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Parkinson's Disease Monitor & Commentary

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

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From the editor...

Andrew D. Siderowf, MD

As many of the scientific articles reviewed in this issue imply, neurological diseases such as Parkinson's disease (PD) develop out of complex and perhaps heterogeneous pathophysiologic pathways. It is increasingly unlikely that the search for better methods of diagnosis and treatment will hinge on a single molecular event. Rather, more effective therapies may require the identification of the many different events driving disease in a given individual. PD may become a particularly salient case for personalized or genomic medicine.

An example is a paper that I review on cerebral fluid amyloid β and tau in carriers of the LRRK2 mutation. Long implicated in α-synucleinopathies, these proteins remain important but not isolated potential participants in PD pathogenesis. They may be useful targets for therapy, but the likelihood that they will emerge as fundamental variables in the pathophysiology of PD seems increasingly remote. In a similar example, Dr. David Russell from the Institute for Neurodegenerative Disorders in New Haven reviews a paper that examines mitochondrial dysfunction as a targetable abnormality in patients with PD. Again, one cannot fully rule out the possibility of a magic bullet in PD treatment, but the complexity of the pathways encourages diverse directions of research to understand what is likely to be a multidimensional disease process.

In this issue, we have also asked experts to review newly published data on an environmental exposure that may precipitate PD, a new trial of deep brain stimulation, the problems with models to test neuroprotection in PD, and the effort to standardize measurements of quality of life in PD. Each of these, including the efforts to better measure quality of life, echo the sentiment that PD is a complex disorder not easily addressed with simple solutions.

In the Q&A section, I tackle dietary issues in PD, while in the Controversies column, Danna Jennings and Samuel Frank debate the utility of dopamine transporter imaging in PD. As always, comments and suggestions are welcome. Please feel free to reach me at info@delmedgroup.com.

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PD Monitor & Commentary

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Faculty Disclosures

Dr. Kelvin L. Chou has consulted for Medtronic and Merz.

Dr. Samuel Frank has consulted for Genzyme and Merz.

Dr. Claire Henchcliffe has served on Advisory Boards for Allergan, GE Healthcare, and Teva Neuroscience, and Speakers' Bureaus for Allergan, Avanir, GlaxoSmithKline, Novartis, and Teva Neuroscience.

Dr. David S. Russell has served on a Speakers' Bureau for Teva Neuroscience.

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In This Issue

Commentaries

Q&A with Andrew D. Siderowf, MD

Controversies in PD

Explaining ADAGIO: A critical review of the biological basis for the clinical effects of rasagiline.

First Author and Institution:
Peter Jenner, DSc, King's College, London, United Kingdom.

Citation:
Movement Disorders. 2011;26:2316-2323.

Objective:
Evaluate the effect of rasagiline on mitochondrial function in providing control of Parkinson's disease (PD).

Type of Study:
Systematic review of evidence that rasagiline influences mitochondrial activity.

Result:
A variety of evidence suggests that changes in mitochondrial function may participate in the pathogenesis of PD and that rasagiline has favorable effects on these mitochondrial changes.

Conclusion:
Abnormal mitochondrial function, which is strongly implicated in the pathophysiology of PD, might be favorably influenced by rasagiline, explaining a possible neuroprotective effect.

Data from the ADAGIO study provided evidence that rasagiline exerts a disease-modifying effect independent of its symptomatic effects in the control of PD. Of several hypotheses to explain disease-modifying activity, a favorable effect on mitochondrial function has recently attracted attention.

In this analysis, the potential role of mitochondrial dysfunction in the pathogenesis of PD as well as the likelihood that rasagiline modifies mitochondrial dysfunction are reviewed by summarizing numerous experimental and clinical studies that have addressed this issue. Most intriguingly, support for a favorable effect on mitochondrial function is drawn from studies that associated rasagiline with potential neuroprotection independent of monoamine oxidase (MAO)-B inhibition.

Among a large body of cited biochemical and genetic evidence implicating mitochondrial dysfunction in the pathogenesis of PD, the observation that mitochondrial complex 1 activity is reduced 30% to 40% in the substantia nigra of patients with PD is emphasized. In addition to a role in oxidative metabolism, the authors highlight the evidence that rasagiline might act via modulation of another mitochondrial function. It may also normalize the prevention or clearance of aggregated proteins such as α-synuclein that may promote PD progression.

The "true cause" of PD remains elusive. It cannot yet be proven that mitochondrial dysfunction has an important role in the pathology of PD or that rasagiline provides neuroprotective effects by normalizing mitochondrial activities, but the authors conclude that there is a substantial body of evidence to support this hypothesis.

Commentary:
David S. Russell, MD, PhD
Associate Clinical Research Director
Institute for Neurodegenerative Disorders
New Haven, Connecticut

Accumulating evidence supports the intriguing hypothesis that mitochondrial dysfunction plays a role in the pathophysiology of PD. There is also evidence that rasagiline influences various mitochondrial activities and that this may underlie the disease-modifying effects seen in the ADAGIO study. This paper nicely assembles a variety of disparate information regarding what is known about mitochondrial function in regard to PD and, further, the evidence that rasagiline might act on this pathway. ADAGIO was a large and ambitious milestone study that provided strong evidence of a disease-modifying effect of rasagiline on PD symptom progression. However, by the nature of this kind of study, it did not address directly whether rasagiline is neuroprotective or achieves disease modification via another mechanism.

This paper explores a potential mechanism of neuroprotection involving modification of mitochondrial activity. If confirmed, this would put together several sets of puzzle pieces. One set of pieces has been the various clues implicating mitochondria in PD pathogenesis. Another set involves the potential for rasagiline to offer neuroprotection. A third set involves a variety of data indicating that rasagiline affects mitochondrial function, potentially linking the first two sets together. This paper does not and cannot attempt to fully answer these questions, but admirably assembles what is known and what remains unclear. Obviously, this is an important inquiry. It is not impossible that controlling abnormal mitochondrial activity will prove to be a magic bullet for preventing PD progression. ■

Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: An open-label randomised controlled trial.

First Author and Institution:
Michael S. Okun, MD, University of Florida College of Medicine, Gainesville, Florida.

Citation:
Lancet Neurology. 2012;11:140-149.

Objective:
Assess efficacy and safety of bilateral constant-current deep brain stimulation (DBS) for individuals with Parkinson's disease (PD).

Type of Study:
Prospective, randomized, multicenter, open-label trial.

Result:
Constant-current DBS produced improvements in motor function and reductions in daily fluctuations in levodopa response that were sustained at 1 year.

Conclusion:
The authors characterize the study as the first well-powered trial to confirm benefit from constant-current DBS; no detrimental effect on cognitive function was observed.

DBS of the subthalamic nucleus (STN) has proven to be a viable treatment option for patients with medication-resistant PD. Relative to voltage-controlled DBS, constant-current DBS permits adjustment for heterogeneity in tissue impedance—a potential advantage for optimal distribution of the electrical field. However, large-scale, controlled studies with constant-current DBS have never been performed.

In this prospective randomized study, the constant-current DBS device was implanted in 136 patients who were then randomized in a 3:1 ratio to receive immediate constant-current DBS or DBS after a delay of 3 months. The primary outcome was the period of time without bothersome dyskinesia (good quality time) as recorded by patients in daily diaries at 3 months.

Both groups improved, but the increase in good quality time was significantly greater in the group that was receiving active constant-current DBS (4.27 versus 1.77 hours; P=0.003). The active therapy group had greater rates of dysarthria, fatigue, paraesthesias, and edema.

The improvement in motor fluctuations demonstrates efficacy for constant-current DBS. The adverse event and safety profile was similar to that reported for other DBS techniques.

Commentary:

Kelvin L. Chou, MD
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This trial looked at the safety and efficacy of a constant-current DBS device implanted in the STN for PD. At 1 year after surgery, constant-current STN DBS improved daily "on" time by over 4 hours and had a safety profile similar to currently available constant-voltage DBS devices.

Constant-current devices have a theoretical advantage over constant-voltage DBS devices in that the shape of the electrical field in constant-current devices is thought to be more stable and change little over time. Current DBS devices seem to have less effect as the battery runs lower. This study did not compare constant-current to constant-voltage DBS, so any advantages of constant-current devices remain theoretical. Nevertheless, investment by other companies in DBS technology will likely accelerate development in this area and benefit patients in the long run.

About 1/4 of the patients had delayed activation of their DBS device, giving us a sense of which effects might be due to surgery and which might be due to stimulation. Based on this trial, we now know that a decline in verbal fluency, the most frequently reported cognitive side effect of STN DBS, is secondary to the surgical procedure. Additionally, the delayed stimulation group experienced an extra 1.5 hours of "on" time at the 3-month evaluation, before stimulation was even started. Such a sustained lesioning effect is important to recognize, although because adjustment of the stimulators was done in an open-label fashion, interpretation is difficult. Finally, it appears that dysarthria, fatigue, edema, and paraesthesias were associated with stimulation only. Knowing which symptoms worsen with the surgical procedure and which worsen with stimulation are important for both clinicians and patients as they contemplate whether to undergo DBS surgery. ■

GDNF fails to exert neuroprotection in a rat α-synuclein model of Parkinson's disease.

First Author and Institution:
Mickael Decressac, MD, PhD, Wallenberg Neuroscience Center, Lund, Sweden.

Citation:
Brain. 2011;134:2302-2311.

Objective:
Determine whether glial cell line-derived neurotrophic factor (GDNF) is neuroprotective in an α-synuclein model of Parkinson's disease (PD).

Type of Study:
Experiments conducted in animal models of PD.

Result:
Unlike previous studies in MPTP-induced models of PD, GDNF had no effect on α-synuclein-induced aggregation in the present model, raising questions about its candidacy as a neuroprotectant.

Conclusion:
The lack of a GDNF-mediated neuroprotective effect in this model of PD indicates that it may be prudent to test putative neuroprotective agents in multiple preclinical models before moving to clinical studies.

GDNF has demonstrated sufficient evidence of neuroprotection in neurotoxin-based models of PD, and GDNF and related factors have now been tested in several clinical studies. Findings have been inconclusive, indicative perhaps that neurotoxin-based models are not representative of clinical PD.

In this study, the goal was to evaluate the effect of GDNF in attenuating the neurotoxicity induced by aggregation of α-synuclein. Over-expression of α-synuclein is strongly implicated in several neurodegenerative disorders, including PD. A series of studies in adult female Sprague-Dawley rats was conducted in which GDNF was surgically introduced into the nigrostriatal system by a lentiviral vector several weeks prior to targeted over-expression of α-synuclein in the substantia nigra using recombinant adeno-associated virus vector (AAV).

GDNF was ineffective for preventing α-synuclein-induced loss of dopamine function. In particular, tissue processing and immunochemistry studies showed no effect on α-synuclein aggregation. The lack of a neuroprotective effect was reinforced by the failure of GDNF to prevent behavioral changes associated with α-synuclein-induced neurodegeneration typical of this model.

The lack of a protective effect from GDNF in this in vivo model using α-synuclein as a substrate for neurodegeneration may explain the lack of clear clinical benefit from this agent in clinical trials. The authors conclude that other agents with potential neuroprotective effects should be tested in a combination of preclinical models to consider the protective activity within different pathological mechanisms relevant to human disease.

Commentary:

Claire Henchcliffe, MD, DPhil
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Translating promising anti-PD therapies in the laboratory into successful clinical trials has often led to frustration. A critical question is how faithfully PD animal models recapitulate features of the disease itself. A number of genetically engineered animal models of PD are now available, and these will potentially add to or replace the "traditional" toxin-based PD models that exploit chemicals. Decressac and colleagues report on the inability of GDNF (expressed from two different viral vectors in striatum and/or substantia nigra) to effectively lead to neuroprotection in an α-synuclein rat PD model. This is in stark contrast to previous, more encouraging findings in MPTP and 6OHDA animal PD models.

The fundamental issue of which animal model of PD will prove most predictive in translation to the clinic is critically important, and different models may be best suited for different therapeutic questions. However, this report calls into question whether GDNF is indeed worth testing in clinical trials. It is more disquieting since a related protein, neurturin, is currently being examined in PD in a gene therapy trial. The authors postulate that in conditions where α-synuclein aggregates are present, GDNF benefit may be disrupted. These results therefore may help understand more complex issues around neurotrophic factor therapy. Although we cannot yet identify the ideal animal model, this study should encourage more pre-clinical testing in other genetic and α-synuclein-based models. ■

Cerebrospinal fluid amyloid β and tau in LRRK2 mutation carriers.

First Author and Institution:
J.O. Aasly, MD, PhD, St. Olav's University, Trondheim, Norway.

Citation:
Neurology. 2012;78:55-61.

Objective:
Determine if leucine-rich repeat kinase (LRRK2) mutation status affects amyloid β and tau and risk of Parkinson's disease (PD).

Type of Study:
Prospective measurements of amyloid β and tau in LRRK2 carriers and non-carriers.

Result:
Alterations in amyloid β and tau were associated with reduced striatal dopamine function in patients with LRRK2 mutations even at the earliest phases of disease.

Conclusion:
The evidence that changes in amyloid β and tau deposition may be involved in PD associated with LRRK2 mutation as well as with sporadic disease suggests that these are important biomarkers.

The association between altered levels of amyloid β and tau in patients with neurodegenerative disorders such as PD has long been recognized, but there is limited evidence that these contribute directly to the progression of disease. More evidence is needed to confirm that progressive changes in these proteins participate in the pathogenesis of PD rather than simply coexist with PD development.

In this prospective study, amyloid β, phosphorylated tau, and total tau were measured in the cerebrospinal fluid (CSF) of 26 individuals carrying autosomal mutations in the LRRK2 gene, which is the most common genetic cause of PD. Of these, 18 were asymptomatic, and eight had phenotypical symptoms consistent with PD. The measurements were conducted with positron-emission tomography (PET) using three different tracers. Results were correlated with measures of striatal dopamine function.

A correlation was found between reductions in amyloid β and tau with lower striatal dopamine function. Reductions in tau, which is the opposite of what is observed in patients with Alzheimer's disease (AD), and amyloid β are consistent with previous reports and suggest that amyloid β and tau metabolism are dysfunctional in LRRK2-related PD even before symptoms develop. The findings support the hypothesis that these have a pathological role in PD, possibly interacting with α-synuclein to facilitate its aggregation.

If additional studies successfully corroborate the participation of amyloid β and tau in PD pathogenesis, these may be potential targets of therapy or useful within a set of biomarkers for early diagnosis or prediction of PD risk.

Commentary:

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This paper reports on the association between three different PET measures of dopamine function and biochemical biomarkers in symptomatic and asymptomatic LRRK2 carriers. The main finding of the paper is that in both symptomatic and asymptomatic individuals, there was an association between lower levels of amyloid β and tau protein and reduced striatal dopamine function. Since amyloid β and tau are both markers of pathology typical of AD, the study suggests a relationship between dopaminergic degeneration in PD due to LRRK2 mutations and amyloid β or tau metabolism. While amyloid β levels are reduced in AD as they are in this study, tau levels generally increase in patients with AD, which is the opposite of the observed relationship in this study. This discrepancy suggests a distinct effect on tau metabolism in LRRK2 carriers compared with AD.

A second key finding of this paper is that the association between amyloid β and tau levels and dopamine imaging is present in asymptomatic LRRK2 carriers as well as symptomatic individuals, indicating that the metabolic abnormalities in amyloid β and tau occur in the earliest stages of neurodegeneration. One question raised by this study is whether the same abnormalities seen in these LRRK2 carriers are present in those with sporadic PD. If this is the case, assessment of these biomarkers could facilitate more accurate early diagnosis of PD. ■

Solvent exposures and Parkinson disease risk in twins.

First Author and Institution:
Samuel M. Goldman, MD, MPH, Parkinson's Institute, Sunnyvale, California.

Citation:
Annals of Neurology. 2011[Epub ahead of print].

Objective:
Test hypothesis that solvent exposure affects risk of developing Parkinson disease (PD).

Type of Study:
Case-control study of twin pairs discordant for PD using a survey about solvent exposure.

Result:
Exposure to trichloroethylene (TCE) was significantly associated with increased risk of PD, while exposure to perchloroethylene (PERC) and carbon tetrachloride (CCl4) trended toward significance.

Conclusion:
This study suggests that particular solvent exposures might increase the risk of PD. Although additional supportive data are needed, the public health implications are considerable if this association is confirmed.

Several reports of PD occurring after exposure to solvents raise the possibility that these chemicals might play a role in the disease. An analysis of twin pairs is attractive because they share similar genetic risks and childhood environments, which provides an opportunity to isolate the role of solvent exposure in adulthood.

In this study, sets of twins discordant for PD were evaluated. Occupational histories were taken from the subjects or from proxies, such as a spouse or the other twin. Lifetime exposures to six different solvents were estimated from these histories by interviewers who were unaware of the participants' case status. Histories were taken for 126 twins with PD, 119 twins without PD, and 99 total twin pairs. About half of the twin pairs were monozygotic.

Relative to unexposed twins, the odds ratio for PD was 6.1 times greater (P=0.034) among twins with ever exposure to TCE. Odds of developing PD were 10.5 times greater (P=0.053) for ever exposure to PERC and 2.3 times greater (P=0.088) for ever exposure to CCl4. The other solvent exposures did not approach significance. These data support the potential for an association between solvent exposure and risk of PD.

Commentary:

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This interesting paper implicates solvent exposure as an etiologic factor in PD using a twin study. This experimental design minimizes the contribution of genetic variability to PD risk and is a study strength. The investigators are to be commended for attempting to contact nearly 20,000 individuals through their initial screening process. Furthermore, validated occupational surveys were interpreted by industrial hygienists and occupational medicine physicians blinded to disease status, and subjects were not explicitly aware of the study objectives, minimizing recall bias.

In cell and animal models, exposure to chlorinated compounds, such as TCE, PERC, and CCl4, can lead to abnormal mitochondrial respiration and increased oxidative stress. As such, this study's discovery that exposure to these compounds increases PD risk is perhaps not surprising. Several of these chemicals cause damage to other organ systems, and efforts to phase out their commercial and industrial use have been ongoing for several decades. Should we tell patients to specifically avoid these solvents to reduce the potential risk of developing PD several decades later? Given the lag time of several decades before exposure and development of disease, such recommendations might not be practical or even warranted. Future risk assessment studies might be better informed by our screening for these particular occupations in newly diagnosed patients. Nevertheless, it is very unlikely that exposure to solvents explains the majority of idiopathic PD cases.

Despite the many questions that remain (How much exposure is "too much"? What pre-existing factors modify this risk? What relevance do these solvents have to PD prevalence as a whole?), these data should draw attention. Further mechanistic studies are needed to establish neurotoxicity considering the complex interaction between toxic exposures and neurodegeneration. ■

Health-related quality-of-life scales in Parkinson's disease: Critique and recommendations.

First Author and Institution:
Pablo Martinez-Martin, MD, PhD, Carlos III Institute of Health, Madrid, Spain.

Citation:
Movement Disorders. 2011;26:2371-2180.

Objective:
Review and evaluate quality of life (QOL) scales in studies of Parkinson's disease (PD).

Type of Study:
Literature review and summary.

Result:
Current scales vary substantially in the types of information they are designed to elicit and have varying degrees of applicability for specific research and clinical goals.

Conclusion:
The wide variety of QOL scales have been designed for different purposes and should not be considered interchangeable, particularly for clinical assessment of response to therapy.

In chronic progressive diseases such as PD, improvement in QOL is an important therapeutic goal. Not all of the tools aimed at measuring QOL in patients with PD have the same goals. For example, one may place a greater emphasis on disease-related limitations on function, whereas another may be primarily designed to elicit the information about a psychological sense of well-being.

This publication captures the effort by the Movement Disorder Society Task Force to rate the psychometric quality of available health-related QOL scales for PD. Both PD-specific and generic scales were evaluated for relevance in PD on the basis of their use, acceptance by research groups, and clinimetric properties. The Task Force then classified them as "recommended," "suggested," or "listed." The Task Force also considered applications of the scales, such as documentation of treatment benefit in clinical research or patient care.

The Task Force evaluated eight generic scales and nine PD-specific scales. Of these, four of the generic scales and five of the disease-specific scales were "recommended." Of the remaining eight scales, four were "suggested," and four, including three of the PD-specific scales, were "listed." The main advantage of generic scales was the ability to compare PD disease burden to other disorders and to the healthy state. The most widely used and tested of the PD-specific scales, the Parkinson's Disease Questionnaire 39 (PDQ-39), was judged to be relatively comprehensive and reproducible.

While the authors conclude that none of the recommended scales is free of limitations, they suggest that each has value when used appropriately. They emphasize that recommended scales should be selected for the specific objectives of the QOL measurement.

Commentary:

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Los Angeles, California

This review of QOL scales by the Movement Disorder Society is one of two similar initiatives. The other is being funded by the National Institutes of Health (NIH).

As documented in this overview, there are a number of generic and disease-specific scales to measure QOL in PD. While these have been primarily applied to clinical research, a need for an independent review of these tools is being driven at least in part by a growing emphasis on QOL in patient care. Although this article may be more useful for a movement disorders specialist, the basic message that different scales have different values for different applications is important even to non-specialists who take care of patients with PD.

For the clinician, this review suggests that the PDQ-8, a shortened version of the PDQ-39, is a simple and useful tool for documenting changes in QOL over time. Understanding QOL measuring tools is relevant to the recent NIH initiative to fund a patient-centered outcomes research initiative (PCORI) that is designed to increase attention to how patients judge their well-being. While objectively measured disease outcomes remain important, clinicians will be increasingly asked to measure QOL, making expert guidance useful for those wishing to understand the differences between options.

NOTE: Commentator Mickie Welsh is only one of the authors of the article summarized here.

Q&A

WITH EDITOR

Andrew D. Siderowf, MD

Question: What are some dietary issues for people with Parkinson's disease (PD)?

Answer: Patients with PD often ask whether they should follow any specific diet—especially since so many competing diets have been published and publicized, including low-calorie and low-carbohydrate plans, the "South Beach Diet," as well as vegetarian, gluten-free, and vegan diets.

Unfortunately, there is scant evidence to support the idea that any food is particularly good for PD. Some people advocate foods such as antioxidant-rich vegetables or dark chocolate as having a beneficial effect on PD symptoms or progression, but there is no reliable data to support these claims. These foods are unlikely to be harmful, however, so I do not discourage my patients from eating them. Likewise, while I do not recommend that my patients take a daily vitamin, there is no harm in it, and in particular some patients (like the general population) may have low levels of vitamin D. There is no convincing clinical evidence that vitamin C or E supplementation is useful in PD, however, and there are some recent studies that suggest that taking additional vitamin E may actually have health risks, including increasing the risk of prostate cancer and overall mortality.[1,2]

Patients frequently ask about how much protein they should have in their diet and whether their diet might affect their symptoms or medications. This is important as we know that dietary protein can compete with levodopa, an amino acid, for absorption in the gut. In some cases, a very-high protein meal can effectively saturate all of the available transport capacity in the gut and prevent the absorption of levodopa. Patients may experience this as a failure of their medication to provide the expected benefit at mealtime.

A few caveats are in order before counseling patients not to eat protein-containing foods, however. First, only a subset of patients are clinically protein sensitive. Most patients with PD eat protein-containing foods without noticing any ill effects. Since there is no other harm to protein-containing foods except the risk of "dose failures," patients who do not experience this problem should not worry that protein is harming them, for example, by accelerating the pace of nerve-cell loss or causing a permanent loss of the ability to respond to levodopa treatment. Most patients who are protein sensitive will quickly learn which foods to avoid. Some patients, however, may associate dose failures with a big meal, rather than specifically with protein-containing foods. It is important to educate them that it is the protein rather than the amount of calories that is responsible for the dose failures. It is also important to remind patients that any protein-containing food can cause dose failures. A big plate of fish or chicken is just as much of a problem as a juicy steak (although probably less deleterious to their heart health).

Ultimately, a balanced diet that is part of a lifestyle that also includes adequate sleep and exercise is the best prescription for patients with PD. Fad diets are not recommended because they may not contain balanced nutrition, could worsen constipation, or provoke dose failures even in patients who would ordinarily not be protein sensitive. Although weight gain should be avoided because it can reduce mobility, weight loss and low lean body mass are generally bigger problems for patients with PD and can lead to increased frailty.

In summary, patients with PD should eat what they like, in moderation, and only a few patients really need to watch their protein intake.

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Controversies in PD

PRO Opinion

Danna Jennings, MD

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New Haven, Connecticut

The recent approval of DaTscan, a DAT imaging agent, in the United States is a major advance toward improving not only the diagnosis, but ultimately, the treatment of individuals presenting with parkinsonism. DAT imaging is most applicable in clarifying the diagnosis in individuals with early suspected parkinsonian symptoms, where it demonstrates a sensitivity of 87% to 98% and a specificity of 80% to 100% in differentiating patients with dopaminergic degeneration from those without (e.g., essential tremor, drug-induced, psychogenic parkinsonism).[1-3]

While the diagnosis of PD remains based primarily on clinical evaluation, DAT imaging provides an important complement when diagnostic uncertainty exists. Based on clinicopathological studies demonstrating a misdiagnosis of PD in 10% to 24% at autopsy and 15% to 47% in the community, there is a clear need for improvement in diagnostic accuracy, as an incorrect diagnosis has significant implications for making appropriate treatment decisions.[4-8] The overdiagnosis of PD often results in unnecessary exposure to dopaminergics and other PD medications with the potential for side effects. Utilizing DAT imaging to clarify the diagnosis at an early stage of disease has the benefit of developing a thoughtful approach to treatment decisions and provides the patient and family information to better plan for the future. DAT imaging has less utility in patients with longstanding, levodopa-responsive parkinsonism, however, given that increased duration of follow-up and evaluation of dopaminergic response improves the accuracy of clinical diagnosis.[9-11]

The impact of DAT imaging on treatment decisions when applied to individuals in the early stages of disease can be substantial. Imaging individuals with subtle parkinsonian symptoms allows for an earlier diagnosis, by up to a year in some cases, compared with clinical diagnosis alone. The timing of initiation of symptomatic therapy in the early stages of PD remains a subject of debate. However evidence from recent studies (CALM-PD, TEMPO, ELLDOPA) demonstrating that earlier treatment with symptomatic therapy may improve the quality of life has shifted the trend in treatment to an earlier stage, underscoring the need to identify patients earlier in the disease process.[10-13]

DAT imaging also has a role in the development of treatments aimed at slowing PD disease progression. Many hypothesize that a possible reason for the recent failures of disease-modifying therapies may be due to trial of these medications too late in the disease process. While the definition of early PD in these trials relates to the first 2 years of diagnosis, this actually represents a fairly advanced stage of disease with dopaminergic degeneration in the range of 40% to 60% by the time motor symptoms to establish a clinical diagnosis are present.[14,15] DAT imaging has the potential to identify individuals in the pre-motor stage. While it is not practical to complete DAT imaging on the population at large, several studies are underway to help define screening strategies to identify individuals at risk, ultimately providing the potential for preventive intervention.

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The Question: Will dopamine transporter (DAT) imaging change the management of Parkinson's disease (PD)?

CON Opinion

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The recent development and availability of a functional diagnostic imaging tool is an exciting development for movement disorders. This imaging technique may be considered for the diagnosis of PD, but it is unlikely to change the management of PD. There may be a role in differentiating progressive parkinsonism from other disorders such as tremor, dementia, and drug effect, but for the majority of clinicians, dopamine imaging will have little impact on the clinical practice of most cases of PD.

A clinical diagnosis of PD is straightforward when patients present with a classic set of symptoms and exam findings. Distinguishing various forms of parkinsonian variants may be more challenging and require more time, but dopamine imaging is unlikely to help in most of these cases. Based on autopsy studies, the positive predictive value of the clinical diagnosis of PD has consistently been reported as extremely high (98.6%).[1] The overall accuracy of a clinical diagnosis of PD is very high and mathematically identical to the accuracy of DaTSCAN imaging.[2] In addition, the dopamine system is only one aspect of PD, and other neurotransmitters that cause issues such as dysautonomia, dementia, other non-motor or even some motor aspects, may not be captured by dopamine imaging alone.

Dopamine imaging should not be the crutch that we rely on as the primary tool to diagnose PD. When patients have PD clinically but normal dopamine imaging, they are referred to as "subjects with scans without evidence of dopaminergic deficit" (SWEDDs) and represent from 5.7% to 14.7% of cases diagnosed as early PD.[3] Clinicians may run into inaccurate diagnosis when relying on normal versus abnormal or even asymmetry on dopamine imaging, since even the expected asymmetry may not be specific for PD.[4]

In patients already diagnosed with PD, it is unlikely that movement disorder specialists or general neurologists will change medication decisions based on imaging alone. Whether dopamine imaging is accurate and reliable in tracking the progress of PD is currently under investigation.[5] Some medications may be tried to treat symptoms, which may also help to confirm the diagnosis. Even in most non-PD parkinsonian disorders, levodopa remains one of the symptomatic treatments used. The response to medications and the emergence of side effects are based on adequate history, rather than imaging. We treat patients, not tests.

In addition to the fact that dopamine imaging is no better than a clinical exam and does not impact ongoing management, no cost-benefit analysis has been performed yet to determine if the costly testing will change quality of life, time to diagnosis, or other factors for our patients.

The gold standard for differentiating PD and atypical parkinsonism remains the clinical history and exam along with "tincture of time" and response to medications. Dopaminergic system imaging may be valuable in some patients with unclear history or exam findings to clearly diagnose parkinsonism or possibly dementia with Lewy bodies. For some doctors who are less familiar with the intricacies of diagnosing the various parkinsonian and tremor disorders, dopamine imaging may play a role. For the majority of neurologists, however, dopamine imaging is unlikely to significantly change the management of PD.

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