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Parkinson's Disease Monitor & Commentary

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

Commentators

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From the editor...

David J. Houghton, MD, MPH

When enlisting experts to comment on the articles we select for *PD Monitor & Commentary*, we always ask for a clinical context to be included. The goal is not only to provide our readers with an independent perspective on emerging research, but also to offer a better idea of how such research might be applied to patient care. The studies reviewed in this issue are no exception. One example is an article on rapid eye movement behavior disorder reviewed by Dr. Ron Postuma of McGill University. While he considers the article a reasonable summary, he does not recommend it to those without a specific interest in the field because the clinical implications remain limited.

However, more often than not, the authors of the studies we review supply their own clinical context, and in this case our reviewers have only to agree or disagree. This is true of a claim that the costs of managing patients after deep brain stimulation (DBS) are lower if the target is the subthalamic nucleus rather than the globus pallidium, which is challenged by Dr. Kelvin Chou of the University of Michigan.

Other studies evaluated in this issue include one of the neuroprotective activity of the MAO-B inhibitor rasagiline, which is reviewed by Dr. Mark Lew of the University of Southern California; a survey of the factors that promote non-adherence to PD medications, which is reviewed by Dr. S. Elizabeth Zauber of Indiana University School of Medicine; and the role of pesticide exposure as an etiologic factor in PD, which is reviewed by Dr. Sam Goldman of The Parkinson Institute and Clinical Center in Sunnyvale, California.

In the Q&A section, I address the types of patients in a practice that might be candidates for clinical trials and how to locate such trials. Finally, in the controversy section, Dr. Mark Stacy of Duke and Dr. Andrew Duker of the University of Cincinnati take opposing views of whether there are pre-existing traits that put patients with PD at risk for developing impulse control disorders (ICDs) when exposed to dopamine agonists. (By the way, I comment on an article on this topic on page 8.)

We hope you like our selections. Suggestions for content are always welcome. Please feel free to reach me at info@delmedgroup.com.

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Plus: Controversies in PD and Q&A with David J. Houghton, MD, MPH

PD Monitor & Commentary

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Faculty Disclosures

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Dr. S. Elizabeth Zauber has served on an advisory board for Eli Lilly.

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In This Issue

Commentaries

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

Controversies in PD

Brain organochlorines and Lewy pathology: The Honolulu-Asia aging study.

First Author and Institution:
G. Webster Ross, MD, Veterans Affairs Pacific Island Health Care System, Honolulu, Hawaii.

Citation:
Movement Disorders. 2012;27:1418-1424.

Objective:
Determine if exposure to organochlorines increases the risk of Lewy pathology.

Type of Study:
Autopsy sampling from longitudinally followed cohort population.

Result:
The presence of Lewy pathology correlated with the detection of organochlorine compounds. The association persisted after controlling for potential confounding factors.

Conclusion:
The findings are consistent with other evidence that organochlorine exposure may increase the risk of Parkinson's disease (PD), but several study limitations indicate a need for further investigation.

Organochlorines comprise a broad class of pesticides, most of which were phased out by the late 1980s. An association between these compounds and PD has been made from epidemiologic studies and supported by experimental studies. The Honolulu-Asia Aging Study (HAAS), which has followed a cohort of Japanese American men since 1991 and includes detailed neuropathologic autopsy examinations as a component of data collection, provides an ideal population for further exploring this association.

In this study, gross and microscopic examinations were performed on brain tissue samples from 225 HAAS decedents. Of these, 122 had no Lewy pathology, 29 had clinical PD or dementia with Lewy bodies (DLB), and 74 had incidental Lewy bodies. Seventeen of the 21 organochlorines evaluated were detected in at least one brain.

Among individual compounds, benzene hexachloride b, heptachlor epoxide isomer b, and methoxychlor were most strongly associated with Lewy pathology, although the association was significant only for benzene hexachloride b. Risk increased with multiple exposures. While Lewy pathology was found in 33% of the 55 tissue samples in which none of the three organochlorines were detected, it rose to 49% in the 162 tissue samples in which one organochlorine was detected, and 75% in the eight tissue samples in which two organocholorines were detected (*P* value for trend=0.007). Results remained significant after adjusting for age at death, body mass index, pack-years of smoking, and coffee intake, and after excluding individuals with PD or DLB (*P*=0.013). However, the results were insignificant when adjustments for multiple variables were made.

Commentary:

Samuel M. Goldman, MD, MPH
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Sunnyvale, California

In conducting case-control studies that correlate any potentially toxic substance with an increased risk of PD or other neurodegenerative process, it is important to show a temporal relationship to establish that the disease follows the exposure. One of the strengths of this study, in addition to its relatively large sample size, is that the finding of Lewy pathology was incidental in 74 of the samples. Prior studies assessed organochlorine levels in individuals with established PD. However, rather than reflecting a causal relationship, having PD could potentially increase levels of organochlorines, for example, due to increased fat catabolism (i.e., "reverse causation"). By studying individuals with incidental Lewy pathology, the risk of reverse causation is diminished, and the likelihood that Lewy pathology is a true consequence of exposure to organochlorines is increased.

These results reinforce experimental evidence that implicates organochlorines in the development of PD. It has been shown, for example, that at least some organochlorines cause specific dopaminergic toxicity and induce aggregation of alpha synuclein, a protein strongly implicated in PD pathogenesis.

Although the authors found a significant trend with increasing number of organochlorines detected, the presence of organochlorines was assessed in a yes-or-no fashion. Future studies showing a dose relationship would increase the strength of the evidence that organochlorine exposure causes Lewy pathology. Certainly, this study raises the index of suspicion that these extremely persistent environmental toxicants might increase the risk of PD. ■

Controlled release of rasagiline mesylate promotes neuroprotection in a rotenone-induced advanced model of Parkinson's disease.

First Author and Institution:
Margarita Fernandez, MD, Universidad Complutense de Madrid, Madrid, Spain.

Citation:
International Journal of Pharmaceutics. 2012;438:266-278.

Objective:
Evaluate effect of rasagiline on measures of neuroprotection in experimental models of Parkinson's disease (PD).

Type of Study:
Cell culture and rat models of PD.

Result:
Whether administered in conventional or a microsphere formulation, rasagiline reduced multiple measures of neurotoxicity in an experimental animal model of PD.

Conclusion:
The neuroprotective effect of rasagiline, which did not differ significantly between the two formulations, reinforces other evidence that rasagiline inhibits neuronal damage.

The ability of MAO-B inhibitors to prolong the activity of both exogenous and endogenous dopamine is credited with the symptomatic benefits these agents provide in PD. There is also a substantial amount of experimental evidence that MAO-B inhibitors may be neuroprotective. The second-generation MAO-B inhibitor rasagiline has specifically been associated with prevention of neuronal cell death in tissue cultures.

In this series of studies, rasagiline in its conventional formulation and in a microencapsulated formulation using the poly (D,L-lactide-co-glycide) (PLGA) polymer was evaluated in cell cultures and in a rat model with a PD-like pathology induced with rotenone injection. In the cell culture study, SKN-AS cells were exposed to peroxide-induced stress. Cell viability was then evaluated through measures of apoptosis, DNA fragmentation, and radical oxygen species after the addition of a standard formulation of rasagiline in various concentrations. In the animal studies, rats were given daily doses of rotenone before the addition of encapsulated or standard rasagiline.

In the cell culture experiments, the addition of rasagiline improved cell viability by all measures employed. In the animals receiving rotenone, which selectively destroys dopaminergic neurons and produces a Parkinson's-like disease, rasagiline in either formulation reduced the characteristic catalepsy by several measures. When sacrificed, the animals treated with either formulation had a reduction in dopaminergic cell loss relative to untreated animals. The effect of the two formulations did not differ significantly.

These sets of experiments support a neuroprotective effect for rasagiline. Although there was no difference between formulations, the controlled-release rasagiline offers the potential advantage of less-frequent dosing.

Commentary:

Mark F. Lew, MD
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This detailed and well-designed study evaluated a controlled-release formulation of rasagiline mesylate in several in vitro and in vivo systems. Testing revealed that the PLGA microspheres of rasagiline showed efficacy lasting up to 15 days in a rat model of advanced rotenone-induced PD. This study suggests that the new delivery system has the capacity to deliver medication to an appropriate anatomic locus with a lengthy effect. This provides a look into the future of drug-delivery systems.

However, neuroblastoma cell lines and Wistar rats do not represent the clinical situation. Studies of efficacy will be needed in patients with early and advanced PD. Although rasagiline has an elimination half-life of 6.2 hours, this is an irrelevant fact in a patient on rasagiline for a week or so. The irreversible MAO-B inhibitor eliminates brain MAO-B within this time frame, and it may take more than a week until the enzyme regenerates. As such, theoretically, it may be possible to dose the current formulation of rasagiline much less frequently and still maintain efficacy. No data exists to support this hypothesis, however.

The provocative implication of this study is that a novel formulation of rasagiline may be able to provide MAO-B inhibition for a much longer time frame than 2 weeks with a single dose, but human clinical trials are needed. ■

Recent data on rapid eye movement sleep behavior disorder in patients with Parkinson's disease: Analysis of behaviors, movements, and periodic leg movements.

First Author and Institution:
Valérie Cochen De Cock, MD, Hôpital Gui de Chauliac, Montpellier, France.

Citation:
Sleep Medicine. 2012;Epub ahead of print.

Objective:
Evaluate relationship of Parkinson's disease (PD) movement with rapid eye movement sleep behavior disorder (RBD).

Type of Study:
Review study.

Result:
Many patients with PD and impaired movement during waking hours appear to have substantially less impairment of movement during episodes of RBD.

Conclusion:
Efforts to understand why atonia is reduced during episodes of RBD may provide insight about both the pathophysiologic relationship between RBD and PD, as well as new targets of therapy.

RBD, which is characterized by dream enacting and can be associated with sleep-related violence, occurs commonly in patients with PD, sometimes preceding the onset of symptomatic PD. The mechanisms that link RBD and PD are unclear, but it has been noted that dopaminergic medications administered in the control of PD often affect the manifestations of RBD.

The reviewers here describe several studies indicating that patients with PD can perform movements during RBD episodes that they cannot perform during waking hours. In one study of subjects with asymmetrical PD, patients tended to move the more-affected rather than the less-affected side during RBD episodes. Movements have also been reported to be less parkinsonian during RBD episodes than in waking hours. The effort to explain why there is a reduction in atonia during episodes of RBD relative to waking hours in patients with PD has the potential to provide insight about how brain activity affects motor symptoms in both diseases.

Some of the observations of RBD in patients with PD have led to speculation that movements during episodes of RBD draw on different functional pathways than movements during waking hours. The authors of this review cite their own work in which an increased perfusion was found in the supplementary motor area (SMA) during RBD episodes in patients with PD. They note that the SMA is closely related to movement execution during both dreams and wakefulness, suggesting that it might be a target for improving movement during waking hours of patients with PD.

Currently, observations to date have implicated several sites in the brain, such as the cortex, as areas in which pathological activity of RBD and PD may be shared. Progress in this area has implications for unraveling the pathology of both conditions.

Commentary:

Ronald B. Postuma, MD
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RBD is frequently associated with, and sometimes precedes, several synucleinopathies such as PD and dementia with Lewy bodies. More than half of patients with PD will eventually develop symptoms of RBD, which can include a broad array of physical activity during dreams, including violence leading to injury.

More than half of patients with PD will eventually develop symptoms of RBD, which can include a broad array of physical activity during dreams, including violence leading to injury.

The often disturbing movements of RBD in a disease characterized by impaired movement have attracted broad efforts to understand the relationship of RBD with PD in order to gain insight into both diseases. This summary of these efforts outlines what types of observations have been made by those active in the study of RBD, including the authors of the review.

For those interested in RBD, a very fascinating area of research, this paper has value in summarizing what research is underway regarding the relationship between RBD and PD. Certainly, an even more intriguing summary will be written when more of the questions they have identified are answered. ■

Parkinson's disease medication use and costs following deep brain stimulation.

First Author and Institution:
Frances M. Weaver, PhD, Hines VA Hospital, Hines, Illinois.

Citation:
Movement Disorders. 2012;27:1398-1403

Objective:
Evaluate change in medication costs after deep brain stimulation (DBS).

Type of Study:
Post-hoc analysis of data generated by a randomized study.

Result:
Medication use and costs were reduced over 36 months after DBS, but the reduction was greater cumulatively for the subthalamic nucleus (STN) than the globus pallidum (GPi) target.

Conclusion:
These data expand the evidence that DBS reduces medication needs and costs, but it also suggests cost savings may be greater when the DBS target is the STN rather than GPi.

One of the potential advantages of DBS is a reduction in the significant medication costs associated with Parkinson's disease (PD). After a recent randomized trial found STN and GPi forms of DBS to provide similar clinical benefits, the data were reevaluated to compare costs.

The original trial had two phases. After an initial phase that included randomization to a best medical therapy arm as well as the two forms of DBS, those initially randomized to best medical therapy were then offered the option of being randomized to STN or GPi DBS. This cost analysis compared the costs of STN and GPi DBS with data generated by both the first and second phases of the study. Overall cost comparisons were made at 6-month intervals out to 36 months of follow-up.

At the end of 6 months, costs were similar for the best medical therapy and DBS groups even though a reduction in levodopa equivalents among those receiving DBS was significant. Over the subsequent 6-month intervals, there was a reduction for DBS in each of the PD medication categories evaluated, which included levodopa or levodopa equivalents, COMT inhibitors, MAO-B inhibitors, dopamine agonists, antivirals, and anticholinergics. Overall, cumulative costs were less in the STN than the GPi groups.

Commentary:

Kelvin L. Chou, MD
Thomas H. and Susan C. Brown Professor
University of Michigan Medical School
Ann Arbor, Michigan

Weaver and colleagues continue to examine issues related to DBS utilizing the robust data from their large, randomized trial of DBS versus best medical therapy for patients with PD (Weaver FM, et al. JAMA. *2009;301:63-73). In this analysis, the goal was to compare costs before and for up to 36 months after DBS. Because medication dose reduction occurs to a greater extent after STN DBS than GPi DBS, proponents of STN DBS may think that medication costs should also be less with STN DBS. However, no large cost analyses have been conducted.*

The savings seen with STN DBS by itself should not sway anyone toward the STN or away from the GPi as a target.

Medication costs did not differ significantly between the DBS and best medical therapy groups even though levodopa equivalent doses were lower with DBS. This is likely because medication adjustments may have still been ongoing in the DBS group.

The main finding of this study, however, is that medication use and costs decreased in both the STN and GPi groups over the 36 months following surgery, but cumulative medication costs were lower in the STN group, by about $2,229 on average. While this may seem to be an advantage for the STN as a DBS target, medication costs are small compared to the costs of surgery. The savings seen with STN DBS by itself should not sway anyone towards the STN or away from the GPi as a target. Both targets have been shown to be effective on motor symptoms in PD, and both reduce medication costs over time. The reason to choose one target over the other will continue to be decided by each center on an individualized basis. ■

Systematic review on factors associated with medication non-adherence in Parkinson's disease.

First Author and Institution:
David James Daley, MD, University of East Anglia, Norfolk, United Kingdom.

Citation:
Parkinsonism and Related Disorders. 2012;Epub ahead of print.

Objective:
Identify clinical and demographic factors associated with Parkinson disease (PD) medication non-adherence.

Type of Study:
Literature review.

Result:
Prominent predictors of non-adherence included mood disorders, cognition, poor symptom control, younger age, longer disease duration, and regimen complexity.

Conclusion:
While identifying common predictors of non-adherence may be useful, interventions specifically targeted at improving adherence in the context of these factors are needed.

As PD progresses, patients are often required to take several therapies in multiple daily doses in order to achieve maximum symptom control. Due to the complexity of these regimens, some studies suggest that only a small minority of patients with advanced PD are fully compliant with their prescribed therapies, which may produce preventable decrements in quality of life. A systematic approach to understanding non-adherence may be useful.

In this study, the immediate goal was to derive information about non-adherence in patients with PD from published studies. Of a large number of studies evaluated from five databases, six were considered eligible for inclusion in this analysis by two independent reviewers. The data from these studies, which included 772 patients, was culled using a standardized extraction method.

Six clinical and five demographic factors were associated with non-adherence from the pooled data. When ranked by overall strength of the evidence these were, in order, mood disorders, cognition, poor symptom control, younger age (or longer disease duration), regimen complexity, risk-taking behaviors, poor understanding of PD, lack of a spouse or partner, low income, concern about how medication affects work performance, and male gender.

While this study was not designed to determine whether interventions directed at factors predicting non-adherence, such as mood disorders, will improve adherence, clinician awareness of these factors may be helpful for identifying those at risk. Many of these risk factors are reversible or might be the targets of interventions to modify their adverse influence on adherence. The authors report that they are now developing a randomized trial that will test strategies for reducing poor adherence, which may have a direct impact on long-term PD control.

Commentary:

S. Elizabeth Zauber, MD
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For clinicians, few of the risk factors for poor adherence identified in this review of the literature will be surprising. Common sense would tell us that mood disorders and impaired cognition, for example, are likely to have an adverse effect on adherence, and this is what most of us encounter in daily practice.

Perhaps one of the more interesting observations was the influence of employment on adherence. This may be a factor in patients avoiding medications during working hours so that side effects do not interfere with their productivity or, conversely, taking more of their medicine in conjunction with working hours to control symptoms that might impair function. In general, though, I think many clinicians find these characteristics track together so that the same patients with depression, cognitive problems, and poor quality of life also have poor adherence.

While this review was conducted by the investigators to summarize what is currently understood about predictors of poor adherence, they now plan a randomized trial to test interventions, which may be more valuable to clinicians. It is useful to know the risk factors for poor adherence, but effective interventions are a pressing need. Symptoms remind many patients to take their medications, but chronic failure of adherence may be an avoidable cause of diminished quality of life. ■

Impulse control disorders in Parkinson's disease: the role of personality and cognitive status.

First Author and Institution:
Michele Poletti, MD, University of Pisa, Pisa, Italy.

Citation:
Journal of Neurology. 2012;259:2269-2277.

Objective:
Examine the influence of baseline characteristics on the risk of loss of impulse control in patients with Parkinson's disease (PD).

Type of Study:
Review of published studies.

Result:
Findings to date, although not definitive, suggest that there are baseline personality characteristics, such as negative affect, that increase the risk of impulse control disorders (ICDs).

Conclusion:
The evidence that baseline characteristics predispose patients with PD to the risk of ICDs needs confirmation from longitudinal studies that follow patients from the time of diagnosis.

There have been numerous studies describing a high rate of ICDs among patients with PD, particularly those taking dopamine agonists. A variety of theories about the pathological link between ICDs and PD have been proposed, but there has been particular controversy about whether baseline personality characteristics are important in creating a predisposition to ICDs.

In this review article, the authors evaluate (1) whether there are premorbid or baseline characteristics that predict ICDs in patients with PD, and (2) whether those who do develop ICDs have some degree of cognitive difficulties important to the risk of ICDs once PD develops or when taking dopamine agonists to control PD.

The medical literature contains a number of studies that support the premise that baseline impulsivity predicts a higher rate of ICDs once PD develops. In addition, there is published evidence that negative affect or depression increase the risk of ICD. However, in both instances there are contradictory findings that challenge definitive conclusions. Few studies have evaluated the relative impact of baseline cognitive difficulties or cognitive problems after developing PD on the risk of ICDs.

It is reasonable to predict that individuals with a high degree of baseline impulsivity might be at a higher risk for developing ICDs in the context of PD, but the studies to date are suggestive rather than definitive, according to the authors of this review. They recommend longitudinal studies be conducted to evaluate potential risk factors, such as impulsivity, negative affect, and cognitive difficulties, at the time of diagnosis.

Commentary:

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Department of Neurology
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New Orleans, Louisiana

Growing reports of impulsivity and compulsive behaviors have accompanied the use of dopamine agonists over the last decade, and the results of the cross-sectional STACCATO study published in 2010 galvanized the problem because a substantial proportion of patients with PD who were treated with dopamine agonists reported pathological ICDs. Given the sensitive nature of many of these behaviors, this may still underestimate the true prevalence of ICDs in PD.

Poletti and Bonuccelli have reviewed the published literature to date regarding risk factors for the development of ICDs in PD. This important clinical question should come to mind as physicians prepare to treat their patients with dopaminergic agents or as the clinician uncovers impulsive behaviors after treatment has begun. Could the ICD behaviors be predicted or prevented?

The study was well written to summarize the literature, and, so far, the results are mixed. Perhaps the mere presence of either positive or negative symptoms of neuropsychological diseases portends less "reserve" in governing the dopaminergic reward centers kindled by anti-PD drugs. The authors are correct to call for well-designed studies to answer these questions and guide our treatment. As the consequences of ICDs can be quite devastating for patients, they deserve our concerted efforts to help mitigate the risks of their pharmacologic therapy. ■

Q&A

WITH EDITOR

David J. Houghton, MD, MPH

Question: Which of my patients should I consider for enrollment in a clinical trial?

Answer: Patients with Parkinson disease (PD) typically show significant interest in becoming involved in research. Yet taking that first step toward a clinical trial can seem daunting.

The horizon of study in PD is best divided into sub-groups based on the patient's stage and needs for disease management. For example, early-course patients are uniquely qualified for interventions aimed at disease modification or symptomatic monotherapy. Advancing patients may be looking for novel medications or delivery systems for add-on therapy, particularly for the management of motor fluctuations and dyskinesias. Non-motor complications, including constipation, urinary incontinence, sleep issues, pain, and others, are being studied independent of motor complications. Improved treatment and understanding of neuropsychiatric issues such as mood, memory, and psychosis are of particular interest within the research community at this time, as these problems are often the most unsettling for patients and care partners. More invasive techniques, such as deep brain stimulation and other novel surgical therapeutics, are being investigated worldwide. And complementary adjuncts to medications (i.e., physical, occupational, and speech therapies) are open to patients in the research arena, and these studies often recruit from all stages of disease.

Consideration for a clinical trial can become a part of the routine clinical care in any practice. Characteristics of an individual's condition should drive this decision, and it is best to keep familiar with what is being studied. Anybody can access the National Institutes of Health-sponsored website www.clinicaltrials.gov and search for PD trials; this platform provides detailed descriptions and contact information for each trial. At the time of this publication, the Clinical Trials website included more than 270 registered open studies for PD worldwide, and over half of them were in the United States. For additional information on available clinical trials and other up-to-date research efforts, one can consult such organizations as the National Parkinson Foundation, American Parkinson Disease Association, Parkinson's Action Network, Michael J. Fox Foundation, Parkinson Study Group, and the Parkinson Pipeline Project, among others.

Most importantly, patients should fully understand the details of volunteering for a clinical study. While this formally occurs during the consent process, well-informed patients from the earliest of consideration make for smoother journeys through the trial. They should clearly understand the purpose, obligations, benefits, risks, and time involvement. Most research studies have no direct cost to the patient, and some will reimburse for certain other incidental expenditures, including travel.

If you as the referring neurologist are not affiliated with an academic institution or group performing research, you can contact other groups directly and inquire about ongoing trials. Patients will also often take the initiative to contact research trialists themselves.

The notion of standardized care combined with investigational care is appealing to many patients, and the resultant collaborations made between patients, their non-research neurologists, and those neurologists performing studies can be quite fruitful.

So the brief answer to the question is quick and simple: all patients! Knowing what trials are recruiting and their potential to help your patients is the first step.

Controversies in PD

PRO Opinion

Mark Stacy, MD
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Behavioral disturbances in patients with PD on dopaminergic therapy have been recognized for more than 40 years. Hypersexuality and hyperlibidinous behavior were listed as potential complications in the early literature on levodopa, and pathological gambling, compulsive shopping, and binge eating are now well recognized. These behaviors are classified as ICDs and include disruptive behaviors (punding), destructive behaviors (compulsive gambling or hypersexuality), and addictive behaviors (excessive use of medications). They affect almost 14% of the PD population.[1]

While the etiology of ICD behavior emergence is unknown, it is reasonable to postulate that both PD and treatment with dopaminergic therapy influence the display of behaviors that are associated with risk factors in the general population. In fact, strikingly similar epidemiological frequencies for problem gambling, alcohol use, and other addiction behaviors are reported in general, or non-parkinson, populations.[2-5]

Determining the risk for the development of ICDs is an important area of study for the PD population in an attempt to reduce the impact of some of these extremely damaging behaviors. However, ICDs are similar in etiology to the development of dyskinesias, and there has never been a debate regarding whether levodopa was the major factor in determining the emergence of this symptom.[6] In addition, the emergence of ICDs are easily correlated with the increasing emphasis on use of dopamine agonists as a "levodopa-sparing" strategy.[7]

Dyskinesias represent novel motor behavior, manifested as uncontrolled expression of motor activity. This motor activity is not thought to be voluntary, and is not considered "new motor behavior" triggered by an anti-parkinson therapy. Rather, dyskinesias are defined as motor complications associated with PD treatment, resulting from changes in striatal signaling following chronic dopaminergic stimulation. The key message is that with treatment, impairment in the gating pathway (the basal ganglia) leads to a disturbance of physiological signals and involuntary movements.

ICDs also represent a disturbance in the signal pathways of the basal ganglia. In that construct, it is reasonable to assume that the emergence of these behaviors is linked to treatment effects on an impaired gaiting system. In that paradigm, the content of thought is not the issue, it is the aberrant expression or action linked to the content.

Philosophically, it remains difficult to understand the marked behavioral changes seen in some patients with PD. How can a person change from a normal, productive society member so quickly to someone addicted to pornography or prostitutes, or who would gamble his or her life savings away, become suicidal, or even commit criminal acts? It is helpful to think about the emergence of these behaviors as similar to dyskinesias—motor behaviors devoid of value judgment. We do not understand how any cortical activity, be it a cognitive or motor impulse, is amplified to a level of behavioral expression. It may be that in PD these thoughts are more easily amplified or rewarded until an aberrant behavior emerges. If the brain is capable of infinite activity, perhaps basal ganglia summation is essential to the expression of motor and behavioral outcome.

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The Question: Are there subsets of patients with Parkinson's disease (PD) who, due to pre-existing traits, are at risk for developing impulse control disorders (ICDs) when exposed to dopamine agonists?

CON Opinion

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ICDs in patients taking dopaminergic therapy (predominantly dopamine agonists) for PD are now increasingly recognized. Despite this, they present in only a minority of patients on therapy, suggesting there may be individualized predispositions for this complication. Could screening for impulse control traits or elevated levels of impulsivity prior to initiating therapy with a dopamine agonist potentially prevent ICDs?

In the literature, treated patients with PD and an ICD were more likely to retrospectively report a history of ICD symptoms prior to disease onset, and scored higher on impulsivity ratings compared to treated patients with PD but without an ICD.[1,2] However, one cannot imply causation based on cross-sectional or retrospective analyses looking at patients currently on treatment. Is the patient with an ICD more impulsive due to a baseline personality trait, or due to the presence of the ICD? To be sure, prospective studies in non-parkinsonian individuals with pathological gambling have identified a higher incidence of impulsivity than controls.[3] But the role of personality measures, for example sensation seeking and extraversion, in the development of ICDs in the general population is still somewhat controversial.[4]

To truly answer this question, prospective, longitudinal studies on drug-naive patients must be performed, evaluating baseline impulsivity and determining whether medicated patients with a high "baseline" impulsivity score have a higher prevalence of ICDs compared to medicated patients with a low "baseline" impulsivity score.[5] Unfortunately, we do not currently have the data available to examine this. One study has shown similar levels of impulsive behavior for drug-naive patients with PD and healthy controls, but there was no longitudinal follow-up reported.[6] Another study did follow patients longitudinally, but only long enough to show that novelty seeking, decreased at baseline, increased after treatment with a dopamine agonist, and follow-up was not long enough to determine if ICDs developed.[7]

There are a number of demographic features such as earlier age of onset, unmarried state, and current cigarette smoking that are more common in patients with PD and ICDs.[8,9] Genetic polymorphisms in the dopaminergic, serotonergic, glutamatergic, or other neurotransmitter symptoms may also play a role in ICD development.[4] Particularly interesting is the increased incidence of ICDs in patients with PD and the AA genotype in the DRD3 gene, given the D3 receptor's ties to the ventral striatum and the limbic system.[10] These factors may ultimately help guide us as to who is at increased risk for developing an ICD on treatment, but until further study is done, the presence of impulsivity in treated ICD patients could be a matter of either the chicken or the egg.

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