Randomized, double-blind, placebo-controlled trial.

Result:
Modest reductions in dementia symptoms at week 24 were observed on the basis of global clinical impression in those with LBD but not in those with PD.

Conclusion:
Memantine offered benefit and good tolerability in patients with mild to moderate LBD dementia, but not in patients with PD.

There is a variety of evidence suggesting that dementia in LDB and dementia associated with PD share pathophysiological features. They are the most common forms of dementia after Alzheimer's disease. Several studies have previously suggested that memantine, an N-methyl D-aspartate (NMDA) antagonist that demonstrates efficacy in Alzheimer's disease, may also be efficacious for dementia in LBD and PD.

In this study, 75 patients with LBD dementia and 120 patients with PD dementia were randomly assigned to memantine 20 mg or placebo. Efficacy was evaluated with the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGI) scale, cognitive test scores, and Neuropsychiatric Inventory scores.

At the end of 24 weeks on treatment, there was a significant difference in the mean change from baseline in ADCS-CGI scores favoring memantine over placebo in patients with LBD dementia (P=0.023), but not in patients with PD dementia. Similarly, there was significant improvement in Neuropsychiatric Inventory scores in LBD dementia subjects receiving memantine relative to placebo (P=0.041) but not in patients with PD dementia. Neither the incidence of adverse events nor the proportion of patients discontinuing for adverse events differed between the memantine and placebo groups.

Commentary:

Laura Marsh, MD
Professor of Psychiatry
Baylor College of Medicine
Houston, Texas

In previous studies that evaluated memantine for the treatment of dementia with LBD and PD, memantine was found to be more effective in PD dementia than LBD dementia. There are several possible explanations why this study is not consistent with those previously published. One is that a higher proportion of patients in the PD dementia group were taking concomitant medications that either have the potential to reduce cognitive performance, such as benzodiazepines and dopamine agonists, or to treat psychopathology, or were taking antipsychotic or antidepressant therapies. Such drugs may have limited or masked the ability of memantine to show a benefit in the PD with dementia group. Also, this study excluded the use of cholinesterase inhibitors, which may be appropriate when the goal is to isolate the effect of memantine, but does not reflect common practice. A synergist effect between discrete effects of memantine and cholinesterase inhibitors could also contribute to a different pattern of results across the different LBD dementias.

Given these limitations and disparate results across studies, I do not think these data are sufficient to conclude that memantine is not beneficial in PD dementia.

Given these limitations and disparate results across studies, I do not think these data are sufficient to conclude that memantine is not beneficial in PD dementia. While the study was well designed, a clinical global impression from the point of view of family members or caregivers might have been a useful additional measure of effect. Overall, I think the data reinforce the benefit of memantine in LBD dementia and suggest that individual patients with LBD dementia should undergo a trial of the medication. What with the challenges of this disease, even a modest improvement from a well-tolerated drug can be important from the clinical perspective. ■

Quality improvement in neurology: AAN Parkinson disease quality measures.

First Author and Institution:
Eric M. Cheng, MD, David Geffen School of Medicine at UCLA, Los Angeles, California.

Citation:
Neurology. 2010;75:2021-2027.

Objective:
Identify measures of quality care in Parkinson's disease (PD).

Type of Study:
Review of medical literature by experts to identify key strategies of quality assurance.

Result:
A 28-member expert panel identified 10 quality measures for ensuring, measuring, and validating appropriate care for patients with PD.

Conclusion:
Quality measurement, an increasingly well-accepted concept for ensuring that patients receive an adequate level of care across settings, is being embraced by the American Academy of Neurology (AAN) to improve outcomes.

Following the lead of primary care organizations, the AAN is overseeing an effort to identify performance measures for evaluating quality of care in various neurologic diseases, including PD. (Other measures to come include those for stroke, epilepsy, dementia, neuropathy, headache, and multiple sclerosis.) As defined by the AAN in this article, a quality measure allows measurement of how appropriate and specific clinical services are delivered to candidates for these services over a reasonable timeframe.

The AAN convened a group of experts to identify evidence-based performance measures from published studies and guidelines. Those processes that appeared to be quantifiable and represented a potential gap in care were ranked for their suitability to be the target of performance measures. By expert consensus, 10 performance measures were selected for further comment by a broader community of clinicians:

1. Annual review of PD diagnosis
2. Assessment of psychiatric disorders or disturbances
3. Assessment of cognitive impairment or dysfunction
4. Querying about symptoms of autonomic dysfunction
5. Querying about sleep disturbance
6. Querying about falls
7. PD rehabilitative therapy options
8. PD-related safety issues counseling
9. Querying about PD medication-related motor complications
10. PD medical and surgical treatment options reviewed

These performance measures are designed to help clinicians identify essential components of care as well as develop a methodology so that third-party payers and others can assess whether key facets of optimal PD care are being delivered routinely to all patients.

Commentary:

Mark Guttman, MD
Director, Center for Movement Disorders
Markham, Ontario, Canada

The efforts by the AAN to establish performance measures in the treatment of PD represent a step in the right direction. Based on the process described in this article, there was a reasonable methodology for identifying which quality measures to include, but it is important to recognize that the final choices selected by consensus from the panel have not yet been validated. Rather, the goal here was to determine what types of processes can be measured and, by validating that they are being performed, have the potential to improve care. Now, studies are needed to show that performing these measurements actually improve care.

Quality performance measures are being embraced by many stakeholders interested in improving care, and other organizations have been involved in developing these measures for PD. The National Parkinson Foundation, with which I am involved, has developed a registry program in which a longitudinal database will allow us to look at several performance measures, including some of those recommended by the AAN, for their impact on outcome. One risk of publishing performance measures before they are validated is that third-party payers and others may be attempted to adopt them in order to judge quality of care even before the value of these measures for improving outcomes is known. Quality assurance does have the potential to improve delivery of health care, including in the management of PD, but objective evidence for benefit is needed. ■

What predicts mortality in Parkinson disease? A prospective population-based long-term study.

First Author and Institution:
Elin Bjelland Forsaa, MD, The Norwegian Center for Movement Disorders, Stavanger University Hospital, Stavanger, Norway.

Citation:
Neurology. 2010;75:1270-1276.

Objective:
Identify independent risk factors for mortality in patients with Parkinson's disease (PD).

Type of Study:
Prospective follow-up of community-based PD population.

Result:
The significant independent predictors of mortality were higher age at PD onset, higher chronological age, male sex, higher Unified Parkinson's Disease Rating Scale (UPDRS) score, and the presence of psychotic symptoms and dementia.

Conclusion:
Of the potentially modifiable risks, progression of motor symptoms, psychosis, and dementia may provide the most promising targets of therapy to prolong survival in patients with PD.

Although life expectancy is reduced in patients with PD, the reasons have been unclear, at least partially obscured due to the heterogeneous course of progression and the fact that many patients have age-related co-morbidities that complicate efforts to discern patterns of risk.

In this study, a community-based sample of 230 patients with PD was followed prospectively beginning in 1993. Cox proportional hazard models were employed to identify independent predictors of mortality. A substantial number of variables were entered into the model, including UPDRS scores, levodopa equivalent dose, probable REM sleep behavior disorder, and psychotic symptoms.

At the end of 2009, 211 (92%) of the sample had died. The median survival from the time of onset of symptoms was 15.8 years (range 2.2 to 36.6 years). For hazard ratio (HR) and significance, the most important predictor of mortality in the proportional model was dementia (HR 1.89; P=0.001) followed by male sex (HR 1.63; P=0.001), chronological age (HR 1.51 for each 10-year increase; P=0.043), psychotic symptoms (HR 1.45; P=0.039), age at onset (HR 1.40 for each 10-year increase; P=0.029), and UPDRS motor score (HR 1.18 for each 10-point increase; P<0.001). There was no significant impact on survival from use of antiparkinsonian or antipsychotic drugs.

The results of this study suggest that treatments to prevent dementia, psychotic symptoms, and advancing disability may delay mortality in this population.

Commentary:

Connie Marras, MD
Associate Professor of Neurology
Parkinson's Disease and Movement Disorders Centre
University of Toronto
Toronto, Canada

Previous studies have associated dementia and psychosis with poorer survival in patients with PD, but this study is unique for several reasons. It was community-based, there was a prospective follow-up, and it had mortality data on more than 90% of the patients.

This study was designed to look at risk factors for earlier mortality rather than specific causes of death. This is important because the underlying issues that make patients susceptible for life-threatening complications may provide the best target for strategies to reduce mortality. For example, psychosis and dementia could increase the hazard of death by increasing the risk of one or more life-threatening complications that commonly lead to death in PD, such as aspiration pneumonia. It is possible, as the authors suggest, that better methods of preventing or treating dementia and psychosis will ultimately have a favorable impact on survival. Although the authors did not associate antipsychotic therapy with an independent reduction in the risk of mortality, this deserves more study. It is worth noting that most patients with psychosis were treated with clozapine, which is not the most commonly used antipsychotic in many countries for practical reasons. This drug may have a different risk profile than other agents.

Overall, this is an interesting and important work, and encourages us to rise to the considerable challenge of conducting clinical trials of therapies for dementia and psychosis in later-stage PD using mortality as an outcome. ■

A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD.

First Author and Institution:
R.J. St. George, PhD, Oregon Health & Sciences University, Portland, Oregon.

Citation:
Neurology. 2010;75:1292-1299.

Objective:
Evaluate the long-term effects of bilateral deep brain stimulation (DBS) to the subthalamic nucleus (STN) and globus pallidus interna (GPi) on postural instability and gait disability (PIGD) in Parkinson's disease (PD).

Type of Study:
Meta-regression analysis of previously published DBS studies in PD.

Result:
PIGD initially improved with DBS relative to the pretreatment off-medication state but performance declined over time. Post-surgery, PIGD improved among those on medication, but in the STN group, this improvement declined and PIGD ratings were worse than pretreatment by 2 years. This decline was not seen in the GPi group.

Conclusion:
DBS has less effect on PGID than on such cardinal Parkinson's symptoms as tremor, but medication plus DBS to the GPi may be superior to the STN for this outcome.

The effect of DBS on PIGD has been inconsistent. It is also unclear if GPi and STN DBS differ for PIGD.

In this meta-analysis of published studies, the goal was to provide more detailed information about the effect of DBS on PIGD. Eleven articles with adequate presurgical data with a breakdown of Unified Parkinson's Disease Rating Scale (UPDRS) scores were identified. Most evaluated bilateral STN DBS only, but several evaluated bilateral GPi DBS, and one evaluated both types of DBS.

DBS improved PIGD relative to presurgical symptoms, but there was a rapid and significant decline in PIGD on medication in patients who received STN DBS so that PIGD function was worse that presurgical measures within 2 years. GPi DBS with levodopa was not associated with the same significant decline in PIGD over time. DBS at both sites maintained improvements in cardinal signs of PD over 5 years in patients on and off medication.

Commentary:

Kelvin L. Chou, MD
Associate Professor of Neurology and Neurosurgery
University of Michigan Medical School
Ann Arbor, Michigan

Though long-term improvement in the cardinal PD symptoms of bradykinesia, tremor, and rigidity from DBS is well-documented, long-term effects of DBS on axial symptoms such as balance and gait remain controversial. This meta-analysis is an attempt to determine if there are differential long-term effects between cardinal and axial PD symptoms.

The improvement observed in the cardinal symptoms of PD did not deteriorate over time, suggesting that DBS may actually have a disease-modifying effect on these symptoms. Such a claim is difficult to prove conclusively, though, as no longitudinal DBS study has a long-term control group (a group that would qualify for DBS but be maintained on best medical therapy instead) for comparison.

The effect of DBS on PIGD symptoms was not so robust, becoming worse than the preoperative "on" medication state in the STN group by 2 years. In contrast, PIGD ratings in the GPi group did not deteriorate significantly over time. Potential explanations for this finding include higher levels of dopaminergic medications after GPi compared to STN DBS and more direct connections to motor and premotor cortices from the GPi compared to STN stimulation.

The key points here are that DBS has a sustained effect on the cardinal symptoms of PD over the long term, but balance and gait functions deteriorate over time despite initial improvement with STN stimulation. The findings also suggest that GPi stimulation, in combination with medications, may ultimately be a better option than STN stimulation for sustaining balance and gait. Here's hoping the randomized, prospective VA trial comparing STN to GPi stimulation (Follett KA, et al. N Engl J Med. *2010;362:2077-2091) will shed more light on this issue.* ■

Gene delivery of AAV2-neurturin for Parkinson's disease: A double-blind, randomised, controlled trial.

First Author and Institution:
William J. Marks, Jr., MD, University of California, San Francisco, San Francisco, California.

Citation:
Lancet Neurology. 2010;9:1164-1172.

Objective:
Test gene delivery by adeno-associated type-2 vector (AAV2) method for improvement in advanced Parkinson's disease (PD) symptoms.

Type of Study:
Double-blind, controlled, multicenter study.

Result:
On the basis of a well-recognized rating system, motor symptoms were not significantly improved with gene therapy delivered to the putamen when compared to a sham control procedure.

Conclusion:
Although benefit was not observed, the potential for efficacy has not been eliminated because of possible modifications in such variables as site of delivery and gene therapy dose.

Gene therapy, with its potential to provide sustained correction of the underlying deficiencies that produce PD, has obvious potential advantages over current therapies that temporarily stimulate dopaminergic activity. Gene delivery of neurturin, an analogue of glial-cell-derived neurotrophic factor (GNDF), has been shown to be beneficial in primate models of PD. It also appeared to provide benefit when delivered via an AAV2-neurturin gene vector in an open-label clinical study.

In this double-blind, controlled study, 58 patients with PD from nine sites in the United States were randomized in a 2:1 ratio to receive AAV2-neurturin injected bilaterally into the putamen or sham surgery. The primary endpoint was change from baseline at 12 months in the Unified Parkinson's Disease Rating Scale (UPDRS) in the practically defined off state. While the neurosurgical team could not be blinded to therapy, the blind was maintained for others.

There were no significant differences in change in UPDRS scores from baseline at 12 months in those who received gene therapy relative to those who underwent a sham procedure. At 18 months, the average 7.6-point advantage in UPDRS score for the gene therapy group suggested modest activity, but the sample size was small. Some improvements in quality of life, such as activities of daily living, approached statistical significance. Adverse events, many of which were serious but anticipated, differed modestly between groups and were largely associated with the surgical procedure.

Commentary:
John C. Morgan, MD, PhD
Assistant Professor
Department of Neurology
Medical College of Georgia
Augusta, Georgia

Based on the encouraging results in the animal models and the previously conducted open-label studies, these results were disappointing, but this study does not rule out the potential for benefit from another approach. As the authors point out, the problem may have been that insufficient neurturin reached the target site. One alternative is to deliver the gene vector directly to the substantia nigra, which, although more difficult, may provide a more direct restoration of dopaminergic function, or to increase the dose of vector genomes injected. However, while the potential for benefit from this treatment has not been ruled out by the results of this study, neither have the risks. One of the major concerns is the possibility of neoplasms developing in the brain with AAV2-neurturin therapy. One subject in the AAV2-neurturin group developed a glioblastoma, but there was no evidence of AAV2-neurturin in the tumor by quantitative PCR and upon further inspection the tumor was present on the magnetic resonance imaging scan obtained prior to study entry.

The authors, noting that benefit appeared to accrue after the 12-month endpoint, suggest that longer follow-up may be required, but we may be early in the trial-and-error phase with more work needed in regard to dose and location of gene delivery. The results of this study demonstrate the importance of double-blind trials and while initially negative, this direction of study is still viable. ■

Q&A WITH EDITOR Andrew D. Siderowf, MD

Question: What are impulse control disorders (ICDs) in patients with Parkinson's disease (PD), and why do clinicians and patients need to know about them?

Answer: ICDs are a group of undesirable behaviors that particularly affect patients with PD who are receiving dopaminergic treatment. The main ICDs are excessive or pathological gambling, binge eating, compulsive shopping, and compulsive sexual behavior. Other, more subtle ICDs include project-oriented behavior, which entails compulsively working on projects (such as home improvements) without necessarily finishing them, and compulsively searching the Internet. These behaviors, which are sometimes called "hobbyisms," are less obviously inappropriate than gambling, eating, and compulsive shopping or sexual behavior, and may be mistaken for healthy industriousness by clinicians who are not familiar with ICDs.

Treatment with dopaminergic medications, particularly dopamine agonists, is the main risk factor for ICDs.

Other behaviors that are related to ICDs include purposelessly taking apart gadgets such as clocks or electronics, called punding, and aimlessly walking or driving around for long periods of time. This latter behavior is sometimes termed "walkabout."

ICDs were initially described in patients with PD in 2003, but probably went unrecognized for a number of years before that time. Treatment with dopaminergic medications, particularly dopamine agonists, is the main risk factor for ICDs. Approximately 15% of patients treated with a dopamine agonist could have an ICD problem, compared to about 5% who are not receiving a dopamine agonist. All medications in this class (e.g., pergolide, which is now off of the market due to cardiac side effects, pramipexole, and ropinirole) are about equally associated with ICDs. Recently diagnosed patients with PD who are not on any medication have a risk for ICDs that appears to be similar to that seen in the general population. Patients receiving other treatments for PD including levodopa or deep brain stimulation have a somewhat increased risk, but not to the same extent as patients treated with dopamine agonists.

Other risk factors for ICDs include younger age, smoking, and a family history of gambling problems. Neuropsychological factors associated with ICDs include more severe depression and anxiety, obsessive-compulsive symptoms, high novelty-seeking, and impulsivity. More severe motor impairment has also been linked to a greater risk for ICDs, but this may also reflect more intensive treatment with dopaminergic medications. In spite of these associations, one of the hallmarks of ICDs is that they often occur in people who have shown no inclination toward impulsive or socially inappropriate behavior in the past. Another hallmark is that they reflect an unmistakable change from a patient's normal personality.

Clearly, ICDs can have substantial financial and social consequences for patients with PD if they persist undetected over time. Many patients act on their impulses in secret because they are aware that the behaviors are socially inappropriate. Patients are also unlikely to connect behaviors to their medical treatment unless they have been made aware of the association. For these two reasons, patients are unlikely to spontaneously report their ICD behaviors to their doctor. It is essential that clinicians are proactive in educating patients with PD about ICDs, particularly those who are about to begin treatment with dopamine agonist medications. It is also essential to probe specifically for the presence of ICDs at follow-up clinic visits. By taking these two relatively simple steps, the vast majority of potentially damaging ICDs can be avoided.

Controversies in PD

PRO Opinion

David Russell, MD, PhD

Associate Clinical Research Director
Institute for Neurodegenerative Disorders
New Haven, Connecticut

"Doc, why does my hand shake? I've got know. I need to make plans." A 60-year-old businessman with one cardinal symptom of Parkinson's disease (PD) sits with me. He's worried and anxious, yet practical. What should I do? If I tell him I believe he may have PD, or if I obtain a scan to support the diagnosis of PD, am I doing the right thing for him? After all, no treatment has been shown to be neuroprotective or restorative. We don't have a cure.

Although this decision must be individualized, in most cases the best clinical decision is to diagnose PD early and accurately.

Broadly, we can consider this patient as "at risk," meaning there is evidence he has an increased risk of developing clinically evident PD. Once someone has reached the point of clear clinical PD, perhaps he can no longer be considered as "diagnosed early." Our patient with just a tremor may or may not have PD, but he wants to know. Of course, there is a practical value for planning ahead. Should he retire early? Should he pursue different health care options? A clear diagnosis helps immensely. But is it too stressful to confirm PD? Studies of individuals at risk for arguably more serious diseases such as Huntington's disease demonstrate that even those who test "positive" for the disease do better psychologically in the short and long term, despite the obvious stressors.[1,2]

Although no treatments are known to be neuroprotective (i.e., to prevent neuron death or damage), evidence shows earlier treatment in PD may be clinically beneficial. The ADAGIO trial, for instance, showed that earlier introduction of rasagiline at 1 mg a day slows symptom accumulation compared with a placebo in early PD.[3] This benefit was retained through the study period. Furthermore, even in early PD, the symptomatic effects provided by rasagiline improved quality of life.[4]

Correct early diagnosis avoids the pitfalls of unnecessary testing, prescription of incorrect medications, the risks of "diagnostic levodopa trials," and misguided second opinions or procedures.[5] Early diagnosis facilitates early access to a PD specialist for an expert consultation. Treating PD can be "tricky" and requires experience and knowledge of a changing literature. The first treatment—or nontreatment—can be a critical decision.

Finally, and very importantly, early, accurate diagnosis facilitates and improves potentially ground-breaking research on PD and a patient's opportunity to participate in this research without the complications of symptomatic therapy. Potentially ground-breaking trials such as PPMI for biomarkers, or of additional potentially disease-modifying treatments like inosine or pioglitazone require early and accurate diagnosis of PD.

Delaying diagnosis and putting off opportunity is antithetical to our medical training and practice. The most meaningful interventions for PD, and perhaps the cure, are likely to come before substantial neuron loss has already occurred—before telltale symptoms. Identifying our foe early and accurately is best for all, from patient to clinician to researcher.

References

1. Wiggins S, Whyte P, Huggins M, et al. The psychological consequences of predictive testing for Huntington's disease. *N Engl J Med*.1992;327:1401-1405.
2. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: A systematic review. *Soc Sci Med*.1999; 49:1571-1598.
3. Olanow CW, Rascol O, Hauser R, et al for the ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361:1268-78.
4. Biglan KM, Schwid S, Eberly S, et al. Rasagiline improves quality of life in patients with early Parkinson's disease. *Mov Disord*. 2006;21:616-623.
5. Scherfler C, Schwarz J, Antonini A, et al. Role of DAT-SPECT in the diagnostic work up of Parkinsonism. *Mov Disord*. 2007;22:1229-1238.

The Question

The diagnosis of Parkinson's disease should be made as early as possible.

CON Opinion

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As clinicians, and especially neurologists, we take pride in our ability to tease out subtle neurological signs and clinical clues from the history in order to make a preliminary diagnosis as early in the clinical course as feasible. If that diagnosis is later proven accurate, the feeling is uplifting and reinforces our sense of ourselves as skilled and superior clinicians.

The diagnosis of PD is currently based purely on clinical criteria and can be imprecise, particularly early in the course of illness. Ultimately, neuropathological evaluation is necessary to make a definitive diagnosis. Reliability data in Lewy body disease (PD or dementia with Lewy body) comparing initial and follow-up diagnoses with neuropathological findings demonstrate that the diagnostic sensitivity increases from 57% to 67% and specificity increases from 87% to 93% from the initial evaluation to the last evaluation.[1] In the PD-only group in this study, the sensitivity and specificity were slightly better initially but also subsequently improved over time. However, the positive predictive value of the initial diagnosis on the pathological diagnosis was quite low (40% initially compared to 56% at the last visit). This suggests that a rush to diagnosis is likely to be less accurate initially, with a tendency towards overdiagnosis of PD. This may lead to an underutilization of diagnostic tests that may help distinguish alternative etiologies to the patient's symptoms and overutilization of therapies that may not be useful. The temporal evolution of illness is therefore necessary to confirm a preliminary diagnostic impression and to target disease-specific treatments.

Assuming an accurate early diagnosis is possible, what is the potential benefit to the patient? It seems reasonable that treatments that slow or halt the progression of disease should be started as early as possible, maybe even prior to the development of clinical symptoms. However, no such treatments have been definitively proven and many treatments have the potential for harm. MAO-B inhibitors, which have shown the most promise, have only demonstrated mixed effects on PD progression and even the positive benefits have been marginal and of unclear clinical meaningfulness.[2-4] In addition, initial treatment strategies do not appear to have long-term consequences with regard to function.[5,6] Finally, dopaminergic therapy runs the risk of both motor and non-motor complications that need to be considered carefully prior to initiating therapy.

A rush to diagnosis is likely to be less accurate initially, with a tendency towards overdiagnosis of PD.

Early diagnosis is likely to be less accurate and lead to treatments that have limited clinical benefit if started earlier and have a potential for harm. Until there are methods to improve diagnostic certainty early in the course of disease and therapies with meaningful long term-clinical impacts are identified; the impetus will not exist to diagnose patients as early as possible.

References

1. Litvan I, MacIntyre A, Goetz CG, et al. Accuracy of the clinical diagnosis of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: A clinicopathological study. *Arch Neurol*. 1998;55:969-978.
2. Olanow CW, Rascol O, Hauser R, et al for the ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361:1268-78.
3. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol*. 2004;61:561-566.
4. Shulman LM, Gruber-Baldini AL, Anderson KE, et al. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol*. 2010;67:64-70.
5. Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol*. 2009;66:563-570.
6. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord*. 2007;22:2409-2417.

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Spring 2011

Parkinson's Disease Monitor & Commentary

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