Early Treatment of Parkinson's Disease: Opportunities for Managed Care

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Abstract

The diagnosis and treatment of Parkinson's disease (PD) typically occur when the disease has already progressed to a relatively advanced stage in which motor symptoms are clearly evident and substantial neurophysiological damage has already taken place. Nonmotor symptoms, which account for a large proportion of PD symptoms, usually emerge much earlier and offer both an early indication for treatment and a therapeutic target. A growing body of data from the medical literature points to several critical advantages that may be associated with early therapeutic intervention in PD. The most evident benefit of early intervention is a reduction in symptoms, particularly dyskinesia, and the delay of levodopa initiation. Clinical trials suggest but have yet to conclusively demonstrate that early treatment can slow disease progression. Both the diminishment of symptoms and the potential for slowing disease progression have large implications for improving patient quality of life. The enormous direct costs associated with PD would also likely be reduced over the long term with earlier treatment. The great majority of costs attributable to PD occur when the disease is at its most advanced stage and when symptoms are most severe. An early-treatment strategy that diminishes symptoms and that has the potential to slow disease progression could have a meaningful impact on PD expenditures. Adherence, too, must be taken into consideration, particularly since PD patients are generally poorly adherent to prescribed therapies, especially therapies with complex dosing schedules. Taking advantage of more convenient and adherence-friendly drug formulations may further help to improve outcomes and lower costs in PD.

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For author information and disclosures, see end of text.

Early Treatment: Benefits and Options

Parkinson's disease (PD) has traditionally been diagnosed and treated when the disease has already progressed to a fairly advanced stage. In recent years, however, the potential benefits of early intervention in PD have been recognized. The primary rationales for early initiation of treatment in patients with PD include slowing disease progression, delaying and diminishing symptoms (both motor and nonmotor), limiting deterioration of patient quality of life (QoL), and achieving long-term cost savings.

Slowing Disease Progression

Patients with PD who remain untreated, or insufficiently treated, will experience ongoing and substantial symptomatic deterioration and negative effects on their QoL.[1,2] Based on relative QoL scores, PD rates as one of the most severe chronic diseases in terms of physical, functional, mental, and social burdens.[2] Although motor symptoms are the most recognizable of symptoms in PD, and are those upon which a PD diagnosis is largely contingent, *non*motor symptoms represent not only a large proportion of overall PD symptoms but, in many cases, emerge earlier than motor symptoms. Indeed, nonmotor symptoms have been shown to exert a greater negative influence on QoL than motor symptoms.[3,4] Three nonmotor symptom domains—apathy, attention/memory, and psychiatric symptoms—have been seen to emerge early in the disease and, thus, offer not only a rationale for early intervention, but also a potential means of identifying patients requiring early intervention.[5] Similarly, sleep disruption and constipation are early and potentially treatable nonmotor symptoms of PD.[6]

The fundamental goal of early treatment for patients with PD is slowing the progression, and the symptomatic manifestations, of the disease. However, slowing disease progression in PD is an exquisitely complex endeavor for several reasons. First, defining what exactly is meant by slowing disease progression is itself a multifaceted issue. Secondly, measuring success in the slowing of disease progression—almost regardless of how that goal is defined—is extremely difficult, and, in some cases, currently impossible. With those limitations in mind, how can we understand what slowing disease progression entails? This question might be approached by considering the appropriate means of measuring disease progression.

The standard means of measuring PD progression is the Unified Parkinson's Disease Rating Scale (UPDRS), an instrument that is widely used for measuring treatment success in clinical trials.[7] The UPDRS, however, is less than ideal in the context of measuring disease progression because it is an instrument largely limited to defining the status of symptoms, and motor symptoms in particular. The problem here is 2-fold: 1) nonmotor symptoms, as previously noted, represent a large part of the symptomatic experience of people with PD, and 2) measuring symptoms does not provide all the necessary information needed to determine disease progression.[5] It should be noted that a newer version of the UPDRS has been developed to evaluate a wider spectrum of symptoms, although its clinical utility remains untested.[8]

It may be the case that neuroimaging studies—for example, single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and positron emission tomography (PET)—offer a more valuable, or at least necessarily additive, perspective on disease progression. However, the utility of these modalities as biomarkers for evaluating the efficacy of therapeutic interventions to slow disease progression remains imperfect, and additional development is necessary to make them fully useful and integrate them into clinical practice. Indeed, for both SPECT and PET, there exists an ongoing debate as to whether changes in radioligand uptake do in fact measure nigralstriatal integrity (or neuronal loss) or simply the effects of medications on synaptic activity.

Two terms often used in the context of slowing disease progression are "neuroprotection," which refers to effecting a change in the pathophysiology of PD, and "disease modification," which would typically refer to an effect upon clinical outcome that is not contingent upon an absolute change in PD pathophysiology.[9] However, a lack of consensus on this terminology in the PD setting makes the use of the term "disease modification" potentially confusing. Therefore, for the remainder of this article, the term "outcome modification" will be used to describe a therapeutic intervention that produces a positive change in clinical outcome without necessarily affecting disease pathophysiology.

It is generally accepted that neuroprotection as a consequence of therapeutic intervention in PD has not yet been demonstrated, although this does not necessarily mean it has not been achieved. Part of the problem in establishing whether a treatment is neuroprotective has to do with designing and executing a clinical trial that is up to the very challenging task of proving neuroprotection.[10] Preclinical studies have the advantage of allowing for measurement of neuronal loss, but this is not, at present, possible in live human patients.[11] Thus, human clinical trials that attempt to measure neuroprotection must do so indirectly. A discussion of the complexity of trial design to determine neuroprotection is beyond the scope of this article; however, Henchcliffe and Severt have provided a useful overview of the subject.[12]

Clinical Trials

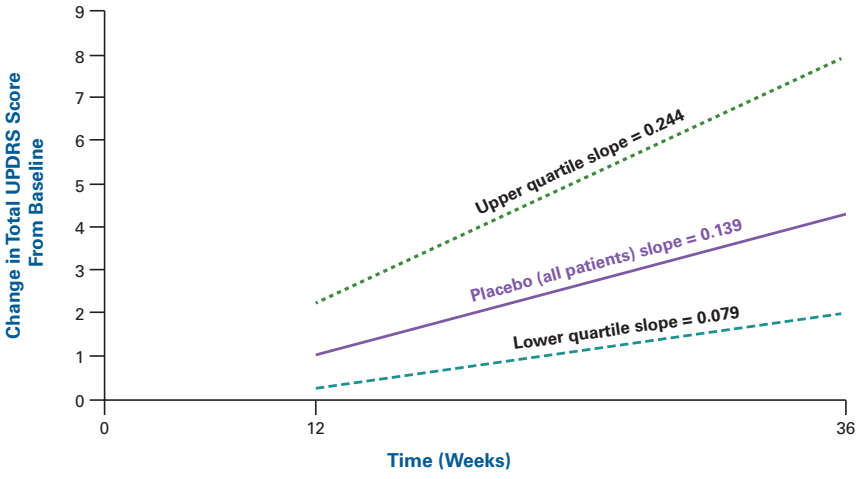
Investigators have employed various clinical study designs in an attempt to accurately determine whether a given agent offers outcome modification and/or neuroprotection in PD. The lack of proven biomarkers to allow for clear confirmation of such end points makes this task very challenging, and different approaches have been tried in order to overcome these limitations.

The Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) trial was a placebo-controlled, double-blind study that employed a delayed-start study design as a means of evaluating the capacity of the MAO-B inhibitor rasagiline to confer outcome-modifying effects in early PD patients. The ADAGIO study population included 1176 untreated subjects with early PD who were randomized to receive either 1 mg per day or 2 mg per day for 72 weeks (designated the "early-start" groups) or to receive placebo for 36 weeks followed by 1 mg or 2 mg rasagiline for the following 36 weeks (designated the "delayed-start" groups).[13] The ADAGIO study included 3 primary end points. The first primary end point was change in UPDRS points per week, also known as the "slope," which was the primary means of measuring disease progression in the 4 treatment groups. The second primary end point was a comparison between the early-start and delayed-start groups for estimated change in UPDRS from baseline to week 76, which was intended to measure if initial benefits gained by patients in the early-start groups were sustained at the end of the study, which would also tend to indicate positive outcome modification. The third primary end point was noninferiority of slope during weeks 48 through 72 for the early- versus delayed-start group, ie, if benefits gained during the second 36-week period remained as robust in the early-start group versus the delayed-start group, this would indicate an enduring positive outcome effect resulting from the early-start strategy.[13]

The ADAGIO trial, in seeking to maintain a type I error of 0.05 across a study that involved 3 primary end points and 2 separate doses in each group, employed a hierarchical design, such that each of its primary end points had to be met for the results to be deemed positive for either of the 1 mg or 2 mg doses.[10,13] At the end of the study, early-start patients receiving 1 mg had achieved all 3 primary end points, while the 2 mg group, though it did achieve the first and third end points, did not achieve the second primary end point.[10]

Numerous explanations have been offered to account for the failure of the 2 mg dose to achieve the second primary end point; the results should be viewed in light of results from the TEMPO trial, which although quite different in design, showed UPDRS benefits with both 1 mg and 2 mg doses of rasagiline.[14] Although the 2-mg treatment group of ADAGIO did not achieve all 3 primary end points, the 1-mg treatment group did demonstrate that outcome modification is achievable with early initiation of treatment in that patients in the early-start group experienced fewer symptoms than those in the late-start group over the course of the study.[10] The benefits of early treatment are further borne out by a group of prespecified and post hoc analyses of the ADAGIO study, which found that early treatment was associated with significantly less need for, and a significant delay in the need for, other additional antiparkinsonian treatments and improved UPDRS ADL subscores at week 72.[15]

Figure 1. Effect of Baseline Disease Severity (per UPDRS) on Rate of Disease Progression in ADAGIO Study[15]



ADAGIO indicates Attenuation of Disease progression with Azilect Given Once daily; UPDRS, Unified Parkinson's Disease Rating Scale.
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Importantly, from the standpoint of understanding the role of early PD treatment in achieving outcome modification, an analysis of the ADAGIO data found that the rate of UPDRS decline was significantly associated with baseline disease severity. This association may be seen in the difference in progression of UPDRS from baseline to week 36 in the highest versus lowest quartiles of UPDRS scores, which was highly statistically significant (P <.0001) (**Figure 1**).[15] Future studies will need to incorporate this finding into their study design and randomization approach to ensure large enough sample sizes and power to detect meaningful differences in outcomes over time.

A number of preclinical studies have offered evidence of neuroprotection from dopamine agonist agents, including pramipexole, ropinirole, and rotigotine.[16-18] With regard to human clinical trials, the CALM-PD study, in a substudy within the larger trial, employed SPECT to evaluate disease progression by evaluating uptake of striatal 2β-carbomethoxy-3β-(4-iodophenyl)tropane(β-CIT), a marker for dopamine neuron degeneration, in 82 subjects with early PD receiving pramipexole or levodopa/carbidopa.[19] At 4-year follow-up, pramipexole-treated patients experienced significantly greater β-CIT uptake decline versus levodopa-treated patients, and β-CIT uptake decline was significantly correlated with change in UPDRS from baseline. These data point to a possible modification of dopaminergic neuronal degeneration with pramipexole that is greater than that seen with levodopa (though levodopa also exerted positive benefits), although the effects of these medications on synaptic activity and β-CIT uptake are not fully understood.[19]

The REAL-PET study employed PET imaging to compare the effects of ropinirole versus levodopa in 186 patients with early PD over the course of 2 years.[20] PET data revealed significantly slower disease progression with ropinirole treatment based on the rate of loss of dopamine-terminal function. However, motor score improvement, which was seen with both treatments, was sustained in the levodopa group but not the ropinirole group. Importantly, in terms of symptomatic effectiveness of treatment, reduced dyskinesia and longer time to dyskinesia were associated with ropinirole versus levodopa, although Clinical Global Impression scores were not significantly different between treatment groups.

One caveat that should be acknowledged with regard to early therapeutic intervention is the risk of additional side effects involved with starting drug treatment early. Certain drugs commonly used in PD—such as levodopa, anticholinergic agents, and dopamine receptor agonists—are associated with side effects as well as nonmotor symptoms that might exert their own effects on QoL and therapeutic adherence. That said, it may be the case that early treatment of PD confers other benefits—whether or not neuroprotection or outcome modification per se can be achieved—such as potentially enhancing effects on mechanisms that compen-

sate for the deficits caused by PD. An analogy might be made to the concept of "cognitive reserve" in dementia, in which a built-in neurological resilience resists the deleterious effects of deterioration. Such a notion, while credible, has not been demonstrated to date, although, like neuroprotection, proof of such a concept is not easily achieved.

In addition to pharmacological therapies, nonpharmacological therapies such as physical therapy (PT) and exercise also offer opportunities for improving patient status in PD. While PT and exercise have been widely studied in PD, this is somewhat less true in early PD. One controlled trial from UCLA by Fisher et al, published in 2008, randomized 30 patients with early PD (Hoehn and Yahr stages 1 or 2) to 1 of 3 different interventions.[21] The first intervention was high-intensity body weight–supported treadmill training, under the supervision of a physical therapist, for 24 sessions over a period of 8 weeks. The second intervention was a more traditional low-intensity PT approach to PD (eg, range-of-motion stretching, balance activities, resistance training), also for 24 sessions over 8 weeks. The third intervention was a series of 6 "zero-intensity" educational classes over 8 weeks, which addressed topics such as improving QoL, dealing with stress, improving memory, and advances in PD treatment. The authors found small improvements in UPDRS for all 3 groups in addition to gait and sit-and-stand improvements. However, the high-intensity group accrued additional significant benefits, including more robust and diverse improvements in both gait and sit-and-stand, and also a lengthening of cortical silent period (CSP) durations. This latter improvement is important since shortened CSP durations are believed to be indicative of the excessive cortical excitability characteristic of PD.

Cost Implications of Early Treatment

Total direct medical costs for PD in the United States have been estimated at $6.2 billion annually, and total costs have been estimated at $11 billion annually.[22] O'Brien et al estimated direct annual per patient costs based on 4 patient categories: 1) a non-institutionalized chronic patient with an acute event possibly requiring temporary hospitalization (representing 23% of PD patients), with estimated direct costs of $16,610; 2) a chronic patient managed on an outpatient basis (54%), with direct annual costs of $3573 ($5363 if medical equipment and transportation are included); 3) an institutionalized patient (11%), whose annual costs are $47,807; and, 4) a patient who dies (12%), with associated direct annual costs of $3769.[22]

A number of cost-effectiveness studies have been undertaken to determine the economic value of early intervention for PD, and the results have been largely, if not unanimously, positive. For example, Haycox et al observed that early rasagiline treatment delayed onset of dyskinesia and levodopa initiation that were associated with cost savings over a 5-year study period.[23] Noyes et al found that treatment with pramipexole in patients with early PD was associated with cost savings versus levodopa in patients with depression and low baseline QoL.[24] Hoerger et al also found overall pramipexole to be cost-effective in patients with early PD despite initially higher drug costs.[25]

It must be acknowledged that pharmacoeconomic studies examining the cost-effectiveness of PD treated early in the course of the disease refer to "earliness" only in the sense of the disease being treated soon after standard PD diagnosis has been achieved. Standard approaches to PD diagnosis are, as previously noted, contingent upon the emergence of motor symptoms, and by that stage of the disease, significant neurological damage may already have occurred. If, however, early PD is defined as that period prior to the emergence of significant motor symptoms, before substantial neurological damage may have occurred, then few data are available that describe the real potential for cost savings.

It should also be noted that the largest part of direct costs in PD occur in advanced disease, when symptoms are at their most severe.[26] It is, therefore, possible that therapeutic interventions offered to patients before significant deterioration has occurred—when the potential for preserving neurophysiologic structures is maximized—may offer long-term cost savings. Indeed, little evidence points to the likelihood of short-term savings with early therapeutic intervention (although little evidence in this area exists in general), but long-term cost savings are entirely credible based on the delay of levodopa therapy and of the motor symptoms that require more intensive therapeutic interventions.

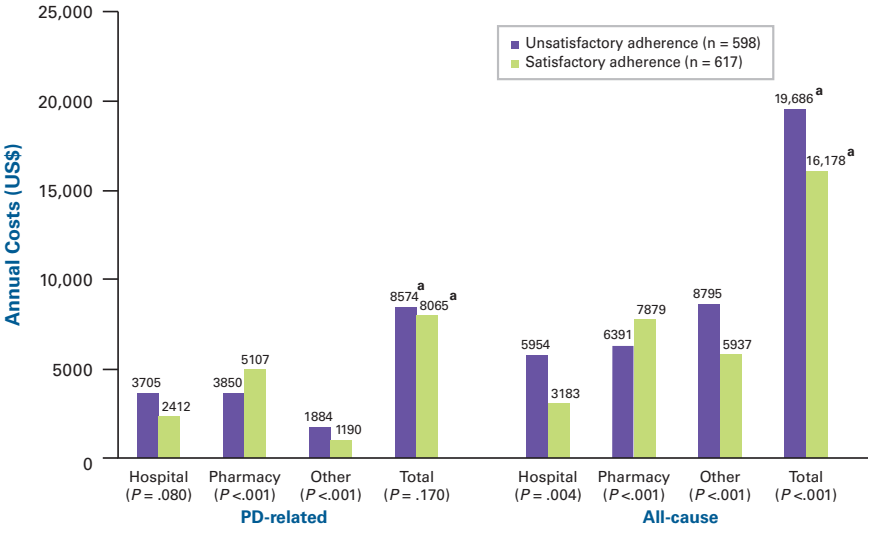
Treatment Adherence and Maximizing Therapeutic Efficacy

Poor treatment adherence is a significant challenge to optimizing outcomes in PD, and any therapeutic strategy must take into consideration those factors impacting treatment adherence. Davis et al, employing insurance claims data from 30 managed care plans (using the Integrated Health Care Information Services Database), estimated that 61% of PD patients were nonadherent to therapy over a 12-month period.[27] Davis et al further estimated that mean medical costs were significantly higher among nonadherent versus adherent subjects ($15,826 vs $9228; $P < .01$) despite the former having significantly lower prescription drug costs ($2684 vs $3854; $P < .05$). These data are consistent with results from a study published in 2011 showing that patients who were satisfactorily adherent (ie, ≥80% medication possession ratio [MPR]) to levodopa/

carbidopa/entacapone therapy had 39% fewer PD-related hospitalizations, 9% greater PD-related prescriptions, 47% lower inpatient costs, and 18% lower total costs than patients with unsatisfactory adherence (ie, MPR <80%) (Figure 2).[28] These results offer strong incentive for employing effective therapeutic interventions that are conducive to patient adherence.

Fargel et al surveyed 500 patients with PD and 592 neurologists who treated patients with PD, in order to determine the causes of poor adherence.[29] The authors found that while physicians described themselves as being satisfied with the "pill load" of prescribed medications for their patients, the PD patients themselves were largely dissatisfied and wished for simpler drug regimens. In fact, a reduction in daily tablet intake was the most common request for treatment improvement in response to an open-ended question. Moreover, patient respondents expressed an interest in additional delivery systems, most of all transdermal patches, to facilitate the ease of delivery of their PD treatment, a view concurred with by neurologists.

Figure 2. Adjusted Mean Healthcare Costs Over 12-Month Period in Patients With Satisfactory Versus Unsatisfactory Adherence to Levodopa/Carbidopa/Entacapone Therapy[28]



PD indicates Parkinson's disease.
[a]The sums of the constituent costs do not add up to the totals owing to the constituent costs being modeled separately by source, and then in aggregate.
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These results are consistent with a recently published study comparing patient preference for pramipexole in once-daily versus 3-times-daily formulations in patients with either early or advanced PD, which found an overwhelming preference (94.4%) for the once-daily formulation.[30] In a recent study from Spain, in which 39 PD patients took part, the investigators observed: a) a strong correlation between treatment adherence to levodopa and the total number of daily drugs (as opposed to pills) prescribed, b) poorer adherence associated with higher levodopa doses, and c) higher rates of adherence in patients who were treated first with a dopamine agonist versus those first treated with levodopa.[31] A transdermal patch of the dopamine agonist rotigotine, which has shown safety and efficacy in early PD—and non-inferiority to pramipexole—was recently approved for PD treatment by the FDA, and offers a therapy that is likely to be associated with higher rates of adherence compared with oral therapies.[32-34]

Opportunities for Managed Care

Early treatment of PD has demonstrated benefits in terms of decreasing symptoms, delaying disease progression, slowing QoL deterioration, and reducing treatment costs. Significant advances in early PD detection, and an increasing understanding of the means of measuring treatment effects on disease progression, are improving the therapeutic landscape such that earlier intervention in PD is becoming more viable than was previously the case. Early intervention, particularly prior to the emergence of substantial motor symptoms, may have benefits in terms of the potential for outcome modification, improved patient QoL, and reduction in medical costs. It is, therefore, important that managed care organizations (MCOs) recognize the changes taking place in the detection and treatment of PD, and take advantage of opportunities for the earliest possible intervention in PD before major neurological damage occurs and treatment may become less effective and more expensive.

MCOs also have the opportunity to improve treatment efficacy and patient outcomes by offering access to treatments and treatment strategies, such as more convenient drug formulations, that maximize therapeutic adherence. Additionally, it is important to bear in mind the complexity of PD; it is a chronic disease with a spectrum of manifestations that appear and change as the disease progresses. Consequently, treatment efficacy and patient well-being are improved when a disease management approach to PD is implemented and specialists (eg, neurologists) are part of the management team when appropriate. By employing a disease-management strategy, clinicians with expertise in PD can provide informed guidance with regard to the selec-

tion of treatments that are likely to be most effective and to which patients are most likely to be adherent.

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