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Parkinson's Disease Monitor & Commentary

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

From the editor...

ANDREW D. SIDEROWF, MD

Whether the data from a controlled trial does or does not support the study's hypothesis, those who interpret the results still must determine whether the study asked the right question, had reasonable design characteristics for a relevant answer, and, if the study has clinical implications, offers meaningful information for typical practice. In every issue of *PD Monitor & Commentary*, this is the key exercise performed by our invited experts, and the story often proves more complex than might be derived from a cursory reading of the study conclusion.

As in past issues, we have asked our experts to explain the significance of an array of negative and positive studies, and, as is typical, the expert commentary generates a better understanding of the significance of the data. For example, the negative results of a study on physiotherapy do not impress our reviewer, Dr. Michael Okun from the University of Florida, as much as the context of the care model in which this approach is evaluated. Likewise, a disappointing study on stimulation of the pedunculopontine nucleus to improve gait provides a forum for Dr. Kelvin Chou of the University of Michigan to offer some background about how studies of deep brain stimulation *should* be performed.

This issue also allows Dr. Laura Marsh of Baylor University an opportunity to explain why a study of dopamine withdrawal syndrome provides a good context to raise awareness of this often misdiagnosed complication, while Dr. Stuart Isaacson of the Parkinson's Disease and Movement Disorders Center of Boca Raton, Florida examines a phase IV study of rasagiline to explain why we need to re-look at drugs proven effective in clinical trials from the perspective of a typical neurology practice.

The perspective of our experts does not supplant but rather adds to the context of the discussion sections of the articles that are reviewed. As always, we strongly recommend going to the original sources for further information.

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Commentators

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PD Monitor & Commentary

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Dopamine agonist withdrawal syndrome in Parkinson disease.

First Author and Institution:
Christina A. Rabinak, BSE, Weill Cornell Medical College, New York, New York.

Citation:
Archives of Neurology. 2010;67:58-63.

Objective:
Characterize dopamine agonist (DA) withdrawal syndrome in Parkinson's disease (PD).

Type of Study:
Retrospective cohort study.

Result:
There is a DA withdrawal syndrome that imposes significant complications similar to other types of drug withdrawal syndromes, such as end-of-dose wearing off.

Conclusion:
Awareness of the DA withdrawal syndrome and its potential association with impulse control disorders (ICDs) can accelerate diagnosis if patients are monitored appropriately.

DAs stimulate mesocorticolimbic dopaminergic neurons, and, like several other agents that stimulate these same neurons (such as cocaine and amphetamines), lead to both dependence and withdrawal phenomena.

The goal of this prospective study of 93 nondemented patients with PD was to characterize DA withdrawal, including psychological well-being and social function. Forty patients were taking a DA and 26 underwent DA tapering. The most common reason for tapering was the emergence of ICDs, which occurred in 58% of the DA tapering cohort.

Of the 26 patients who underwent DA tapering, five (19%) developed a DA withdrawal syndrome, characterized by symptoms such as anxiety, dysphoria, drug cravings, irritability, and fatigue, which were similar to end-of-dose wearing-off phenomena. All who experienced withdrawal symptoms had ICDs. Symptoms were refractory to antidepressants, benzodiazepines, and cognitive behavioral therapy. When DA therapy was restored, however, symptoms improved.

The authors conclude that there is a substantial risk of mistaking DA withdrawal symptoms for underdosing or wearing off of anti-PD medications.

Commentary:

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

This is an interesting and practical article that draws attention to an important clinical problem that is challenging to manage even when identified early. The most important point is that some patients taking DAs will develop a serious and disabling drug withdrawal syndrome that consists of the same physical, behavioral, and emotional symptoms observed in withdrawal states from other addictive drugs. In addition, there is a significant risk of confusing the DA withdrawal syndrome with a separate psychiatric disturbance, such as panic attacks or a mood disorder, or with end-of-dose wearing off from antiparkinsonian medications, which can exhibit some of the same features. By contrast, the withdrawal symptoms are relieved only with resumption of the DA, as opposed to other dopaminergic medications or antidepressants.

It is remarkable that almost 20% of those who tapered DAs developed a clinically significant withdrawal syndrome. Although it is not clear that these patients from a tertiary care clinic are representative, it does suggest that DA withdrawal is a common problem. While nonmotor withdrawal phenomena have been associated with dopaminergic replacement therapy, this article points out a withdrawal syndrome associated specifically with DAs. It further underscores the need to monitor motor and nonmotor phenomena when prescribing DAs, and to consider a DA withdrawal syndrome in the differential diagnosis when patients complain of depression or anxiety or other signs of a change in well-being. ■

Efficacy and tolerability of rasagiline in daily clinical use–a post-marketing observational study in patients with Parkinson disease.

First Author and Institution:
Heinz Reichmann, MD, University of Dresden, Dresden, Germany.

Citation:
European Journal of Neurology. 2010; Epub ahead of print.

Objective:
Evaluate efficacy, safety, and tolerability of rasagiline in routine clinical practice.

Type of Study:
Post-marketing observational study.

Result:
Consistent with the double-blind, randomized studies that led to approval of rasagiline for Parkinson's disease (PD), this post-marketing evaluation in Germany associated this agent with efficacy, safety, and an improvement in quality of life (QoL).

Conclusion:
In daily clinical use outside the confines of a clinical trial, rasagiline provided a similar degree of symptom control and tolerability as that observed in controlled studies, supporting its clinical utility.

Rasagiline, a highly selective monoamine oxidase-B (MAO-B) inhibitor, was approved for use as a PD treatment on the basis of a series of large, multicenter, double-blind, randomized studies, such as TEMPO, which tested rasagiline as a monotherapy, and the LARGO and PRESTO studies, which tested rasagiline as an adjunct to levodopa. All of these studies found rasagiline to be well tolerated and effective for reducing symptoms of PD.

The goal of this post-marketing study was to determine whether the efficacy and safety associated with rasagiline in clinical trials was similar in the hands of neurologists working in the private practice setting. The study included 754 patients treated at 256 centers, most of which were private neurology practices. Patients received rasagiline 1 mg daily either as a monotherapy or in combination with levodopa. Over the 4-month observation period, efficacy was measured as a change from baseline with the Columbia University Rating Scale (CURS), the Unified PD Rating Scale fluctuation subscale, and daily off time, and QoL with the PD-Questionnaire-39.

Relative to baseline, patients treated with rasagiline achieved a reduction in PD symptoms, a reduction in off time, and an improvement in QoL. Patients switched from oral selegiline to rasagiline showed significant symptomatic improvements. Tolerability was rated as good or very good in 97% of rasagiline-only therapy patients and 90% in combination therapy patients. Only 1% on monotherapy and 5% on combination therapy withdrew due to adverse events. These safety and tolerability results were consistent with the randomized trials.

This study provides confirmation of the efficacy and tolerability of rasagiline in "real world" practice. The findings suggest that the performance of rasagiline is similar in daily clinical use as previously reported in the randomized trials.

Commentary:

Stuart Isaacson, MD
Associate Professor of Neurology
FIU Wertheim College of Medicine
Miami, Florida
Director
Parkinson's Disease and Movement Disorders Center of Boca Raton
Boca Raton, Florida

Although this study was not placebo-controlled, blinded, or randomized, it provides post-marketing evaluation of rasagiline in daily clinical use in a large population of patients with PD at more than 250 private practices in Germany. The investigators report similar efficacy, tolerability, and safety as was seen in the three pivotal double-blind trials (TEMPO, PRESTO, and LARGO) of the drug. In view of the recently published ADAGIO study and the TEMPO extension report, it will be important to continue efforts to accumulate additional post-marketing surveillance data with rasagiline to try to confirm clinically meaningful improvements on long-term outcomes.

It is reassuring that this report identified no unexpected adverse events with rasagiline in patients treated by practitioners in routine clinical care, and confirmed the efficacy of rasagiline when used either as early monotherapy or later as adjunctive therapy to levodopa. This report thus enhances the evidence base that rasagiline can provide clinically meaningful benefits for patients with both early PD treated initially with rasagiline, as well as those with advancing disease treated adjunctively with rasagiline to reduce daily off time. ■

Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease.

First Author and Institution:
Murielle U. Ferraye, MD, Grenoble Institute of Neuroscience, Grenoble, France.

Citation:
Brain. 2010;133:205-214.

Objective:
Evaluate stimulation of the pedunculopontine nucleus (PPN) as a treatment for gait disturbances.

Type of Study:
Double-blind, crossover study.

Result:
Major improvement was observed in several measures of gait function in one of five evaluable patients, minor improvement was observed in four patients, and one patient had worsening of gait function.

Conclusion:
The results are disappointing relative to much more consistent benefits observed previously in open-label studies, but the treatment was safe and additional studies appear to be warranted.

Stimulation of the PPN, which has been shown to control locomotion in experimental studies, has been associated with symptom improvement in several previous open-label studies conducted in patients with Parkinson's disease (PD). These results prompted this controlled trial.

In this study, six patients with severe freezing of gait unresponsive to levodopa or subthalamic nucleus (STN) stimulation were enrolled. Patients were evaluated prior to bilateral placement of electrodes in the PPN and then in a series of double-blind, crossover evaluations with and without PPN stimulation. The primary outcome measures included a composite gait score, duration of freezing 1 year after surgery relative to baseline during a standardized walking test, and a gait questionnaire score.

One patient was unevaluable because withdrawal of STN stimulation caused severe akinesia and breathing difficulties. Of the other five, one patient improved on all gait function measures whether on or off PPN stimulation. Three patients improved on some but not all scores, again independent of whether on or off PPN stimulation. The last evaluable patient slightly worsened on gait scores whether on or off PPN stimulation. For the whole group, objective freezing off levodopa was significantly improved on PPN stimulation (P=0.046) but not off PPN stimulation (P=0.08). Neither surgery nor PPN stimulation were associated with any significant complications.

The results are disappointing relative to greater benefit previously observed in open-label studies, but the authors suggest that more consistent improvements might be achieved with improvements in patient selection.

Commentary:

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

The PPN has drawn considerable interest as a target for deep brain stimulation (DBS) due largely to several reports of gait improvement and postural instability with low-frequency PPN stimulation in patients with PD. This study reports 1-year outcomes of PPN DBS for six patients with PD who developed gait difficulty and freezing. Only one patient still had falls secondary to freezing at 1 year, but ratings of gait and motor symptoms were unchanged. The investigators also carried out a double-blind, crossover study in these patients between months 4 and 6 with PPN stimulation on and off, but there was no change in Unified Parkinson Disease Rating Scale (UPDRS) scores or duration of freezing episodes.

Unfortunately, the findings were not as robust as previous reports of PPN stimulation, which not only reported significant improvement in gait, but also improvement in global motor functioning. These patients were also difficult to program because there were no acute effects from turning the stimulation on or off, and chronic stimulation effects could last for days.

The findings in this study suggest that PPN stimulation may not be as promising for gait disorders as once thought. Future controlled trials with blinded evaluation measures will be necessary. The issue of how to stimulate will also need to be further explored. Programming the PPN appears to be more complex than programming the STN, and may require patients to be seen only at large DBS centers with specific expertise. ■

Efficacy of community-based physiotherapy networks for patients with Parkinson's disease: A cluster randomized trial.

First Author and Institution:
Marten Munneke, MD, Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands.

Citation:
Lancet Neurology. 2010;9:46-54.

Objective:
Assess the benefit of physiotherapy care delivered within patient care networks.

Type of Study:
Cluster randomized trial.

Result:
There was no difference in the primary outcome of disability score or in secondary outcomes from physiotherapy care within networks relative to controls, although network health care costs were lower.

Conclusion:
Although this study failed to show an advantage for physiotherapy delivered within a network care setting, the authors remain supportive of the network approach to delivery of Parkinson's disease (PD) care.

Physiotherapy has been frequently employed to improve outcomes in patients with PD but there is limited standardization of this care, creating the possibility of wide deviations in the quality of treatment. The potential for substandard care is particularly high among physiotherapists who infrequently treat patients with PD. To improve overall care in The Netherlands, a system of patient care networks, called the ParkinsonNet system, was created. In this system, physiotherapists are specifically and expertly trained to treat patients with PD.

The current study's goal was to evaluate the benefit of physiotherapy administered from the ParkinsonNet system relative to usual care. The 699 participating patients were randomized to 16 regional clusters in which they received care either in a ParkinsonNet program (eight clusters) or outside of such a program (eight clusters). As the assigned program was the only one available in that region, neither the patients nor the caregivers were aware that care differentiated between these clusters. The hypothesis was that the specific training of physiotherapists participating in the ParkinsonNet program would improve outcomes.

When the groups were compared, there was no significant difference between the two groups in a patient preference disability score, the primary measure. There were also no significant differences in secondary outcomes, which included functional mobility and mobility-related quality of life. However, the costs of care were lower in the ParkinsonNet group. The difference was driven primarily by a reduction in the need for home care and hospital outpatient rehabilitation.

Even though this study did not prove its hypothesis, the reduction in cost was considered to provide some validation for the ParkinsonNet programs. Further studies looking at whether other aspects of care can improve outcome if delivered through these specialty programs are anticipated.

Commentary:
Michael Okun, MD
Co-Director, Movement Disorders Center
National Medical Director
National Parkinson Foundation
University of Florida
Gainesville, Florida

The concept of an integrated care model for the management of PD is very attractive. Although the results of the Munneke paper were somewhat disappointing (failing to validate the specific physiotherapy approach attempted), there were some advantages to the program, especially in cost savings. These current data in my opinion should not discourage the future development of ParkinsonNet concepts of care delivery. We should keep in mind that there are many potential benefits that may be derived from excellent physiotherapy, and there are accumulating numbers of clinical studies that suggest improved function from therapy. Improvements in motor and nonmotor function as well as disease-modifying effects are currently being sought by many investigators, but we should remain cautious in rendering an opinion until we see solid results.

The authors tell us that the ParkinsonNet program, which has been expanded since this current study was conducted, may now be exportable to other countries and other types of health care systems. This is a concept that deserves further refinement and study, despite the failure of the current study to reach the predefined primary outcome. ■

Does clinical rapid eye movement behavior disorder predict worse outcomes in Parkinson's disease?

First Author and Institution:
Sophie Lavault, MD, Sleep Research Unit, Assistance Publique-Hôpitaux de Paris, Paris, France.

Citation:
Journal of Neurology. 2010; Epub ahead of print.

Objective:
Evaluate rapid eye movement disorder as a marker of degenerative Parkinson's disease (PD).

Type of Study:
Longitudinal cohort study.

Result:
At baseline, rapid eye movement (REM) sleep disorder (RDB) predicted greater disability, but not faster progression of PD. Moreover, the presence of this disorder was not consistent over time.

Conclusion:
Contrary to previous reports, the presence of rapid eye movement sleep disorder may not be a sign of a more rapid neurodegenerative subtype of PD.

RBD is characterized by a variety of changes in sleep patterns, such as enacted dreams. There are several lines of evidence that suggest it is mediated by non-dopaminergic neurologic abnormalities and may be a negative prognostic marker for PD.

In this study, RBD was evaluated in a prospectively collected cohort of 61 patients with PD. These patients were followed over a 2-year period. All evaluations during the course of the study were conducted by the same examiners using the same standardized examinations.

Although 64% of patients had RBD at the baseline examination, only 52% had RBD 2 years later. A substantial proportion of patients switched status during the course of the study. At baseline, there was greater disability in those with RBD than those without, but there was no difference in worsening of symptoms for those with RBD at baseline. The authors report that there was no evidence that PD drugs had a specific impact on RBD.

Rather than being an early sign of progressive PD, the results of the study suggest that RBD symptoms fluctuate. The authors note that RBD symptoms not only ranged substantially in severity on a nightly basis, but appeared to resolve in individual patients for indefinite periods. They conclude that RBD is not a marker of severe PD, nor does it predict an increased propensity for progression. Rather, RBD appears to develop and resolve without any clear pattern.

Commentary:

Ron Postuma, MD
Assistant Professor
Department of Neurology
McGill University
Montreal, Canada

There have been a number of publications from several different centers examining whether patients with PD and RBD represent a distinct subset of patients who may have a poor prognosis and a greater risk for specific complications of PD, such as cognitive impairment. This study continues this story.

Perhaps one of the most important observations of this study is that clinical symptoms of RBD are often transient, appearing and then resolving in individual patients without a clear pattern (without sleep studies, we cannot be sure that the RBD did actually resolve). Of the patients in this study, approximately 15% switched categories over the course of follow-up. Even though the sample size was small, the fact that the investigators were able to evaluate patients over a 2-year period is a study strength.

In our work in RBD, one of the strongest correlations we have seen has been with cognitive impairment. Although the authors of this study did not make the same correlation, cognitive change was measured with the Mini-Mental State Examination (MMSE), which is relatively insensitive.

The authors did not find RBD to be a marker of more aggressive PD, but it is still important to identify patients with this condition, because effective treatment of RBD may improve quality of life.

The basic question of whether we can find specific symptoms, such as RBD, that will identify subtypes of PD remains interesting, even if this study did not support that premise. ■

Responsiveness of the EQ-5D and 8-item Parkinson's disease questionnaire (PDQ-8) in a 4-year follow-up study.

First Author and Institution:
Nan Luo, MD, National University of Singapore, Singapore.

Citation:
Quality of Life Research. 2010;19:565-569.

Objective:
Compare the EQ-5D and the Parkinson's Disease Questionnaire (PDQ-8) for assessing disease-related decline in health-related quality of life (HRQoL) in patients with Parkinson's disease (PD).

Type of Study:
Secondary analysis of data collected from two clinical surveys conducted 4 years apart.

Result:
Over 4 years, both the EQ-5D and PDQ-8 tests detected HRQoL deterioration with comparable sensitivity in patients with PD.

Conclusion:
Although the PDQ-8 detected a greater effect size than the generic EQ-5D for disease burden, the EQ-5D remained sensitive for large changes and may have similar accuracy over extended periods.

Serial measurements of HRQoL in patients with PD have potential clinical utility for understanding the burden of this disease. Although both disease-specific and generic QoL instruments have been evaluated, neither have been well studied for relative sensitivity to changes over time.

In this study, conducted in Singapore, HRQoL was measured in 31 patients with the generic EQ-5D, PDQ-8, Hoehn and Yahr (H&Y) staging for PD, and the EQ visual analog scale (VAS). Most subjects were male. The initial assessments were conducted in 2002 and then again 4 years later. The Cohen's Effect Size (ES) and the standardized response mean (SRM) were evaluated for each method of QoL assessment.

On the basis of the ES and SRM indices, the ranking of the HRQoL measures from most to least sensitive was the PDQ-8, EQ-5D, H&Y staging, and EQ-VAS. For the PDQ-8, there was significant deterioration from baseline in mobility, activities of daily living, well-being, and social support. Although the EQ-5D was not considered less sensitive overall than the PDQ-8 in this study, the authors suggest that it may be best suited for capturing large changes in HRQoL (such as those that occur over extended periods of follow-up).

On the basis that both the EQ-5D and the PDQ-8 were found to be sensitive for evaluating deterioration in HRQoL over extended periods of time in patients with PD, the authors suggest that disease-specific tests may not be essential for measuring many types of domains, such as deterioration in the ability to perform normal daily activities, when measured over many years. However, disease-specific evaluations may be more sensitive for evaluating short-term changes.

Commentary:

Andrew D. Siderowf, MD
Associate Professor of Neurology
Parkinson's Disease and Movement Disorders Center
University Of Pennsylvania
Philadelphia, Pennsylvania

This study addresses the issue of responsiveness of two self-report HRQoL scales. Although the study has methodological limitations (including small sample size), it is useful in that it shows that both the PDQ-8 and EQ-5D are responsive to change over a 4-year period of time in patients with PD.

This study complements a recent report (Schrag et al. Movement Disorders. *2009;24:813-818) that showed less responsiveness for both the EQ-5D and the PDQ-39 to change over 1 and 4 years than standard clinical measures such as the Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn and Yahr staging. In the prior study, the PDQ-39 was more responsive than the EQ-5D over short periods of time, but the two scales were similarly responsive to change over 4 years. Taken together, these two studies suggest that brief self-report instruments such as the PDQ-8 and EQ-5D are probably not responsive to short-term changes in PD disability, but may be useful in longer studies. In order to determine how these scales should be used in clinical trials, future studies should compare the responsiveness of these instruments to a variety of interventions.* ■

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