Redefining Efficacy in Parkinson's Disease—Early Motor Phase Treatments and the Potential for Treating during the Pre-motor Phase

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Abstract

Until recently, Parkinson's disease (PD) treatments have overwhelmingly focused on motor rather than non-motor symptoms. Early and accurate detection of PD is considered desirable, with major research initiatives presently focused upon identifying and validating clinical batteries and biomarkers to this end. This raises the question of how the patient deemed at high risk of developing PD should be counseled and treated. Currently there are no approved treatments for pre-motor PD, and thus any pre-motor complaints are treated for specific symptom relief, such as for sleep or mood disorders. For individuals known to be at risk, for example non-manifesting gene carriers, there is likewise a lack of consensus on management, and no proven means of risk reduction. Here we examine options for early PD treatment and clinical evidence for disease modification that might favor 'pushing back' treatment to the pre-motor stage.

Keywords

Parkinson's disease, neuroprotection, disease modification, selegiline, rasagiline, pre-motor phase

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Parkinson's disease (PD) is diagnosed on the basis of characteristic motor signs following clinical examination, and treatment has been overwhelmingly focused upon motor rather than non-motor symptoms until recently. Early and accurate detection of PD is considered desirable, with major research initiatives presently focused upon identifying and validating clinical batteries and biomarkers to this end. However, with increased appreciation of the occurrence of non-motor symptoms, and development of sophisticated biomarker methodology, it now seems possible to address risk assessment and diagnosis earlier in the course of the disease. The term 'Parkinson's associated risk syndrome' (PARS) has been coined to describe individuals at risk of developing PD,[1] and it is proposed that non-motor symptoms—for example, olfactory dysfunction, autonomic instability, constipation, and rapid eye movement (REM) sleep behavior disorder (RBD), in addition to neuroimaging or other biomarkers—might identify individuals in a 'pre-motor' phase of PD.[2,3]

Advances in understanding the course of PD raise the question of how the patient with pre-motor signs should be counseled and treated. Currently there are no approved treatments for pre-motor PD, and thus any pre-motor complaints are treated for specific symptom relief only; for example, RBD is treated by medications such as clonazepam rather than by addressing the possible underlying pathology. However, there is presently a growing number of clinical trials studying early PD, specifically assessing agents predicted to provide disease-modifying benefits.[4] Here we consider the medications approved for use in early motor PD, and examine clinical evidence for disease-modifying properties that might favor 'pushing back' their use to the pre-motor stage. We describe new approaches to disease modification, and their potential applicability to the pre-motor stage. We also consider the potential impact of existing and potential treatments on long-term outcomes, and the challenges in measuring their effectiveness.

Effects of Antiparkinsonian Drugs in Early Parkinson's Disease

Medications approved for use in early motor PD are almost exclusively aimed at motor symptoms and are summarized in *Table 1*. Their pharmacology and use in the clinical realm are well reviewed elsewhere,[5] and the American Academy of Neurology has published guidelines on the treatment of motor symptoms in early PD.[6] A major unmet need, however, is to slow the progression of PD. If such an intervention could be employed during early motor PD, it might provide long-term benefit

Table 1: Medications Currently Used in the US in Early Motor Parkinson's Disease

Antiparkinsonian Medication	Major Mechanism of Action	Clinical Effects
Dopamine agonists • Bromocriptine[52] • Pramipexole[19,21,53] • Ropinirole[22,54]	Direct binding to dopamine receptors	• Improve motor function, ADL, quality of life • Decrease incidence of motor complications[55,56]
Levodopa • Carbidopa/levodopa • Carbidopa/levodopa extended release	Dopamine precursor	• Improve motor function, ADL, quality of life • Risk of motor complications[18]
Monoamine oxidase-B inhibitors • Rasagiline • Selegiline	Inhibit dopamine breakdown, other non-dopaminergic activities[12,57]	• Improve motor and non-motor symptoms, possibly cognition and freezing[8,10,11,13,15,17,42] • Rasagiline demonstrates benefits of early start at 1 mg daily dose, and may alleviate fatigue[17,42] • Selegiline has possible long-term benefits[8,10,11]
Amantadine	NMDA receptor antagonist, other activities	• Improves motor symptoms • Efficacy in reducing dyskinesias[58]
Benztropine, orphenadrine, trihexyphenidyl	Anticholinergic activity	• Reduce tremor[58]

ADL = activities of daily living.

and possibly delay or prevent later complications, such as freezing phenomena or cognitive decline. Moreover, if employed prior to the early motor stage, it might be possible to delay or even prevent the onset of motor symptoms. A number of clinical trials have now been completed that have evaluated the potential for approved antiparkinsonian drugs not only to provide symptomatic relief, but also to potentially modify the disease course.

Selective Monoamine Oxidase-B Inhibitors

Selegiline

As long ago as 1985, a large, uncontrolled nine-year study that simply examined the effect of adding the monoamine oxidase-B (MAO-B) inhibitor selegiline to levodopa for PD therapy showed not only amelioration of disability, but increased life expectancy in the selegiline-treated cohort.[7] Following this, the deprenyl and α-tocopherol antioxidative therapy of Parkinsonism (DATATOP) study was the first major clinical trial to attempt to ascertain whether selegiline might slow PD progression. Potential effects of α-tocopherol, a potent antioxidant, were simultaneously examined. Eight hundred subjects with early PD were randomized to four treatment arms: selegiline/placebo; placebo/α-tocopherol; placebo/placebo; and selegiline/α-tocopherol. Selegiline, but not α-tocopherol, delayed the need for levodopa by approximately 11 months, initially raising hopes of a neuroprotective effect.[8] However, there was a clear, previously unappreciated, symptomatic benefit from selegiline apparent at one- and three-month time points. Moreover, during a washout phase, superior Unified Parkinson's Disease Rating Scale (UPDRS)[9] scores in the selegiline arm declined after two months. This symptomatic benefit meant it was not possible to attribute selegiline benefits to disease modification, as the benefit in delaying levodopa therapy could have been due to symptomatic effects.

Further studies, however, have reopened the question of whether selegiline could slow disease progression. Subjects who met the endpoint in DATATOP were allowed to enroll in an open-label extension, the BLIND-DATE study,[10] in which they received selegiline for a further 18 months and were then re-randomized to treatment with selegiline or placebo. Here, the selegiline group had a significantly lower rate of development of freezing of gait (16 % versus 29 %; $p<0.0003$), a significant cause of falls in advanced PD and often refractory to treatment. Additionally, a multi-step trial of selegiline in 157 individuals newly diagnosed with PD found that the rate of progression of disability, measured by UPDRS scores, was significantly slower in the selegiline cohort, and a statistically significant difference in UPDRS scores was maintained after an extended washout period.[11] These data have therefore lent support to further studies of MAO-B inhibitors.

Rasagiline

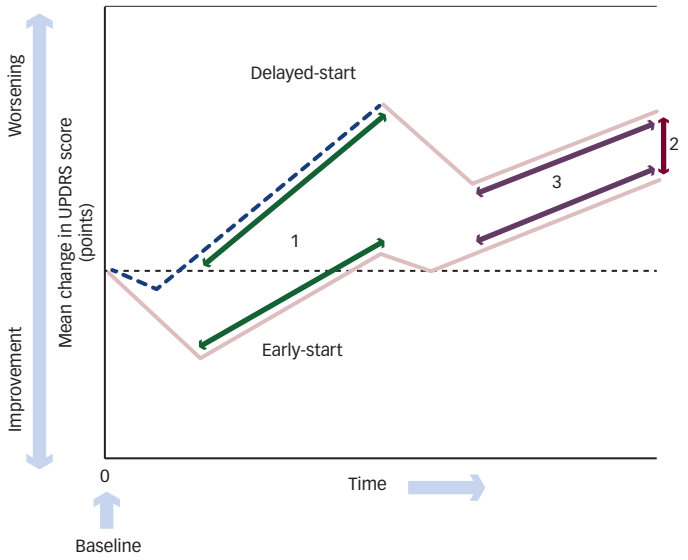
Rasagiline, like selegiline, is an irreversible and specific MAO-B inhibitor used in early and advanced PD for symptomatic benefit. Neuroprotective effects are well documented in multiple cell culture and animal models of PD.[12] The Rasagiline mesylate (TVP-1012) in early monotherapy for Parkinson's disease outpatients (TEMPO) trial enrolled 404 subjects with early, untreated PD, who were randomized to placebo, rasagiline 1 mg daily, or rasagiline 2 mg daily. At six months, both doses of rasagiline demonstrated benefit in total UPDRS scores over placebo (-4.20 points for 1 mg rasagiline versus placebo; -3.56 points for 2 mg rasagiline versus placebo).[13]

Although initiated primarily to examine symptomatic efficacy, at the end of this first six-month phase the TEMPO study became the first of two delayed-start design clinical trials implemented to specifically distinguish between symptomatic and disease-modifying effects,[14] illustrated and summarized in *Figure 1*. Those taking rasagiline continued at their assigned doses, and those taking placebo were now reassigned to rasagiline 2 mg daily.[15] At the end of the second phase, i.e. after 12 months, total UPDRS score had increased (worsened) by 3.01 ± 8.26 points for the early-start 1 mg group, by 1.97 ± 7.49 points for the early-start 2 mg group, and by 4.17 ± 8.83 points for the delayed-start 2 mg group, indicating a significant advantage for early-start versus delayed-start, and providing a basis for further testing. Moreover, benefits in the early-start group appeared to be sustained. In an open-label extension of the TEMPO study, 306 subjects were followed for up to 6.5 years total, with additional antiparkinsonian medications

allowed.[16] Change in total UPDRS score from TEMPO baseline to last observation continued to demonstrate a difference in favor of early- versus delayed-start (2.5 ± 1.1 points, p=0.021). Although only 117 of the baseline 404 subjects completed this open-label phase study, the maintenance of benefit in the early-start group again supports possible disease modification.

The Attenuation of disease progression with azilect given once daily (ADAGIO) study was designed to test disease modification in a second, larger, delayed-start design trial of 1,176 patients with early, untreated PD (time since diagnosis: 4.5 ± 4.6 months).[17] For the first nine-month phase, subjects were assigned to rasagiline 1 mg or 2 mg daily or placebo. For the second nine-month phase, subjects either continued on their assigned doses of active drug, or those in the placebo arm were now assigned to rasagiline 1 or 2 mg daily. Rasagiline 1 mg daily early-start met all three of the study's hierarchical primary endpoints, when compared with rasagiline 1 mg delayed-start: (1) slower rate of change of UPDRS score versus placebo in the first phase (0.09 ± 0.02 versus 0.14 ± 0.01 points/week; p=0.01); (2) superiority of early- versus delayed-start rasagiline UPDRS score at 18 months (2.82 ± 0.53 versus 4.52 ± 0.56 points; p=0.02); and (3) identical rates of progression of UPDRS scores in the second phase. The authors concluded that, for the 1 mg daily dose of rasagiline, the benefit of early versus delayed treatment in this early motor PD cohort may have been due to disease modification. However, results for the rasagiline 2 mg early- versus delayed-start groups have complicated this interpretation. Rasagiline 2 mg daily failed to meet the second endpoint in that it did not meet statistical significance for sustained superiority over placebo at 18 months. A *post hoc* subgroup analysis demonstrated that subjects with baseline UPDRS scores in the upper quartile, i.e. those with more severe PD, in the 2 mg group met all three endpoints, pointing to the possibility that current measures may not be sensitive enough to determine changes in subjects with very mild symptoms. This still remains to be resolved.

Figure 1: Schematic Representation of the Three Hierarchical Endpoints in a Delayed-start Clinical Trial of Rasagiline



Study endpoints are: (1) difference in rate of change from baseline (slope) between early-start treatment versus placebo in the first period of the study (green arrows); (2) difference in Unified Parkinson's Disease Rating Scale (UPDRS) scores at the end of the trial period (red arrow); (3) difference in rate of change from baseline (slope) between early-start versus late-start treatment in the second period of the study (purple arrows). Placebo arm = dashed blue lines; rasagiline arms = pink lines. In this trial design, participants are randomized in the first phase to placebo or rasagiline, and in the second phase all participants are assigned to rasagiline. Slope analysis in the first placebo-controlled phase allows the comparison of rate of symptom progression, with a shallower slope indicative of slower change in symptoms and therefore supporting disease modification. In the second phase, with all participants receiving active intervention, similar rates of progression of disease symptoms are now expected. The net effect is that any difference in ratings at the end of the clinical trial will reflect the effects of early versus later start of rasagiline. Adapted with permission from Olanow et al., 2009.[17]

Dopamine Replacement—Levodopa

The early versus later levodopa in Parkinson's lisease (ELLDOPA) study examined efficacy over a range of doses and additionally employed a drug washout design to determine the potential effect of levodopa upon PD progression in early disease.[18] Subjects were randomized to receive placebo, 150 , 300 , or 600 mg levodopa daily over 40 weeks, at which point levodopa had a clearly superior symptomatic benefit compared with placebo, although a significant number developed motor complications even in this short trial period. A two-week drug washout period followed, at which point any symptomatic benefit was predicted to have disappeared due to the short half-life of levodopa. At the end of the washout period, despite the predicted lack of symptomatic effect, a significant difference in UPDRS scores persisted between placebo and those who received the highest daily dose of levodopa, consistent with disease modification. However, a substudy of single photon emission computed tomography (SPECT) imaging of 116 subjects found that mean percentage decline in [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-tropane ([^{123}I]β-CIT) uptake was less with placebo than with levodopa. Additionally, levodopa may have a longer-term effect on Parkinsonian symptoms than anticipated and a two-week washout period may not be long enough. Currently, use of levodopa in early PD has to be weighed against the development of motor complications, and its use is therefore delayed in many patients.

Dopamine Agonists

The dopamine agonists bromocriptine, pergolide (no longer used), ropinirole, pramipexole, and rotigotine (unavailable in the US at the time of writing) have all demonstrated efficacy in treating motor symptoms and activities of daily living (ADL) in PD (see *Table 1*). An apparent advantage for the management of motor symptoms of PD is that these medications lead to fewer motor complications than levodopa. For example, in a study comparing pramipexole to levodopa treatment,[19] those assigned to initial pramipexole experienced significantly less wearing off and fewer dyskinesias or on-off motor fluctuations (28 %), compared with those assigned to initial levodopa (51 %).

Two clinical trials in early motor PD, using ropinirole and pramipexole, have examined the effects of treatment upon neuroimaging measures of PD progression. Pramipexole has neuroprotective properties in preclinical studies.[20] The Comparison of the agonist pramipexole versus levodopa on motor complications of Parkinson's disease (CALM-PD) trial[19,21] enrolled 301 patients with early PD requiring dopaminergic therapy, who were randomized to treatment with pramipexole or carbidopa/levodopa. A subgroup underwent [^{123}I]β-CIT SPECT scans to assess dopamine transporter density, with a smaller decline in striatal [^{123}I]β-CIT uptake in

those receiving pramipexole compared with carbidopa/levodopa (16 versus 25.5 % at 46 months, p=0.01). Using a similar approach, the REAL-PET study examined changes in [18F]-dopa positron emission tomography (PET) in subjects with early PD taking either levodopa or ropinirole, as part of a two-year, randomized, double-blind trial. The reduction in putamenal [18F]-dopa uptake in those randomized to ropinirole (plus supplemental levodopa) was smaller at two years compared with those receiving carbidopa/levodopa (13 versus 20 %; p=0.022).[22] While further studies are needed to determine precisely how to interpret neuroimaging results, the delay in developing motor complications favors the use of dopamine agonists over levodopa in early motor PD, unless adverse effects rule otherwise. However, with the lack of a placebo group in either the CALM-PD or REAL-PET trials, it is unclear whether dopamine agonists might have benefit for PD progression, and therefore whether they would be helpful in the pre-motor phase. In an attempt to answer this question, the Pramipexole on underlying disease (PROUD) study evaluated pramipexole for a potential disease-modifying effect using a delayed-start study design.[23] Unfortunately, results did not support a disease-modifying benefit of a 1.5 mg dose of pramipexole,[24] and use of these drugs in early motor PD therefore remains based upon symptomatic motor benefits.

Agents that Modulate Glutamate Activity

Amantadine is used for therapeutic benefit in early and advanced motor PD and its use has been associated in one study with improved 10-year survival rates.[25] This is interesting, since a modified form of acute excitotoxic injury, 'weak excitotoxicity', involving calcium influx via NMDA receptor channels, has been proposed as a potential mechanism of cell injury and cell loss in PD.[26] This suggests that agents directly acting at the NMDA receptor, such as amantadine, or, alternatively, interventions that indirectly modulate glutamate activity, might slow disease progression. At this time, however, there are no clinical data to support the use of anti-excitotoxic agents for the purpose of neuroprotection in PD. Amantadine has not been evaluated specifically for disease progression effects, and nor has the related glutamatergic agent memantine. A two-year placebo-controlled, double-blind, multi-center trial of riluzole, approved for use in amyotrophic lateral sclerosis, in 1,084 PD subjects was terminated early after meeting predefined criteria for futility.[27] Attention is now turning to other glutamate receptors, notably the AMPA receptor, and the metabotropic glutamate receptors (mGluRs), with promise for both symptomatic and disease-modifying effects in preclinical studies.[28]

New Developments in Parkinson's Disease Therapeutics

New targets are being addressed in drug development including α2-adrenergic receptors, adenosine A2a receptors, and agents with multiple modes of action including safinamide, which is a reversible MAO-B inhibitor, reduces dopamine re-uptake, and has antiglutamatergic effects,[29] and piribedil, a partial dopamine receptor D2/D3 agonist and α2-adrenergic receptor antagonist.[30] As yet, there are no clinical data supporting their potential use as disease-modifying drugs.

Ongoing Clinical Trials Examining Disease Modification

A novel, orally active, small molecule, PYM50028 (Cogane), is currently being tested in a Phase II trial in early motor PD (CONFIDENT-PD: NCT01060878). This agent has both neuroprotective and neurorestorative iproperties in preclinical studies and, in one study in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned mice, led to an increase in striatal glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) (297 % and 511 %, respectively).[31] Isradipine, a dihydropyridine L-type calcium channel blocker shown to confer protection in animal models of PD, is being tested for safety, tolerability, and efficacy in a Phase II clinical trial, Safety, tolerability and efficacy assessment of dynacirc CR for Parkinson's disease (STEADY-PD: NCT00909545).[32] Similarly, a Phase II clinical trial of inosine, Safety of urate elevation in Parkinson's disease (SURE-PD, NCT00833690, Parkinson Study Group) is under way to examine the safety and tolerability of increasing urate levels, associated in multiple studies with decreased risk of PD and slower decline.[33,34] Creatine, a nutritional supplement that plays an important role in mitochondrial energy production, was found to be non-futile in a double-blind, futility clinical trial of creatine and minocycline in early PD.[35] It is now being investigated in the NET-PD LS-1 study, in which 1,720 participants will be randomly assigned to receive either creatine or a placebo for a minimum of five years (NCT00449865). Coenzyme Q10 (CoQ) is an antioxidant and an electron acceptor in the mitochondrial electron transport chain that showed possible slowing of disease progression at high doses in a small placebo-controlled Phase II clinical trial.[36] A 16-month Phase III clinical study (NCT00740714) was implemented to compare the effect of two dosages of CoQ (1,200 and 2,400 mg/day) with placebo on total UPDRS score in early motor PD.

Finally, there are intensive efforts in testing surgical approaches to neuroprotection and slowing (or reversing) disease progression, including infusion of neurotrophic factors, in particular GDNF, and gene therapy. A recent landmark sham-surgery controlled six-month study of glutamic acid decarboxylase (GAD) gene delivery to the subthalamic nucleus in advanced PD patients, using the adeno-associated virus 2 vector (AAV2), demonstrated greater improvement in UPDRS scores between baseline and end of the study in the group receiving gene therapy intervention compared with the sham-surgery control group.[37] It is too early to determine how these interventions may be applied to early motor PD, and especially pre-motor PD; such approaches are beyond the scope of this article and have been discussed elsewhere.[38,39]

How Can Measures of Efficacy be Refined in Parkinson's Disease?

With improved understanding of the clinical features and progression of PD, it is important to understand how best to test the efficacy of a given intervention. Discussion in the preceding sections has focused upon the UPDRS score[9] comprising subscales of 1) mental dysfunction and mood, 2) motor disability, 3) motor impairment, and 4) treatment-related motor and non-motor complications. Data from recent pre-specified and *post hoc* analyses of the ADAGIO clinical trial have shed light on UPDRS performance characteristics in early PD. The investigators demonstrated slower progression, as measured by UPDRS scores, in those with milder baseline disease, and, importantly, the ADL subscale was deemed to be more sensitive to change than the motor scale. This merits further attention, and supports the notion that 'patient-oriented' ratings may prove superior in evaluating early PD, and that quality-of-life measures, such as the Parkinson's Disease Questionnaire,[40] are critical in evaluating the broader impact of an intervention upon study subjects. However, a

revised scale, the Movement Disorder Society UPDRS (MDS-UPDRS),[41] may be more sensitive to changes in very mild signs and symptoms, and an expanded UPDRS Part I, now titled Non-motor aspects of experiences of daily living (nM-EDL), increases the ability to capture non-motor symptoms. The MDS-UPDRS was used in the ADAGIO trial of rasagiline, and rasagiline demonstrated benefit in nM-EDL scores compared with placebo, suggesting that the use of the MDS-UPDRS score does indeed add valuable information related to drug efficacy in domains not previously emphasized.[42] Other rating scales are employed for better evaluation of non-motor features that may occur in PD at various stages; for example, the benefit of rasagiline versus placebo for relief of fatigue was specifically addressed in the ADAGIO trial.[42] The Quality Standards Subcommittee of the American Academy of Neurology published a systematic review on screening tools for psychosis, dementia, and depression in PD,[43] and certain studies have now specifically evaluated antiparkinsonian drug effects on non-motor symptoms. For example, the Randomized evaluation of the 24-hour coverage: efficacy of rotigotine (RECOVER) trial used the UPDRS score and the modified Parkinson's Disease Sleep Scale (PDSS-2) to evaluate co-primary endpoints of the effects of rotigotine, a transdermal dopamine agonist, on motor function and sleep.[44] Another randomized, double-blind, placebo-controlled trial examining the effects of pramipexole used the Beck Depression Inventory as primary endpoint to demonstrate benefits on depression in PD.[45]

What change in a rating scale makes a meaningful difference for the patient? One study suggested that a mean UPDRS motor score change of at least five points or a mean percentage change of at least 20 % were applicable thresholds of a minimal clinically relevant difference in early PD.[46] However, this is not designed to address benefits seen in disease modification trials (for example, trials of creatine or rasagiline) as it is simply unknown at present how measures taken in a relatively brief period of an individual's disease duration will manifest over the longer term. If individuals with pre-motor PD can be identified, what measures would be useful in testing possible disease-modifying agents? The most obvious would be measuring the time taken to develop clinically defined PD, but that may be difficult to define accurately and the time taken to attain the endpoint might be too long to be practical in a clinical trial. A current focus, therefore, is upon developing surrogate markers of PD progression. The Parkinson's progression markers initiative (PPMI: NCT01141023) aims to identify markers of disease progression in early motor PD using an array of neuroimaging, plasma, and cerebrospinal fluid analyses.

Conclusions

The recognition of a pre-motor phase, and possibly earlier stages of PD raises the critical question of how this might change the approach to PD management in the future, and what impact it may have on patients' lives. Can anything be learned from studies in early motor PD that point to possible strategies? Effective treatment in pre-motor PD will require disease-modifying medications, likely targeting mechanisms of neurodegeneration. Currently there are no drugs clinically proven to possess such properties, and few of the orally available drugs in development will address this urgent clinical need. The TEMPO and ADAGIO trials of rasagiline, however, have provided some hope that earlier treatment with this drug may provide long-term benefit. Longer-term follow-up of ADAGIO trial participants will add to our understanding of the impact of earlier intervention. Moreover, ongoing clinical trials of PYM50028 (Cogane), isradipine, creatine, inosine, and other agents are supported by encouraging preclinical data on their neuroprotective effects. Thus far, efforts to translate promising neuroprotectants in the laboratory into disease-modifying drugs in the clinic have been frustrating, but new clinical trial designs and improved understanding of PD pathogenesis now seem to provide new hope.

As agents become available that have disease-modifying effects in diagnosed PD, is it reasonable to 'move earlier': to employ them in the pre-motor phase or in even earlier stages of PD? A major, and as yet unanswered, question is how to ascertain the health-related advantages of such an approach, given that at present there is not even a validated marker of disease progression in motor PD. Drug interventions in early stages will increase initial healthcare costs, and, with the incidence of PD increasing worldwide, the impact of early treatment strategies will need to be analyzed in economic terms.[47] The advantage of delaying therapy could be to reduce initial costs, but might there be a missed opportunity to improve prognosis, and thereby decrease health-related, social, and economic burdens?

Finally, there are valuable lessons to be learned from extensive experience in other disorders, such as vascular disease, in which lifestyle is shown to play an important role. There is increasing evidence that diet may modify PD risk. For example, in the Health professionals follow-up study and the Nurses' health study, individuals who followed a so-called 'prudent' dietary pattern, with high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry, low intake of saturated fat, and moderate intake of alcohol, were at less risk of developing PD.[48] In the National Institutes of Health–American Association of retired persons (NIH-AARP) diet and health study cohort, higher levels of moderate to vigorous exercise were associated with a lower risk of developing PD.[49] Other modifiable factors, such as hypertension in women, have been linked to PD risk.[50] Environmental risks are also a potential target for modification, as pesticide exposure has now been linked to PD risk in multiple studies.[51] These studies, as well as research efforts to identify neuroprotective agents, underscore the possibility of a shift in thinking from symptomatic treatment to disease modification and eventually prevention. ■

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