WHAT DO I DO NOW?

SECOND EDITION

MOVEMENT DISORDERS

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Robertus M.A. de Bie
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Preface

In this second edition of *What Do I Do Now? Movement Disorders*, we have added 14 new chapters and updated others that appeared in the first edition. The field of movement disorders remains one of the most exciting subspecialties within neurology, with continued advances in our understanding of the genetic and pathological basis for these diseases. While attempting to include some new themes to reflect these changes, the focus remains almost entirely clinical, with a pragmatic and practical approach offering solutions to commonly encountered problems. As before, we have aimed to keep chapters short and accessible, with 'high yield' information presented in an informal, problem-solving manner.

This book is suitable for general neurologists, trainees in movement disorders, as well as community and hospital-based general physicians who will encounter many of the more common and some of the rarer presentations included in this edition. Information provided is digestible and equally amenable to being carried in a white coat or used as a ready reference text in the clinic or office. We hope each time you dip into a chapter you come away with a clinical pearl or nugget that enhances your knowledge and your practice.

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PART I

Parkinson's Disease

1 Smoothing out the Ups and Downs

Richard A. Walsh

You are reviewing a 63-year-old man with a diagnosis of idiopathic Parkinson's disease of 10 years' duration, treated for 8 years. He has had a relatively uncomplicated course to date, continuing to work at a bank, with no cognitive complaints and good tolerance of the dopamine agonist you had started him on 7 years ago. Four years ago, you added low-dose levodopa due to progression of his tremor that had become a nuisance at work, where colleagues, unaware of his condition, had commented on it. It had failed to respond to increasing doses of ropinirole. He is currently taking 18 mg ropinirole once daily and levodopa–carbidopa 100 mg/25 mg four times daily. He reports continued good "on" time where he feels he moves normally. His only new complaints are increasing weight, often snacking throughout the day, and a return of the right upper limb tremor 30 minutes predose. He is unaware of dyskinesia, but you note some mild dyskinetic movement of his right foot when animated.

What do you do now?

INITIAL MEDICAL MANAGEMENT OF MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

It is sometimes helpful to use the analogy of a game of chess when explaining the approach to managing the motor complications of Parkinson's disease to newly diagnosed patients. I describe how the disease can be expected to change slowly as time goes on and the aim of the physician to outmaneuver it by being a few moves ahead at all times. We know this is possible because the emergence of motor complications tends to be reasonably predictable and almost an inevitability as years on therapy pass by. The analogy can be useful in helping patients understand the complexity and dynamic nature of their disease as well as preparing them for what will be many years of regular medication adjustments. This explanation can even be reassuring to patients who like to believe their doctor knows what to expect and has a number of treatment options to introduce when needed in the future.

THE THREE STAGES OF PARKINSON'S DISEASE

In simplistic terms, the natural history of the motor aspect of Parkinson's disease can be categorized into three main epochs, not all equal in duration:

1. The so-called "honeymoon period" is when motor symptoms respond well to dopaminergic therapy, allowing many patients to feel close to normal for much, if not all, of their day. This phase often includes treatment with a dopamine agonist in monotherapy but also the early stages of levodopa therapy in which the "long-duration effect" allows the benefit from individual doses to merge seamlessly together. This phenomenon is due to the buffering effect of surviving nigral neurons, which take up ingested levodopa and store it for later use well beyond its 90-minute plasma half-life.
2. After 5 or more years of levodopa therapy, most patients will experience motor complications, typically beginning with an awareness that the benefit of the first of three daily doses has faded by the time the next dose is due. This "wearing off" is characterized by a re-emergence of previously well-controlled symptoms. Dyskinesia may also be noticed for the first time, initially as subtle and nonbothersome choreiform movements, often unnoticed by the patient. Dyskinesia can be expected in 50% of patients after 5 years of levodopa therapy. A spouse may report a tendency to rock back and forth or dyskinetic neck movements coinciding with the peak effect of each or some doses of levodopa.

3. "Advanced" Parkinson's disease is a term sometimes used to describe patients who have had many years of disease and for whom motor complications (on–off fluctuations and troublesome dyskinesia) have become a prominent and constant problem. Patients in this stage of disease often have additional nonmotor and levodopa-unresponsive complications such as dementia and postural instability. The nondisabling wearing-off experienced in the earlier stages is replaced by sudden and unpredictable "off" periods, dose failures, delayed responses, and freezing. These severe motor fluctuations can leave patients experiencing brief islands of relatively good movement in a day otherwise marked by hours of disabling "off" time in which freezing, akinesia, and tremor can leave them fully dependent.

PRINCIPLES TO GUIDE MANAGEMENT OF MOTOR FLUCTUATIONS

Listen to the Patient to Allow Treatment to Be Titrated to the Patient's Movement Requirements

A 40-year-old professional golfer with early onset Parkinson's disease will have very different expectations and requirements compared to an 80-year-old nursing home resident. This is not to imply that the older patient's needs are less important; however, for a patient largely confined to a chair or bed, the re-emergence of a moderate tremor for 1 hour before each dose may be tolerated, whereas in the golfer it clearly would not. It is also important not to change treatment just because you can do so. I always ask patients, "Would you be happy if I said your last week would reflect how you are likely to function for the next 12 months?" If they are broadly happy with this notion, I tend not to tinker with their pills for the sake of it. If they believe they have daily symptoms that adversely affect function on a social, professional, or recreational level, then I believe there is good rationale for a change.

Take the Time to Get an Accurate Picture of a Typical Day

When first questioned about their motor performance, patients with Parkinson's disease will often explain how yesterday was particularly bad or how their morning dose prior to clinic did not work as well as expected and provide their own interpretation of why this was the case. These are important issues for them of course, but isolated fluctuations may not always be representative of the larger picture. While acknowledging that day-to-day fluctuations occur, emphasize that what you need is an *average* picture of their day. With some help, most

patients will be able to provide a good outline of how long their "on" response tends to last with each dose and for what proportion of the day they are bothered by dyskinesia. With this information taken in a patient manner, it is far easier to make treatment changes. There will always be patients for whom motor fluctuations are so unpredictable that it is impossible for them to give a broad overview, and managing these patients can present a particular challenge. In the future, there will likely be increased use of automated technology that patients can wear on a wrist to give an automated and objective assessment of bradykinesia and dyskinesia.

Know When Less Is More

For the first 10–15 years of disease, the symptoms of Parkinson's disease are managed by the addition and layering of dopaminergic agents and enzyme inhibitors in an attempt to deliver a steady state of performance. Many patients will be treated with adjuvant agents such as anticholinergic drugs or amantadine for dyskinesia. As the condition progresses with an accumulation of cortical disease and the emergence of hallucinations and cognitive impairment, a measured retreat is often necessary to minimize side effects. Anticholinergics and amantadine are particularly poorly tolerated in patients older than age 70 years, and the improvement in what was believed to be disease-related cognitive decline can sometimes be dramatic once they are slowly withdrawn.

STRATEGIES FOR THE SECOND STAGE WHEN MOTOR COMPLICATIONS EMERGE

Motor fluctuations will not typically emerge for patients maintained on a dopamine agonist or monoamine oxidase B (MAO-B) inhibitor in monotherapy, or indeed in combination. As time progresses, the tendency is for additional dopaminergic therapies to be layered on to achieve an adequate motor response, and there are a number of options (Table 1.1) Ultimately, as was the case in this patient, it becomes necessary to add in levodopa when these less potent agents are not sufficient to manage symptoms or when side effects make dose increases a less attractive choice. Levodopa is typically started on a three-times-daily regimen, but over time the long-duration effect wanes, bringing on the wearing-off phenomenon. This early tailing off of individual levodopa doses can be managed by increasing the dose of a longer acting dopamine agonist being used or addition of a once-daily MAO-B inhibitor if not already in place. If these options are not available or not tolerated due to

TABLE 1.1 **Treatment Options for the Management of Motor Symptoms in Parkinson's Disease**

	Advantages	*Disadvantages*
MAO-B inhibitors Selegiline Rasagiline	Once-daily drugs Generally well tolerated	Small overall symptomatic response Selegiline can cause sleep disturbance, particularly when taken late in the day
Dopamine agonists Ropinirole Pramipexole Rotigotine	Available in once-daily or patch formulations, improving convenience and compliance Very low incidence of dyskinesia in monotherapy Can provide adequate symptom relief in monotherapy	Impulse control disorders are an increasingly recognized side effect Contribute to cognitive impairment and hallucinations in older patients Inevitably need bolstering with levodopa with disease progression
Levodopa/ carbidopa	Most effective oral agent for symptom control Generally better tolerated than all other options	Contributes to genesis of dyskinesia Short-acting drug; multiple doses required with advancing disease Can also cause impulse control disorders and a greater cause of punding than dopamine agonists
COMT inhibitors Entacapone Tolcapone	Useful for maintaining duration of motor response with levodopa Generally well tolerated Available in compound preparation with levodopa	Can worsen previously nonbothersome dyskinesia Potential hepatotoxicity with tolcapone
Amantadine	Useful for reducing dyskinesia Mild antiparkinsonian effect, useful for some levodopa refractory tremor Worth trying for intractable freezing of gait	Poorly tolerated over the age of 65 years Commonly contributes to hallucinations
Anticholinergics	Can help otherwise refractory tremor	Poorly tolerated in older patients

side effects, a catechol-*O*-methyltransferase (COMT) inhibitor (entacapone, 200 mg with each levodopa dose) can be added. Tolcapone, an alternative COMT inhibitor, is available in some countries and requires strict monitoring of hepatic function. The addition of a COMT inhibitor will also have the effect of increasing the peak effect of levodopa, which can produce or exacerbate dyskinesia. If these options are already exhausted, a reduction of the interdose interval can be a simple way to attack wearing off, albeit with the added inconvenience of having to remember to take an extra dose.

APPROACH IN THIS CASE

As described previously, this patient has had a predictable emergence of early motor fluctuations with wearing off that is, although mild, troublesome in his opinion. He continues to work and would like to avoid visible manifestations of his Parkinson's disease, in the form of either dyskinesia or tremor. It is important to take note of the weight gain because this suggests a possible impulse control disorder as a complication of his dopamine agonist, which he is taking at a reasonably high dose. He is on a four-times-daily regimen, giving him a 4-hour interval between doses at 7 a.m., 11 a.m., 3 p.m., and 7 p.m. The final point to note is the evident dyskinesia, which is not an issue for him currently but must be taken into consideration when making a treatment change.

My instinct here would be to avoid pushing the dopamine agonist higher. The tremor had failed to respond to increasing doses in the past and is therefore unlikely to respond now. Increasing doses of dopamine agonists can often demonstrate a law of diminishing marginal returns, with only increasing side effects as you move upward from moderate to high doses. On this note, this patient has already demonstrated some impulse control disorder features that will undoubtedly worsen with higher agonist doses.

A simple move would be to change interdose interval from 4 to 3 or 3.5 hours. This will make his regimen more complicated and does often have the effect of increasing peak dose dyskinesia, particularly toward the end of the day when there tends to be a cumulative effect of levodopa ingested earlier in the day. The addition of a COMT inhibitor can prolong the effect of each dose, buying back approximately 1 hour of good "on" time each day. This is sometimes sufficient, but there is also often a tendency to increase peak dose dyskinesia. It is often suggested that individual doses of levodopa should be reduced by 20–30% to combat this effect, but in practice each dose of levodopa can only be halved on a practical level, which is an excessive reduction for the addition of a COMT inhibitor.

The best choice in this man may be the addition of rasagiline or selegiline. This step is often unavailable because of the fact that many patients are started on these agents at onset due to interest in their disease-modifying potential, although this is not evidence based. Addition for motor fluctuations is a conservative step that can also buy back approximately 1 hour of effective "on" time without running the risk of agonist-related side effects with less potential to exacerbate dyskinesia.

It is inevitable that this patient will need up to a five-times-daily regimen during the next 3 years, and as options to smooth out motor fluctuations are used up, advanced therapies may come into play. The goal of the current consultation, however, is to make a change that restores some function while avoiding side effects.

KEY POINTS TO REMEMBER

- Treatment in Parkinson's disease is not disease modifying, only symptomatic. Therefore, the aim should be to maximize symptom control when the patient believes he or she needs it and not just because you can do so.
- Parkinson's disease progresses slowly. Sudden deteriorations in function are typically due to extrinsic factors such as intercurrent illness and do not warrant a treatment change. When a patient gives a reasonably reliable picture of motor fluctuations that have a meaningful impact on quality of life, discuss a change of timing, dose, or drug.
- Not all wearing off, even where predictable, needs a change in treatment regimen. Many patients will report a re-emergence of symptoms that are neither bothersome nor disabling. Although the mantra is to smooth out dopaminergic stimulation, smoothing out every crease for the sake of making a change is not always a necessity.
- Dopamine agonists remain very useful agents for the management of mild to moderate parkinsonism in young to middle-aged patients. These agents can reduce the amount of levodopa required, acting as a levodopa-sparing agent. It is important to know when dopamine agonists are no longer effective in controlling symptoms or are causing unwanted side effects.

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2 "He Wants It All the Time, Doctor"

Robertus M. A. de Bie

The patient is 57 years old and has had Parkinson's disease for 17 years. The disease started with slowness and stiffness on the right side. Nine years into the disease, he had right-sided symptoms only, though severe, and he underwent a left-sided pallidotomy. This was very effective. Over time, the symptoms worsened, and now he has medication-induced motor response fluctuations, dysarthria, and difficulty walking. He is referred for treatment with deep brain stimulation. Upon inquiry, it appeared that he experienced problems with gambling and hypersexuality during the past 7 years, but he denies this to be a problem. He takes levodopa/carbidopa 100/25 mg 5 tablets per day, levodopa/carbidopa sustained release 100/25 mg 12 tablets per day, selegiline 5 mg BID, entacapone 200 mg QID, amantadine 100 mg BID, and ropinirole extended release 24 mg per day. He initially visits you alone, without his wife.

What do you do now?

IMPULSE-CONTROL DISORDERS IN PARKINSON'S DISEASE

Parkinson's disease (PD) may be accompanied by impulse-control disorders such as pathological gambling, hypersexuality, compulsive shopping, and compulsive eating. Patients may also display addiction-like behavior toward taking levodopa, referred to as "dopamine dysregulation syndrome." Typically, patients with PD are not distressed by the behaviors associated with the impulse-control disorders, and the aberrant behaviors often go unnoticed because patients experience these as internally consistent with their thoughts and behaviors. From studies into the prevalence among patients who visit specialized PD clinics, it appears that pathological gambling occurs in 4% of patients. In patients who use dopamine agonists, the frequency is higher—up to 8%. The frequency of hypersexuality is 3–8%; that of compulsive shopping is almost 2%.

There is an individual susceptibility (hereditary and/or environmental) for impulse-control disorders within the framework of PD. Factors associated with a higher risk for impulse-control disorders are a young age at disease onset, a history of addictive behavior before the disease started, a family history of addiction such as alcoholism, and being male. In addition, there is a relationship with medication use, with dopamine agonists having the highest risk. The treatment of impulse-control disorders consists of lowering or stopping the dopamine agonist, treating any possible depression or anxiety disorder, and involving the family and spouse. Referral to a psychiatrist may be required. There are reports that impulse-control disorders disappeared following treatment with deep-brain stimulation of the subthalamic nucleus because the dopamine agonists were subsequently stopped.

Another behavioral disorder that may be seen in the context of PD is "punding." Punding is defined as complex, prolonged, aimless, and stereotyped behavior with a fascination for repetitive actions of, for example, machines, sorting and investigating ordinary objects (e.g., buttons, labels, and tools), grooming, hoarding, driving or walking around aimlessly, and elaborate monologues. Patients experience punding as disruptive and unproductive but appear to find it very unpleasant to be disturbed during the behavior.

If the patient and spouse recognize that the behavior is abnormal, they may not be aware that it could be due to the anti-PD medication. Frequently, patients have enormous debts or serious issues in their relationship before the treating physician knows about the problem and can try to help. Therefore, it is very important to inform every patient and spouse about impulse-control disorders, especially when the patient starts taking dopamine agonists. In particular, the clinician should ask the patient and especially the family members about any impulsive behavior.

In this case, we invited the patient to come to another appointment with his wife. She confirmed that he was hypersexual and that he made unreasonable and frequent demands. The patient did not believe that the hypersexuality was a problem. Five years ago, they had decided to live apart, but they had not told their adult children. Usually, the patient visited the neurologist alone. Once, he brought his wife and the hypersexuality was discussed. The neurologist advised him to reduce the dopamine agonist dosage (ropinirole). Subsequently, he continued to visit the neurologist on his own and denied any hypersexuality. The ropinirole dosage was increased again. We stopped the ropinirole, and he had a successful deep-brain stimulation treatment. To date, the hypersexuality did not recur.

KEY POINTS TO REMEMBER

- Inform the patient and spouse that impulse-control disorders are possible sequelae of the PD medication, especially the dopamine agonists.
- The impulse-control disorders occur commonly without subjective distress or are frequently hidden or go unnoticed because they are experienced as being internally consistent with the patient's thoughts.

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