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Parkinson's Disease Monitor & Commentary

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

From the editor...

ANDREW D. SIDEROWF, MD

Several papers reviewed in this issue of *Parkinson's Disease Monitor & Commentary* address non-motor features of Parkinson's disease (PD). These studies provide yet more data to support the widely held understanding of the importance of these disabling and often treatment-resistant aspects of PD. The Italian PRIAMO study illustrates exactly why patients with PD need to be specifically questioned about non-motor systems from the first office visit. Our expert commentator, Dr. Hubert Fernandez of the University of Florida, points out that it is no surprise that almost 100% of patients in the PRIAMO study reported non-motor symptoms, a growing focus of efforts to improve quality of life. Likewise, Dr. Sotirios Parashos of the Struthers Parkinson's Center in Minnesota evaluates a study of the prevalence of anxiety disorders, which may not always be easily detected, in patients with PD.

In another commentary relevant to clinical practice, a second expert from the University of Florida, Dr. Michael Okun, reviews the results of a randomized trial of glutathione that showed no benefit of treatment on PD symptoms. He emphasizes that nothing has changed about the status of intravenous glutathione since publication of a double-blind study that showed reassuring safety but no clear signal of efficacy.

In each issue, we look for a broad array of topics, ranging from efforts to move the field forward at the level of basic science to novel therapeutic techniques that are entering human studies but may still be some distance away from clinical significance. Our format is specifically designed to produce information that is easy to digest, interesting to read, and relevant to a better understanding of PD. As always, we encourage readers who find a particular topic compelling to go to the original source. The discussion sections often provide valuable insights beyond what we can accommodate in these summaries. Suggestions are always welcome. Please feel free to reach me at info@delmedgroup.com.

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Adherence to antiparkinson medication in a multicenter European study.

First Author and Institution:
Donald Grosset, MD, Institute of Neurological Sciences, Glasgow, Scotland.

Citation:
Movement Disorders. 2009;24:826-832.

Objective:
To assess adherence of patients with Parkinson's disease (PD) to therapy.

Type of Study:
Prospective study.

Result:
The correct drug dose was taken on the correct day by 86.2% of patients, but only 24.4% of the doses were taken at the correct time intervals. Suboptimal dosing was associated with more symptoms.

Conclusion:
Patients may require specific education about the need for adherence.

Suboptimal adherence is common to essentially every type of therapy, but the patterns and consequences of nonadherence to medications for PD deserve attention because of the importance of timing of medication. For short-acting medications such as levodopa, the risk of inappropriate adherence includes increased wearing-off effects.

One hundred and twelve patients taking PD medications at eight European centers were evaluated for adherence to dopamine agonists over a period of 4 weeks. Electronically monitored pill containers recorded the date and time of cap opening.

Total adherence in the study was 97.7% and the total number of days that the correct dose was taken was 86.2%, but adherence for timing of the doses was only 24.4%. When those with suboptimal total adherence were compared to those with acceptable or optimal adherence, the median Parkinson motor score was found to be significantly higher for the former (29 vs. 19; P=0.005). There was also a highly significant adherence advantage for once-daily drugs vs. drugs taken more frequently (P<0.0001).

Commentary:

Norman A. Leopold, DO
Director, Parkinson Disease and Movement Disorder Center
Crozer-Chester Medical Center
Upland, Pennsylvania

Adherence is always an important issue in medicine, but this study examined several aspects of medication adherence relevant to PD. After determining whether subjects with PD were taking their medications daily, the most important questions asked were whether the correct number of daily doses were taken and whether they were taken at the prescribed intervals. Only 1/4 of subjects timed their doses correctly.

*This and the overall rates reported are very likely to be a serious overestimation for several reasons. Subjects were aware that their dosing schedules were being evaluated; caregivers were allowed to assist if they were doing so prior to the study; and once-daily dosing was permitted. In a prior study using the same technology to monitor medication adherence but without these limitations, daily adherence rates were 51% vs. 86% (*Movement Disorders. *2005; 19:513-517). Also, in the prior study, subjects significantly overestimated their adherence when compared with the objective data provided by electronic monitoring bottles.*

Regardless of the disease being treated, the more frequently patients take medications, the more likely they will be non-adherent. Ideally, to improve drug adherence in PD, levodopa needs to be formulated as once per day (or longer) dosing. As we wait for this breakthrough, discussions with patients regarding the importance of medication adherence cannot be overemphasized. The benefits of good adherence are supported by Grosset et al. When compared to non-adherent subjects, those that followed their schedules were less symptomatic on significantly less medication. ■

The PRIAMO Study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease.

First Author and Institution:
Paolo Barone, MD, Università Federico II and IDC-Hermitage-Capodimonte, Napoli, Italy.

Citation:
Movement Disorders. 2009; Epub ahead of print.

Objective:
Assess the prevalence of non-motor symptoms in Parkinson's disease (PD).

Type of Study:
Multicenter survey.

Result:
Almost 100% of patients with PD reported non-motor symptoms, of which fatigue, anxiety, and leg pain were the most common.

Conclusion:
Non-motor symptoms are an important part of the disease burden of PD and deserve to be included within management targets in order to improve quality of life.

The onset of PD is generally defined by such classic symptoms as tremor and bradykinesia, but non-motor symptoms such as anxiety may actually precede the definitive signs and symptoms of PD. The prevalence rates of different types of non-motor symptoms have not been well characterized.

In this study, semistructured interviews were conducted over a 12-month period at 55 participating treatment centers in Italy. The goal was to establish the prevalence of non-motor symptoms and assess their impact on quality of life. The 12 domains assessed in the interview included those involving sleep, psychiatric complaints, respiratory deficits, and pain. Quality of life was assessed with the 39-item Parkinson's Disease Questionnaire (PDQ).

Of 1,072 consecutive patients evaluated, 98.6% reported at least one non-motor symptom. Most reported several. These included fatigue in 58%, anxiety in 56%, leg pain in 38%, insomnia in 37%, nocturia or urinary urgency in 35%, drooling in 31%, and difficulties concentrating in 31%. The mean number of non-motor symptoms per patient was 7.8. Many of these symptoms had a substantial negative effect on quality of life.

The high prevalence of non-motor symptoms reinforces the importance of routinely inquiring about these complaints in order to improve quality of life in the PD population.

Commentary:

Hubert H. Fernandez, MD
Associate Chair of Academic Affairs
Co-Director, Movement Disorders Center
Department of Neurology, University of Florida
Gainesville, Florida

This was a very well-performed study concerning an important topic in the management of PD. There is a growing appreciation for the fact that non-motor symptoms often exert a greater clinical burden on the patient than do motor symptoms with which PD is still currently defined. To those of us with an interest in this area, it is not surprising that essentially 100% of patients had at least one non-motor symptom.

One of the strengths of this study, unlike most previous studies that concentrated on one set of non-motor symptoms, is that it attempted to evaluate a full spectrum of complaints in a variety of organ systems. This provides an opportunity to consider the relative importance of these symptoms. In this context, the finding that fatigue, anxiety, and leg pain were the most prevalent non-motor symptoms, even in a relatively early disease cohort, was surprising. These symptoms, especially pain, are not typically brought up by the patient or questioned by the doctor early in the disease process. Another important finding from this study was that apathy had the strongest negative impact on quality of life. While the authors found a correlation between apathy and impaired cognitive function, one criticism of the study is that the Mini-Mental State Examination (MMSE), which is not very sensitive in patients with PD, was the tool used to make this correlation. However, this does not detract from the potential importance of evaluating patients with PD for the presence of apathy, and the slowly growing literature on its cognitive implications, which require further clarification.

Overall, these data strongly support greater attention to non-motor symptoms, which may not necessarily be volunteered. ■

Randomized, double-blind, pilot evaluation of intravenous glutathione in Parkinson's disease.

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

Citation:
Movement Disorders. 2009;24:979-983.

Objective:
Evaluate safety and efficacy of intravenous (IV) glutathione in Parkinson's disease (PD).

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

Result:
Over 4 weeks, glutathione was well tolerated. The efficacy data were not convincing for a symptomatic effect, but a larger study may be more definitive.

Conclusion:
From the safety point of view, there were no significant adverse events that would prohibit a larger clinical study, but there was little clinical activity. Further studies may require alternative dosing schedules.

Glutathione has several activities in the brain that are consistent with neuroprotection, particularly antioxidant effects. Previous studies have suggested that glutathione levels fall by as much as 50% in PD, correlating with symptom severity. Experimental studies and small preliminary clinical studies have suggested that administration of exogenous glutathione may have mild benefits in patients with PD.

In this study, patients with PD who were not adequately controlled on their current therapy were randomized to receive 1,400 mg of glutathione or placebo diluted in 10 mL of normal saline administered over 10 minutes by IV push 3 times a week for 4 weeks. The primary objective of the study was to evaluate the safety of glutathione over the 4 weeks of therapy and an additional 8 weeks of follow-up, although changes in PD symptoms were also monitored over this period.

Ten patients were enrolled and evaluable in each treatment arm. Over the 4 weeks of active treatment and 8 weeks of subsequent observation, there were no clear differences in the type or severity of adverse events between the active treatment and placebo groups. There were also no significant differences in symptom scores when compared on such standard methods as the Unified Parkinson's Disease Rating Scale (UPDRS).

This study confirms the short-term safety of glutathione. There was no sign of efficacy, but the authors stressed that the study was not powered for efficacy endpoints and further studies are warranted.

Commentary:

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

Glutathione, a tripeptide of glutamate, cysteine, and glycine, is associated with several properties that suggest a potential for benefit in PD. Depleted in the brains of patients with PD, glutathione has antioxidant properties that might be anticipated to be neuroprotective. This study is the first randomized, double-blind, placebo-controlled trial for an agent that is already being administered at some centers on the basis of its theoretical benefits. The study underlines the importance of withholding treatments until there is controlled evidence of benefit. This study only randomized 20 patients, and there remains no convincing evidence that glutathione offers any worthwhile efficacy for patients. Glutathione was well tolerated, but delivery through an IV line has both short- and long-term risks. Oral delivery may not be an alternative, because it has not yet been clearly demonstrated that glutathione crosses the blood:brain barrier even when administered via IV. The likelihood of penetrating the brain would be expected to be even less with oral delivery.

Due to the potential promise of glutathione, there has been a demand for treatment despite a lack of controlled evidence of benefit. Although the results of this study do not preclude the potential for benefit in a larger study, particularly using alternative dosing schemes, it is important to emphasize to patients and physicians that there is no evidence of benefit from glutathione for PD at the current time. ■

Human substantia nigra neurons encode unexpected financial rewards.

First Author and Institution:
Kareem A. Zaghloul, MD, University of Pennsylvania, Philadelphia.

Citation:
Science. 2009;323:1496-1499.

Objective:
Monitor activity of substantia nigra (SN) neurons during reward conditioning to evaluate their role in learning.

Type of Study:
Electrode monitoring of brain activity in patients with Parkinson's disease (PD) undergoing deep brain stimulation (DBS) surgery.

Result:
SN neurons fired at an increased rate in patients experiencing unexpected gains vs. losses in a probalistic learning task. There were no differences when gains or losses were expected.

Conclusion:
The findings provide compelling evidence that SN neurons are involved in human reward-based learning.

In non-human primates, midbrain dopaminergic neurons have been shown to be particularly active after an unexpected reward but depressed when there is an unexpected omission of a reward. These observations have contributed to the hypothesis that this area of the basal ganglia is crucial to learning, and particularly to learning reinforced by rewards.

This study attempted to evaluate the same neuronal activity in humans participating in a probabilistic learning task. The participants were patients with PD undergoing surgical DBS, which allowed microelectrode placement. The SN neuron firing rate was monitored while the patients participated in a card-selection task, which generated both expected and unexpected gains and losses. These gains and losses were expressed in financial rewards, although no money was ultimately distributed. There were six male and four female patients with an average age of 61 years.

When SN neuron firing was stratified into unexpected gains or losses and expected gains and losses, the greatest neuronal firing rate was observed after unexpected gains. This rate of neuronal firing was significantly less when losses were unexpected. There was no difference in neuronal firing for expected outcomes, whether positive or negative.

This study, the first to directly measure neuronal activity in humans during learning tasks, reinforces previous evidence that neurons in the basal ganglia play an important and perhaps key role in reward-based learning. The findings are highly consistent with studies performed previously in non-human primates, providing support for the relevance of these studies to human functions. The activity observed in the SN neurons is also consistent with the hypothesis that abnormal activity of the basal ganglia may be involved in disorders affecting reward-seeking behavior, such as addictions.

Commentary:

Andrew D. Siderowf, MD
Associate Professor of Neurology
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University of Pennsylvania
Philadelphia, Pennsylvania

Classical conditioning and reinforcement theories postulate a central role for the dopamine system in learning from positive and negative feedback, a role that has previously been demonstrated in non-human primates. This study makes a crucial contribution because it is the first direct demonstration of this phenomenon in humans. The investigators, producing a pattern of neuronal firing that closely follows the pattern previously observed in primates, used a well-established model of reward learning, as well as an innovative approach to differentiating dopaminergic neuron firing from other cell types. They demonstrate that the human SN responds preferentially to novel stimuli that are associated with positive feedback. It is particularly remarkable that the investigators were able to show the expected pattern of firing in patients with PD in whom the population of dopaminergic neurons was depleted.

The main relevance of this study is as a significant contribution to experimental psychology and clinical neurophysiology. It is also relevant to the understanding of cognition in patients with PD. This study, along with other recent studies, emphasizes that the ability to learn from novel stimuli depends on dopaminergic transmission. These studies show that reward learning may be impaired in PD, may be directly affected by dopaminergic medications, and imply conditions under which patients with PD may optimally learn new information. ■

Deep brain stimulation and cognitive functions in Parkinson's disease: A three-year controlled study.

First Author and Institution:
Roberta Zangagalia, MD, IRCCS C. Mondino Institute of Neurology Foundation, Pavia, Italy.

Citation:
Movement Disorders. 2009; Epub ahead of print.

Objective:
Evaluate cognitive effects of deep brain stimulation of the subthalamic nucleus (STN-DBS).

Type of Study:
Prospective, non-randomized, controlled, naturalistic follow-up study.

Result:
Except for verbal fluency, DBS did not adversely affect cognitive function relative to controls with Parkinson's disease (PD) when evaluated after 3 years of follow-up.

Conclusion:
This study does not corroborate an increased risk of dementia or cognitive dysfunction after DBS among patients followed for 3 years, but does not rule out accelerated cognitive loss over longer periods.

The growing appreciation for the risk of cognitive dysfunction in PD has prompted numerous investigators to consider the effects of surgical therapy on this endpoint, which is now widely regarded as an important non-motor PD symptom that adversely affects quality of life.

In this naturalistic study conducted over 3 years, 32 patients with PD who underwent STN-DBS were compared to 33 patients with PD who were eligible for STN-DBS but declined this therapy and received best medical care. These two groups were evaluated with a battery of examinations, including a long-term memory task test, a verbal fluency test, and the Wisconsin Card Sorting Test (WCST). The evaluations were conducted at baseline prior to surgery in the DBS group, at intervals over the 36 months of follow-up, and at the end of follow-up.

At baseline, there were no significant differences in cognitive function between the two groups. Relative decrements in executive function were observed among DBS subjects at 1 month compared with baseline, but this decrement had disappeared by 6 months. Verbal fluency was also less at 1 month after surgery; it returned to the normative range by month 6, but by month 36 FAS scores were significantly worse in the STN-DBS group than in the placebo group. Cognitive function remained relatively stable over the subsequent 36 months in both groups. There were no observed effects on memory.

The authors concluded that DBS does not appear to pose a significant threat to cognitive performance over a 3-year period.

Commentary:

Kelvin L. Chou, MD
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The frequency and severity of cognitive changes after DBS in PD is controversial despite many studies that have addressed this issue. Few of the previous studies were controlled, and those that were controlled generally followed patients for a relatively short period. The article by Zangaglia et al. is significant because it is the first long-term, controlled, prospective study of cognitive outcomes following STN-DBS surgery. At 36 months, no cognitive domain was significantly different from baseline, except for the Mini-Mental State Examination scores, which had declined in both groups (but were still within the normal range). However, the DBS group had worse verbal fluency than the control group at 36 months, a finding consistent with other studies. This study, like most previous studies, was limited to individuals with generally good baseline cognitive function, so it may not be relevant in those with more deficits. Also the repeated administration of the neuropsychological test battery may have produced a learning effect, masking deterioration. In addition, the patients were not randomized and the neuropsychologists were not blinded to the treatment.

When combined with previous studies, these data support the conclusion that STN-DBS surgery does not result in significant cognitive changes in carefully selected (i.e., non-demented) patients with PD. However, even when stringent selection criteria are applied, there is still a minority of patients with PD who worsen cognitively after surgery. We need more studies to understand what variables predispose these patients to cognitive decline. ■

Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease.

First Author and Institution:
Gregory M. Pontone, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Citation:
Movement Disorders. 2009; Epub ahead of print.

Objective:
Determine prevalence of anxiety disorders in patients with Parkinson's disease (PD).

Type of Study:
Prospective evaluation in consenting patients.

Result:
Forty-three percent of patients had at least one anxiety disorder. The estimated lifetime prevalence of anxiety disorders in PD was 49%.

Conclusion:
Anxiety is a common complication of PD and may be under-recognized, particularly because the symptoms are not always consistent with recognized subtypes.

The association between PD and anxiety is sufficiently common to raise the possibility that they are pathophysiologically related. Better characterization of anxiety, which is a heterogeneous disorder, in patients with PD may lead to a better understanding of the relationship between these conditions, thereby improving diagnosis and treatment.

In this study, a sample of 127 patients with PD from three community practices underwent comprehensive assessments that included both neurological and psychiatric evaluations by a movement disorders specialist and a psychiatrist. The major exclusion criteria was a Mini-Mental State Examination (MMSE) score of <24.

At the time of evaluation, 43% of patients were diagnosed with anxiety. The most common type of anxiety was non-specific, a category used by the *Diagnostic and Statistical Manual (DSM)* for those who do not fit into common subcategories, such as social phobia. These accounted for 25% of all cases of anxiety disorder. The next most common type of anxiety was specific phobias (13%), which were often associated with PD-related motor deficits, such as fear of falling or wearing-off of medication.

The study contributes new evidence to previous assertions that anxiety is highly prevalent in patients with PD, and that the forms of expression of anxiety are often atypical. The fact that some of the anxiety in PD is not easily classified to specific *DSM* subtypes may explain why anxiety is not a better recognized co-morbidity of PD. More attention to anxiety in patients with PD appears to be warranted.

Commentary:

Sotirios Parashos, MD, PhD
Chair, Medical Research
Struthers Parkinson's Center and Minneapolis Clinic of Neurology
Golden Valley, Minnesota

There have been many studies over the years linking PD to anxiety, but this study has several strengths. It is one of the largest studies conducted so far and it employed a relatively rigorous methodology, including diagnosis of anxiety by a consensus of experts. It was also a community-based study, suggesting that the findings may be representative of patients with PD commonly seen in daily practice. The emphasis on differentiating anxiety types is also important.

The potential weaknesses of the study are that the average duration of PD was only 8 years, and only 15% of patients had advanced disease. Also, participants were volunteers, which may have produced a selection bias. However, the study contributes substantially to the previous evidence that PD and anxiety may have a common etiology and that there may be PD-specific phenotypes for anxiety, such as anxiety correlating with motor fluctuations. It is also interesting that the average age of the onset of anxiety was about 10 years earlier than the average age of onset of PD, suggesting that anxiety could be an early sign of PD if, in fact, they are driven by common pathophysiologic mechanisms.

For the clinician, this paper does have important implications. By finding that half of patients with PD have anxiety, the paper suggests physicians should be pro-active in querying patients for symptoms of anxiety and in considering treatments that might control symptoms and improve quality of life. ■

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In This Issue:

- Adherence to antiparkinson drugs
- Assessment of non-motor symptoms
- DBS and cognitive function
- Anxiety disorders and PD