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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

This issue of *Parkinson's Disease Monitor & Commentary* is particularly strong on topics of immediate relevance to patient care. This includes management of the many potential complications of Parkinson's disease (PD), such as an increased risk of falls. In his commentary on a study attempting to predict the risk of falls in this patient population, Dr. Ergun Uc of the University of Iowa has some reservations about the investigators' conclusions but used the data to draw attention to this important but often overlooked clinical issue. Even though the study specifically enrolled patients at an early stage of disease, almost half had a fall within 6 months of follow-up.

As for new data to guide treatment, Dr. Grace Liang of The Parkinson's Institute and Clinical Center in Sunnyvale, California notes that although entacapone did not delay dyskinesias in patients on levodopa/carbidopa therapy in the STRIDE-PD study, it did generate some potentially useful information about risk factors for dyskinesias. Next, Dr. Lawrence Elmer of the University of Toledo discusses the clinical implications of long-term safety and efficacy data with rasagiline in terms of where it fits with other options, while Dr. Kelvin Chou of the University of Michigan evaluates what a comparison of deep brain stimulation targets may mean for patient selection.

The complex relationship between depression and PD is raised by a study that attempted to evaluate whether pramipexole, a dopamine agonist, relieves depressive symptoms independent of its benefit on movement symptoms. While the authors conclude that it did, Dr. Laura Marsh of Baylor College of Medicine explains why caution about this conclusion is needed. This study, like one that associated vitamin D with protection from PD, evaluated by Emory University's Dr. Marian Evatt, may raise more questions than it answers.

When providing their commentaries, we ask our experts to look for potential clinical implications in the studies they review, even within the basic science studies we often include. I believe this issue demonstrates that the commentaries can be as clinically valuable as the studies themselves. For those intrigued by a topic addressed in this or any issue, we strongly recommend going to the original source. Our reviews are not a final analysis, but a second perspective. As always, comments and suggestions are welcome. Please feel free to reach me at info@delmedgroup.com.

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

Commentators

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

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

Marian Evatt, MD
Wesley Woods Geriatric Hospital &
Emory University
Atlanta, Georgia

Grace S. Liang, MD
The Parkinson's Institute and Clinical Center
Sunnyvale, California

Laura Marsh, MD
Baylor College of Medicine &
Michael E. DeBakey Veterans Affairs Medical Center
Houston, Texas

Ergun Y. Uc, MD
Carver College of Medicine
University of Iowa &
Veterans Affairs Medical Center
Iowa City, Iowa

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In This Issue:

PD Monitor & Commentary

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

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66 S. Maple Avenue, 3rd Floor
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Fax: 201-612-8282
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Publishers
Joseph D'Onofrio
Frank M. Marino

Editorial Director
Nancy Monson

Senior Writer
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Art Director
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Serum vitamin D and the risk of Parkinson disease.

First Author and Institution:
Paul Knekt, DPH, National Institute for Health and Welfare, Helsinki, Finland.

Citation:
Archives of Neurology. 2010;67:808-811.

Objective:
Determine if serum vitamin D levels correlate with the risk of Parkinson's disease (PD).

Type of Study:
Retrospective cohort analysis of national health survey database.

Result:
The risk of PD was 67% lower among those with the highest vitamin D levels by quartile at baseline relative to those with the lowest vitamin D levels after adjusting for other factors.

Conclusion:
The study offers the first epidemiological evidence that low vitamin D is associated with an increased risk of developing PD.

Several cross-sectional studies have associated low levels of vitamin D with an increased risk of PD. Experimental evidence suggests low levels of vitamin D lead to chronic loss of dopaminergic neurons. The Mini-Finland Health Survey (MFHS), conducted from 1978 to 1980 across Finland, included measurement of serum 25-hydroxyvitamin D levels, providing an opportunity to evaluate the relationship of this variable and the subsequent development of PD.

The MFHS included a representative sample of 3,173 men and women aged 50 to 70 without PD. Fifty subsequent cases of PD were identified through the year 2007 from an examination of a health reimbursement register that captures data on all Finnish citizens.

When the lowest quartile of 25-hydroxyvitamin D levels was used as a reference, there was a stepwise reduction in relative risk (RR) of PD for each higher level. The RR for PD between the highest and lowest quartiles was 0.33 after adjustment for sex, age, and other potential confounders, a trend that was highly significant (P=0.006).

Commentary:

Marian Evatt, MD
Assistant Chief of Neurology
Wesley Woods Geriatric Hospital
Emory University
Atlanta, Georgia

These are intriguing results because they demonstrate a relatively strong association. However, we also have plenty of experiences in which retrospective data proved to be misleading. The lack of cardiovascular protection from hormone replacement therapy is one example.

The strength of this study is that it collected representative data from an entire country, but it should be noted that the quartiles of vitamin D in Finland are lower than we would expect in the United States. This is an issue because there is evidence from other retrospective studies that beneficial effects from vitamin D exhibit a U-shaped dose-benefit curve, which would predict a diminishing benefit after some optimal level is reached. In addition, animal studies support the potential neurotoxicity of vitamin D at high doses.

Another limitation of this analysis is that we do not have data on vitamin D over time. Also, as the authors acknowledge, it is difficult to control for all confounding factors. One potential problem with the vitamin D story and PD is a lack of consistent evidence of a north-south gradient for PD risk. We now need prospective studies to explore the possibility that the correlation between low vitamin D and PD is causal, but these data suggest this hypothesis deserves further study. ■

Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease.

First Author and Institution:
Kenneth A. Follett, MD, PhD, Iowa City Veterans Affairs Medical Center, Iowa City, Iowa.

Citation:
New England Journal of Medicine. 2010;362:2077-2091.

Objective:
Compare 24-month outcomes from bilateral stimulation of the globus pallidus interna versus the subthalamic nucleus in patients with Parkinson's disease (PD).

Type of Study:
Prospective, multicenter, randomized trial.

Result:
Mean changes in motor function and the rates of serious adverse events were comparable for both types of stimulation, but there were modest differences in non-motor functions.

Conclusion:
Due to the similarity in outcomes for PD motor symptoms, other outcomes, such as changes in cognition or mood, may make one stimulation method more attractive than another.

Both the globus pallidus interna and the subthalamic nucleus are accepted targets for deep-brain stimulation (DBS) to control PD, but they have not been directly compared for efficacy or safety in a large, multicenter study. The primary endpoint in this study was motor function, but secondary endpoints included neurocognitive function, quality of life, and side effects.

In this study, 299 patients with idiopathic PD were randomized at 13 participating hospitals to bilateral pallidal or subthalamic stimulation. The average duration of PD medication use was 11 years and the mean age of the subjects was 61 years.

After 24 months of follow-up, the reductions in the part III (motor subscale) of the Unifed Parkinson's Disease Rating Scale (UPDRS-III) were similar for the pallidal and subthalamic stimulation groups (11.8 versus 10.7 points; *P*=0.5). Serious adverse events were also similar (50.7% versus 56.5%; *P*=0.35). While patients who received subthalamic stimulation required a lower dose of dopaminergic agents (*P*=0.02), they had worsening of depression from baseline (versus improvement in the pallidal group) and a greater decline in visuomotor processing speed (*P*=0.03).

The authors conclude that it may be appropriate to consider non-motor symptoms that affect quality of life when selecting a stimulation target, but caution that the goals of stimulation and the experience of the surgeon at the target site may also be important.

Commentary:

Kelvin Chou, MD
Director, Deep Brain Stimulation Clinic
Department of Neurology
University of Michigan Health System
Ann Arbor, Michigan

This large, well-designed, and well-conducted prospective study involving almost 300 patients provides a rare head-to-head comparison between two DBS targets for PD. The bottom line is that DBS improved motor function in patients with PD who underwent either pallidal or subthalamic stimulation with no significant difference in primary outcome or self-reported function during 24 months of follow-up. Currently, most DBS centers tend to target the subthalamic nucleus, despite almost no data to support its superiority. This study demonstrates that, in terms of motor outcomes, the globus pallidus is an equally attractive option.

However, each target had its own unique advantages. Patients undergoing subthalamic nucleus stimulation were able to reduce their dopaminergic medication more than in the pallidal stimulation group, and they had lower stimulation amplitudes and pulse widths on average. On the other hand, patients in the subthalamic stimulation group declined more on a measure of visuomotor processing speed. Furthermore, Beck depression scores improved in the pallidal group but worsened in the subthalamic group. However, the Beck scores only worsened by about 1.3 points on a 63-point scale, making the clinical significance of this finding unclear.

Nevertheless, these findings suggest that non-motor factors may become important in selecting a surgical target. Future studies of DBS in PD will need to focus on these outcomes in order to guide clinicians on how best to tailor this therapy to individual patients. ■

Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease, the STRIDE-PD study.

First Author and Institution:
Fabrizio Stocchi, MD, Institute of Neurology, Rome, Italy.

Citation:
Annals of Neurology. 2010;68:18-27.

Objective:
Test the effect of early entacapone use in patients with Parkinson's disease (PD) on levodopa/carbidopa (LC) therapy.

Type of Study:
Prospective, double-blind, randomized trial.

Result:
The addition of entacapone to levodopa/carbidopa (LCE) early in the course of PD shortened the onset time to and frequency of dyskinesias relative to LC alone.

Conclusion:
With the protocol used in this study, early use of entacapone was not an effective strategy to delay or reduce the motor complications of levodopa in patients with PD.

The continuous dopamine stimulation (CDS) hypothesis holds that the risk of motor complications from levodopa may be reduced if stimulation of dopamine neurons is achieved in a more physiologic manner. An inhibitor of catechol-O-methyltransferase, entacapone has the potential to reduce motor complications by extending the half-life of levodopa and delivering it more continuously.

In the prospective, double-blind STRIDE-PD study, 747 patients with a PD disease duration of <5 years were randomized to initiate therapy with LC or LCE. Both were administered four times daily at 3.5-hour intervals. The primary endpoint was the time to onset of dyskinesias. A variety of secondary endpoints were also evaluated, including frequency of dyskinesias, Unifed Parkinson Disease Rating Scale (UPDRS) scores, and time to and frequency of wearing-off episodes.

At the end of 134 weeks of follow-up, the hazard ratio (HR) for dyskinesias was 29% higher (HR 1.29, 95% CI 1.0-1.65; *P*=0.038) among those randomized to LCE versus LC alone. The median survival time without dyskinesias was 90.7 weeks in the LCE group versus 117.1 weeks in the LC group. In addition, there was a significantly increased frequency of dyskinesias in the LCE group (42% versus 32%; *P*=0.02). Frequency and risk of dyskinesias were more pronounced among patients receiving dopamine agonists at baseline. Time to wearing off did not differ significantly between the two groups.

For the purpose of delaying dyskinesias, combining entacapone with levodopa/carbidopa early in the course of PD was not effective at the doses used in this study. Although other regimens might prove effective, the authors suggest that more studies are needed to determine whether the CDS hypothesis is an appropriate basis on which to design optimal regimens.

Commentary:

Grace S. Liang, MD
Movement Disorders Specialist
The Parkinson's Institute and Clinical Center
Sunnyvale, California

This study demonstrates that early use of entacapone with levodopa is not effective for delaying the onset of levodopa-associated dyskinesias. Although entacapone was associated with an increased frequency and shorter time to onset of dyskinesias overall, this study is informative in the analysis of factors associated with a higher risk of developing dyskinesias: They occurred more frequently in subjects on entacapone who were already on a dopamine agonist or an MAO-B inhibitor, patients younger than 65, and patients with a shorter duration of disease.

While higher rates of some side effects with LCE—such as gastrointestinal adverse effects—had been seen in prior studies, an unexpected finding in this study was slightly higher rates of prostate cancer (2.4% versus 0.5%) and myocardial infarction (1.9% versus 0%) among those taking entacapone versus those who were not. However, the absolute numbers of these events were small, and further analysis is needed to determine if the difference is attributable to the use of entacapone or other factors. Understanding and assessing these various risk factors against the benefits of using entacapone for improved motor function and reduced wearing off will be important for individualizing patient therapy decisions. ■

Long-term efficacy of rasagiline in early Parkinson's disease.

First Author and Institution:
Mark F. Lew, MD, Keck/University of Southern California School of Medicine, Los Angeles, California.

Citation:
International Journal of Neuroscience. 2010;120:404-408.

Objective:
Evaluate long-term efficacy, safety, and tolerability of rasagiline for Parkinson's disease (PD).

Type of Study:
Extension of placebo-controlled, multicenter TEMPO trial.

Result:
After a mean follow-up of 3.5 years, rasagiline—typically in combination with a dopamine agonist—showed significant benefits with good tolerability and safety.

Conclusion:
Rasagiline therapy for early PD is effective and well-tolerated.

Rasagiline, a selective, irreversible inhibitor of monoamine oxidase B (MAOB), was approved for the treatment of PD on the basis of a series of placebo-controlled, phase III studies that demonstrated clinical benefit. One of the trials, called TEMPO, included an open-label extension trial in which patients from the placebo group were crossed over to rasagiline.

In this analysis, 306 TEMPO participants who received rasagiline were followed in an open-label analysis over a median of 3.5 years. Additional therapies were permitted during this time. Numerous outcomes were measured, including annual rate of Unified Parkinson's Disease Rating Scale (UPDRS) progression, safety, tolerability, and time to Hoehn and Yahr (H&Y) stage III progression.

Forty-six percent of the study population remained on rasagiline monotherapy at 2 years. For those who required adjunctive therapy—an increasing percentage over time—the most common addition was a dopamine agonist before turning to levodopa. On rasagiline alone or with additional therapy, the mean annual UPDRS progression was 1.93 units. The median time to H&Y stage III was not reached. Reported adverse events diminished over time with only 11.3% of subjects discontinuing therapy due to an adverse event. Additional agents did not appear to alter the safety profile of rasagiline alone.

The authors note that the high proportion of patients on rasagiline monotherapy over the first 2 years reinforces the conclusion that this agent is an effective and safe early PD treatment. The pattern of early use of rasagiline followed by supplemental dopaminergic agents may be appropriate as a strategy in PD.

Commentary:

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

In this review of the rasagiline open-label extension data, the authors demonstrate the long-term safety and efficacy of rasagiline monotherapy. Although there are always potential problems with an open-label extension study, this particular analysis was balanced at least in part because investigators were not informed of the patients' original assignment to early versus delayed start of rasagiline.

By offering participants a "best practice" approach, one of the strengths of this study is that it reflects a "real world" scenario. Patients on rasagiline were permitted to receive a variety of treatments, typically beginning with dopamine agonists before progressing to the addition of levodopa preparations. It is reassuring to see this type of "rational polypharmacy" work itself out in multiple practice settings. The observation that less than a quarter of the participants reached a H&Y stage III during the 5-year period is a positive commentary on our modern pharmacological arsenal.

In specialty practices, treatment is appropriately individualized, but the possibility exists that negative attention given to the cost of rasagiline has prevented some patients from receiving this medication. Every treatment needs to be considered in the management of PD, especially when the risk of uncontrolled and progressive symptoms may mean nursing care or institutionalization. The evidence that rasagiline actually delays disease progression is still being debated, but this therapy should be considered in the interim as a potentially effective and unusually well-tolerated therapeutic option for early symptom control in people with PD. ■

Predictors of future falls in Parkinson disease.

First Author and Institution:
Graham Kerr, PhD, Queensland Institute of Technology, Brisbane, Australia.

Citation:
Neurology. 2010;75:116-124.

Objective:
Identify a methodology for predicting falls in patients with Parkinson's disease (PD).

Type of Study:
Prospective clinical study.

Result:
The best sensitivity (78%) and specificity (84%) for a high risk of falls was achieved when findings from five tests of motor function, gait, and balance were combined.

Conclusion:
The risk of falls can be predicted with reasonable accuracy in patients with PD through a combination of assessment tools.

Relative to individuals without a neurological disorder, patients with PD are at a high risk of falls. Although there are a variety of methods that can be used to measure motor function, gait, and balance, better methods for predicting falls are needed.

In this study, 101 patients with early-stage PD underwent a battery of tests designed to measure motor function, gait, and balance. These included parts 1 through 4 of the Unifed Parkinson's Disease Rating Scale (UPDRS), the Berg Balance Scale (BBS), the Timed Up and Go (TUG) test, the Tinetti test, and the Functional Reach test. Several other questionnaires, including the Freezing of Gait (FOG) and the Mini-Mental State Examination (MMSE), were also administered.

Over a 6-month follow-up, 48% of patients fell, and 24% reported more than one fall. On multivariate analysis, the authors found that the greatest sensitivity (78%) and specificity (84%) for predicting falls was produced by combining abnormalities on the total UPDRS score, the FOG score, the Tinetti total score, the presence of symptomatic postural orthostasis, and postural sway in the anterior-posterior direction.

Commentary:

Ergun Y. Uc, MD
Associate Professor of Neurology
Carver College of Medicine
University of Iowa &
Veterans Affairs Medical Center
Iowa City, Iowa

This paper makes the important point that even patients with early PD are at an increased risk for falls, but there are several weaknesses in the study that limit its clinical utility. For one, patients are identified as falling or not falling without any reporting on the number and severity of the fall or whether the fall led to an injury—despite the fact that the Methods section indicates such information was collected. Not all falls are equal, and falls that have clinical consequences, such as a broken bone, subdural hematoma, or loss of mobility, deserve more attention than those that do not. For another, although the authors evaluated patients with the MMSE, more detailed information about cognitive dysfunction (e.g., executive function) or the presence of visuospatial problems might have been useful, as these disorders are present early in PD and may be associated with falls.

The authors have identified a group of tests that provide some predictive accuracy, but they did not provide cut-off values for these tests, which would have been useful for considering their relative sensitivity in identifying increased risk. An in-person repeat assessment at the end of 6 months might also have been useful to show which changes from baseline were associated with fall risk.

Despite these criticisms, this study clearly shows that fall risk begins early and is not only present in those with advanced PD but also those with early PD. This study draws attention to the problem, but would be more clinically useful with greater details that might allow clinicians to consider relative risks. The authors identify their battery of tests as easy to administer, but in aggregate they may require substantial extra time during a busy clinic day, and more information for stratifying patients would be helpful. ■

Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: A randomised, double-blind, placebo-controlled trial.

First Author and Institution:
Paolo Barone, MD, University of Naples Frederico II, Naples, Italy.

Citation:
Lancet Neurology. 2010;9:573-580.

Objective:
Evaluate efficacy of pramipexole for depressive symptoms in Parkinson's disease (PD).

Type of Study:
Double-blind, placebo-controlled, randomized trial.

Result:
Pramipexole significantly reduced depressive symptoms in patients with PD relative to placebo with acceptable safety. The benefit was attributed to a direct antidepressant effect.

Conclusion:
Pramipexole, which also favorably affects motor symptoms, should be considered among treatment options in patients with PD who have depressive symptoms.

Patients with PD often also suffer with depression. Open-label studies have suggested that PD drugs that stimulate dopamine receptors may have an antidepressant effect. Pramipexole is a dopamine agonist with particular affinity for the D3 receptor, but it also has been shown to increase dopaminergic and serotonergic neurotransmission.

In this multinational study, 296 patients with mild to moderate PD on stable antiparkinsonian medication with depressive symptoms were randomized to 0.125 to 1.0 gm of pramipexole or placebo taken 3 times daily. The primary endpoint was change in the Beck Depression Inventory (BDI). Change in motor score was also assessed with the Unifed Parkinson's Disease Rating Scale (UPDRS).

Both the BDI score (-5.9 versus -4.0 points; *P*=0.01) and the UPDRS motor subscore (-4.4 versus. -2.2; *P*=0.003) were reduced significantly on pramipexole relative to placebo. The authors primarily attribute the reduction in depression to an antidepressant effect. They suggest that pramipexole be considered as a therapeutic option in patients with PD who are clinically depressed.

Commentary:

Laura Marsh, MD
Professor of Psychiatry and Neurology
Baylor College of Medicine
Executive Director, Mental Health Care Line
Michael E. DeBakey Veterans Affairs Medical Center
Houston, Texas

This study confirms the benefits of pramipexole on motor function, but the clinical significance of the effects on PD-associated depression are less clear. Although this study, which was well controlled and had a satisfactory design, suggests a "two-fer" of treating mood and motor symptoms with one medicine, the authors enrolled patients with depressive symptoms based on a cross-sectional rating scale score rather than a diagnosis of a depressive disorder. In general, treatment decisions should be driven by diagnoses, especially in conditions such as PD, where there are overlapping somatic and depressive phenomenology and the longitudinal course of these phenomena is important to confirming both the diagnosis of PD and the presence of psychiatric disturbances.

While the screening scales used are highly predictive of the presence of a depressive disorder, they are not 100% sensitive. Despite a significant change in depressive symptoms on the BDI, there was no significant change in depressed mood on the part 1 UPDRS scale, which is often used to track mood symptoms in clinical neurology practices. Perhaps more concerning, the authors were also unable to detect a significant change in quality of life (as measured by the PDQ-39, the 39-item PD questionnaire).

The authors state that the benefit against depressive symptoms can be traced to the dopamine agonist mechanism of action, but this effect was modest.

In clinical practice, it is important to evaluate patients for depressive symptoms, a source of a diminished quality of life, to identify those who require therapy. In those who do, the goal is full remission not just symptom improvement. Control of motor symptoms may be sufficient to improve both mood and quality of life, particularly in patients with depressive symptoms rather than established depression. This study implies that pramipexole might be a first-line choice in patients with PD and depressive symptoms, but this has not been clearly shown. ■

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66 South Maple Avenue
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201-612-7676

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