

IN SESSION with Daniel Weintraub, MD

Psychiatric and Cognitive Complications of Parkinson's Disease and Dementia with Lewy Bodies



Dr. Weintraub is Associate Professor of Psychiatry and Fellow at the Institute of Aging at the University of Pennsylvania in Philadelphia. His areas of research interest include the psychiatric and cognitive complications of Parkinson's disease. Dr. Weintraub recently completed a 5-year Career Development Award from the National Institute of Mental Health titled "Depression Diagnosis and Treatment in Parkinson Disease." In addition, he was coordinating investigator for a multi-site, international, industry-sponsored study of the frequency and correlates of impulse control disorders in Parkinson's disease.

What is Parkinson's disease and why does dementia with Lewy bodies (DLB) tend to get clustered in with it in discussions?

Parkinson's disease is defined by its motor characteristics, whereas DLB is defined primarily by its cognitive and other non-motor deficits.

To meet criteria for idiopathic Parkinson's disease, a person must have primary motor symptoms, the most common ones being tremor (upper extremity tremor in particular, usually asymmetric at the time of disease onset); bradykinesia, or slowness of movement; stiffness; and, at times, impairments in balance, although that tends to happen later in the course of the illness. Some combination of those types of motor symptoms is what helps patients meet criteria for Parkinson's disease, often supported by a response to dopamine-replacement therapy.

In contrast, DLB is characterized at disease onset by a dementing illness consisting of impairment in memory and other cognitive abilities. Supporting features include psychotic symptoms, particularly visual hallucinations. Impairments in attention or fluctuations in alertness are also characteristic. Parkinsonism—some of the same features that I mentioned

before—is also characteristic of DLB, although the response to dopamine-replacement therapy is typically less in DLB than in Parkinson's disease.

Would it be confusing for a non-neurologist to distinguish between one or the other?

There is the potential for confusion. One main reason is that a fair number of Parkinson's disease patients, even at the time of illness onset or diagnosis of motor symptoms, are already demonstrating some level of cognitive impairment.

The two can go hand in hand fairly early in the course of either illness, and therefore there is sometimes a blurring between diagnostic categories. Expert opinion is that if there is an established diagnosis of Parkinson's disease and at least 1 year has gone by before the patient meets criteria for dementia, then the diagnosis is Parkinson's disease dementia. If that dementia diagnosis either predates the onset of the motor symptoms or comes within the first year of the parkinsonism, then the patient would meet criteria for DLB.

The reason there seems to be so much overlap is that from a neuropathologic standpoint, the illnesses are very similar. The

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core neuropathology and even the brain regions that are affected appear to significantly overlap between Parkinson's disease, Parkinson's disease dementia, and DLB.

Compared to a decade ago, is there better understanding of the pathophysiology of Parkinson's disease and DLB?

There has been some evolution in terms of understanding. One change to highlight over the past 10 years is that the neurotransmitter deficits really are beyond dopamine in Parkinson's disease. The noradrenergic deficits are probably as significant or close to as significant as the dopaminergic deficits. In addition, serotonergic deficits can be prominent in the illness. However, it appears that all of the brain stem monoamines are affected to some degree in Parkinson's disease, so it really is more than just a dopamine disorder.

Another prominent neurotransmitter deficit is in acetylcholine. The cholinergic deficits in Parkinson's disease dementia are greater than in Alzheimer's disease. Even non-demented Parkinson's disease patients have significant cholinergic loss, so that probably helps explain the high frequency of cognitive impairments in Parkinson's disease.

Have anticholinergics been used to treat Parkinson's disease?

Yes, and they still are, though less commonly now. They have to be used cautiously in patients who are more likely to suffer the side effects of anticholinergics, which would include older patients or patients with preexisting cognitive impairment. Younger patients who are more intact cognitively still receive those treatments.

How common are Parkinson's disease and DLB?

The primary risk factor for Parkinson's disease and DLB is increasing age. Accurate prevalence and incidence estimates for Parkinson's disease are hard to come by. The general estimate of Parkinson's disease in the United States is anywhere between 500,000 and 1 million people. In Western societies, it is the second most common neurodegenerative disease after Alzheimer's disease.

Looking at only the dementia end, DLB is thought to be the second most common dementing illness after Alzheimer's disease. Part of the problems with the prevalence estimates are the overlapping diagnoses of DLB and Parkinson's disease, so it is sometimes difficult to disentangle those two groups. Still, those are the general prevalence estimates. Increasing age is the main risk factor; however, compared with Alzheimer's disease, it is not as uncommon for patients in their thirties, forties, or even fifties, to develop Parkinson's disease, much more common relatively than in Alzheimer's disease.

When people lose 80% of their neurons they get clinical manifestations of Parkinson's disease. Does everybody as they get older lose these neurons? Is it only a matter of time?

Parkinson's disease is a disorder of aging. It is unclear if the incidence of Parkinson's disease will peak at a certain age or whether it just continues to go up. All evidence to this point is that it continues to go up with advanced age. A person needs to lose ~80% of the neurons in the substantia nigra before clinically manifesting the motor symptoms of Parkinson's disease. Another advancement in the past decade has been the work of Professor Heiko Braak and other neuropathologists that have not only staged Alzheimer's disease, but also showed a staging process for Parkinson's disease. Clearly, the brain stem changes in the majority of patients occur even before 80% of those neurons are lost in the substantia nigra, which helps explain some of the pre-motor symptoms that can occur. Beyond the substantia nigra in the later stages of the illness, the pathology spreads to cortical areas; by then it really becomes very much a diffuse brain disease.

Are there certain non-motor cognitive or psychiatric symptoms in Parkinson's disease that will present before any movement disturbance is detected?

Yes, there has been significant research conducted in that area in the past decade, both from large European databases where patients are followed prospectively from young adulthood annually, as well as from case-controlled studies. There is now convincing evidence that patients with Parkinson's disease compared to non-Parkinson patients are more likely to have a lifetime history of either depression or an anxiety disorder in the 5–10-year period, and perhaps even up to 20 years for anxiety, preceding the onset of Parkinson's disease.

Another common psychiatric or non-motor disorder reported to occur prior to Parkinson's onset is rapid eye movement behavior disorder, which is a parasomnia where patients are able to verbally or physically act out their dreams. This has been reported to occur up to 20 years prior to the onset of Parkinson's disease. When most of us dream we are in an atonic state; we cannot physically or verbally act out our dreams. This atonia seems to be lost in a fair percentage of Parkinson's patients, and apparently may be lost prior to the onset of Parkinson's disease, which is thought to represent a brain stem dysfunction.

Other non-motor symptoms that have been reported to occur prior to Parkinson's disease include impaired smell or olfaction, which is very common in Parkinson's disease; constipation; and altered sympathetic intervention of the heart. All are testable.

What are some of the cognitive symptoms you observe in patients with Parkinson's disease?

It was taught in the past that Parkinson's disease patients compared with Alzheimer's disease patients are less likely to have memory or language deficits and more likely to have deficits in other domains.

For patients that have memory deficits, it is less likely to be an encoding deficit, as seen with Alzheimer's disease, but more of a retrieval deficit, which was thought to reflect more subcortical dysfunction.

However, accumulating research has found that Parkinson's disease patients can have impairments in a range of cognitive domains, including memory, attention, executive abilities, and visual-spatial abilities. This has been one major shift in the perception of the disease.

The other major shift is the recognition that, whereas cross-sectional studies have demonstrated that ~30% of Parkinson's disease patients have dementia, more careful longitudinal studies^{1,2} have shown that the overwhelming majority of patients with Parkinson's disease do develop dementia if followed long enough. Early stages of these deficits can be detectable often at the time of diagnosis in 20% of patients. If the clinician asks the right questions and uses appropriate assessment instruments, the disease can be detected early.

What kind of visual-spatial disturbances are involved?

A common example would be the judgment of line orientation tests, which is the ability to conceptualize lines in three dimensions, so to speak. However, it can be detectable even at a much simpler level, just with pentagon or clock drawing. Another difficulty for Parkinson's patients is drawing a cube. The disease can be detected even on simple paper-and-pencil tests.

Are some subtle dysfunctions picked up early and more inevitable ones later on?

Yes. Heterogeneity is the one word that I use more than any to describe all the motor and non-motor features of Parkinson's disease. There is such a range of presentations of Parkinson's in patients from both a non-motor and a motor standpoint. This is one area where I think our research has failed us to some extent, in that most studies will present means and averages for patients on a particular score or domain; however, the individual presentation of patients is really lost that way. The means really mean less in Parkinson's disease than how individual patients present.

Some patients do have cognitive deficits early on, and others do not for 15 years. Somebody may have a primary memory deficit, while another may have impairment in multiple domains. Presentations are all over the board.

Do treatments for psychiatric symptoms and Parkinson's disease adversely affect each other?

This is a very controversial and complex area. Early in the course of Parkinson's disease, a *de novo* case, for example, who has not been treated ever, often would respond with exposure to dopamine-replacement therapies, whether it is levodopa or dopamine agonists. For instance, some patients show improvements in psychomotor speed, attention, and concentration. However, the results are mixed, with some patients or cognitive

abilities improving, and others worsening. Thus, it is difficult to offer a generalization in this regard.

As patients advance in the course of their illness, where they age and the pathology becomes more severe, it seems more likely that the medications, if anything, are not beneficial to cognition. Rather, they may be potentially harmful, particularly with higher dosages when patients can become delirious or psychotic, which certainly has an effect on the cognition, as well.

Deep brain stimulation (DBS), which is increasingly used as a treatment for Parkinson's disease, is thought to perhaps impair verbal fluency and some aspects of memory. That may be a complicating effect of that specific treatment. The anticholinergics and amantadine are probably the most notorious medications in terms of worsening cognition.

In terms of psychiatric medications, in general the newer antidepressants are thought to be safe and well tolerated from both a motor and cognitive standpoint. Recent studies show benefit for tricyclic antidepressants in Parkinson's disease.^{3,4} One concern there, of course, is that with a heavier anticholinergic load, cognition could potentially worsen.

It is unclear from a cognitive standpoint whether antipsychotics have deleterious effects on Parkinson's disease, but certainly there is concern about them worsening motor symptoms in Parkinson's patients.

Finally, the last class of psychiatric medications commonly used is benzodiazepines. These medications must be used very cautiously in Parkinson's disease patients because common side effects include impaired gait, sedation, and worsening cognition.

Are any therapies currently available for Alzheimer's disease effective in improving cognitive symptoms in patients with Parkinson's disease and DLB?

The cholinesterase inhibitor rivastigmine actually has Food and Drug Administration approval for the treatment of Parkinson's disease dementia. This was on the basis of one large European study⁵ that showed significant, but modest, benefits in the treatment of Parkinson's disease dementia, similar to what would be present in Alzheimer's disease patients. A more recent placebo-controlled study⁶ in patients with both Parkinson's disease dementia and DLB showed benefit for memantine. Those are really the two large-scale studies that have been positive to date for the treatment of cognitive dysfunction in Parkinson's disease.

Another common non-motor disturbance in Parkinson's disease is apathy, often in the context of cognitive impairment, but not always. We really do not have good treatments for apathy in the context of any other disorder. We extrapolate what people use in other populations, including the use of stimulants. Clinicians, myself included, may use methylphenidate and dextroamphetamine as a trial for apathy in particular. Bupropion is also used to some extent because of its stimulant-like properties, the reason being that it has some dopamine-enhancing effects, as well.

Have there been any meaningful advances in the treatment of the motor symptoms of these disorders in recent years?

The one class that was not available 10 years ago that is readily available now and used as a first-line agent in younger patients particularly are the dopamine agonists. The ones being used now are more selective and better tolerated overall than the older ones. This class of medication has been added to the armamentarium, in addition to levodopa, although levodopa still is the most potent in terms of its motor effects.

DBS has been a significant advancement, particularly for patients with more advanced disease, because those patients really had no option previously. Once they developed dyskinesias and other motor fluctuations, they were really at a dead end in terms of treatment. This often can be a successful treatment for patients that enables them to make a significant decrease in their dopamine-replacement therapy. Other fine tuning has been the increased use of catechol-O-methyl transferase inhibitors, that do allow a better management of motor fluctuations in off periods.

That being said, I think treatment has not advanced so significantly. I do think patients are better managed overall. Clinicians are able to go deeper into the course of their illness without significant complications compared with previously.

Does using these other, more indirect interventions delay some of the secondary complications of taking levodopa, such as the dyskinesias?

Yes. A preferred medication choice in this day and age

would be to start with a dopamine agonist, or even for milder symptomatic benefit something like a monoamine oxidase-B inhibitor early in the course of the illness, and to delay the introduction of levodopa as long as possible.

Is there anything you would like to add?

One other interesting area for psychiatrists that has come to the forefront recently—and we have been involved in a fair amount of research with this—is impulse control disorders in response to dopamine agonist treatment. Parkinson’s patients can develop compulsive behaviors (the four that have been reported have been gambling, sexual behavior, buying, and eating) in connection with their Parkinson’s treatment. It is quite a problematic disorder, but also an interesting one from a psychiatric standpoint in that the disorder can be essentially induced by these dopaminergic medications. *PP*

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