Monoamine Oxidase Type B Inhibitors in the Treatment of Early Parkinson's Disease

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Abstract

Therapy in Parkinson's disease (PD) needs to be individualized since patients differ in symptom expression and responsiveness to pharmacotherapy. Disease-modifying drugs should be considered early in the course of the disease, but none is currently US Food and Drug Administration (FDA)-approved for this indication. Symptomatic therapies should be optimized to keep the patient independent and functioning for as long as possible. Early therapies in PD consist of dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, and, in some patients, carbidopa–levodopa (depending on age and symptom severity). MAO-B inhibitors are approved by the FDA for monotherapy in treatment of early PD and as an adjunct to levodopa in advanced disease. This article focuses on the role of MAO-B enzymes in PD pathogenesis and reviews clinical evidence for the use of MAO-B inhibitors in the treatment of early PD.

Keywords

Parkinson's disease, monoamine oxidase type B (MAO-B) inhibitors, rasagiline, selegiline, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study, Rasagiline Mesylate (TVP-1012) in Early Monotherapy for PD Outpatients (TEMPO) study, Effect of Rasagiline Mesylate in Early PD patients (ADAGIO) study, dopamine agonists, carbidopa–levodopa

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Parkinson's disease (PD) is a progressive neurodegenerative disorder. It has been classically described as a movement disorder involving the striato-nigral pathway characterized by resting tremor, bradykinesia, rigidity, and postural instability. It is now considered a multisystem disorder that includes motor and non-motor symptoms.[1] The early form of the disease can have predominantly non-motor symptoms, which are non-specific and can be overlooked for years until the cardinal motor symptoms emerge. The non-motor symptoms can be sensory, cognitive/psychiatric, or autonomic. The non-motor features by themselves can be a considerable cause of disability for many patients.

Options for Initiation of Treatment in Parkinson's Disease

There are several US Food and Drug Administration (FDA)-approved options for monotherapy in PD. Treatment of early disease can be initiated with amantadine, anticholinergic agents, monoamine oxidase type B (MAO-B) inhibitors, dopamine agonists or carbidopa–levodopa (CD/LD). Levodopa initially provides stable relief for the symptoms of PD; however, 50–90% of patients develop motor complications (such as motor fluctuations and dyskinesias) after five to 10 years of CD/LD therapy.[2,3] Delaying the initiation of levodopa may be appropriate to defer these problems. Dopamine agonists are useful in initial monotherapy for controlling motor symptoms with less risk of developing motor complications. Studies suggest that the mechanism by which agonists delay complications is by permitting a delay in the starting of levodopa rather than by any direct disease-modifying effect.[4] Dopamine agonists are associated with a number of side effects such as hallucinations, impulse-control disorders, excessive daytime sleepiness, vomiting, and orthostatic hypotension.[5,6] Amantadine has been shown to be somewhat helpful with rigidity and akinesia initially,[7] but these effects are not long-lasting and livedo reticularis, edema, confusion, and hallucinations are common side effects. Anticholinergics can be used in younger patients with predominant tremor,[8] but their use is limited by peripheral cholinergic side effects, confusion, memory impairment, and possible withdrawal effects.

Monoamine Oxidase Type B Inhibition and Parkinson's Disease

Dopaminergic neurons decline steadily in PD, with motor symptoms emerging when about 50% of nigral neurons have degenerated.[9] At

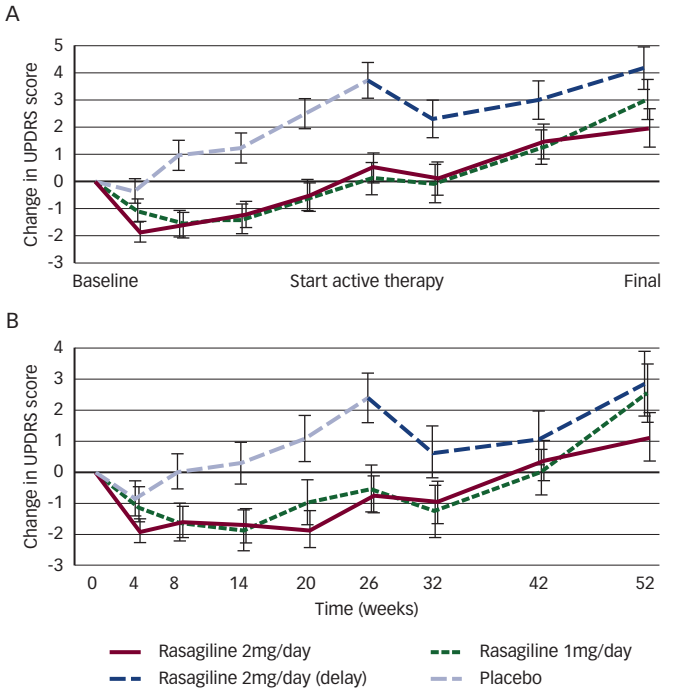
disease presentation, there is a 70–80% loss of striatal dopamine concentration.[10] MAO-B levels increase with age, with *post mortem* brain samples showing increases of 41.5 and 30.4% in the putamen and globus pallidus lateralis, respectively, between 60 and 90 years of age.[11] In positron-emission tomography studies of healthy living subjects, the increase in MAO-B levels in the basal ganglia is estimated to be 8% every 10 years from 23 to 86 years of age;[12] in normal aging, the average increase in MAO-B levels in all brain regions is 7.1% (±1.3%) every 10 years.[12] MAO-B inhibitors increase dopamine availability by inhibiting the breakdown of dopamine by MAO-B.[13] MAO-B inhibitors can be used in the treatment of early PD; their mechanism of action (i.e. preserving endogenous and exogenous dopamine) is unique compared with other antiparkinsonian medications.[14] The propargyl ring in its molecular structure may be important for reasons unrelated to MAO-B inhibition. Propargylamines appear to bind to glyceraldehyde-phosphate dehydrogenase (GAPDH), blocking apoptosis in certain pre-clinical models of PD, and also induce synthesis of neurotrophic factors.[15,16] The two MAO-B inhibitors used are selegiline (selegiline hydrochloride [L-deprenyl], a levorotatory acetylenic derivative of phenethylamine[17]) and rasagiline. Rasagiline is a secondary cyclic benzylamine and a derivative of indane, and like selegiline has a propargyl group but no amphetamine metabolites.[13,14,18–20] MAO-B inhibitors are well tolerated with minimal side effects when used before patients have started taking levodopa, although there is a theoretical risk for hypertensive reactions at doses significantly higher than the FDA-approved doses.

Clinical Trials of Monoamine Oxidase Type B Inhibitors in Early Parkinson's Disease

DATATOP Study

The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study was designed to assess the effects of treatment with selegiline and/or tocopherol on the onset of disability requiring levodopa in patients with early untreated PD.[21–23] The study involved 800 patients. The primary end-point was the onset of disability prompting the clinical decision to begin administering levodopa. There were four treatment arms: placebo, active tocopherol and deprenyl (selegiline) placebo, active selegiline and tocopherol placebo, or both active drugs. The patients were followed for a mean of 14±6 months. Selegiline 10mg/day significantly delayed the primary end-point by about nine months, which indicates either a symptomatic or disease-modifying effect; it is impossible to differentiate these possibilities because of concerns that the one-month wash-out period was insufficient to allow complete elimination of the symptomatic effect of selegiline. Open-label extensions with selegiline 10mg/day for up to 18 months were conducted in both patients who reached and did not reach the end-points.[24,25] These clinical studies showed that prior treatment with selegiline did not lead to superior survival with respect to the end-point of disability requiring levodopa, and it did not reduce the occurrence of subsequent levodopa-associated adverse effects in this population. On the other hand, a long-term naturalistic study suggests that levodopa-treated PD patients who had previously been treated with selegiline compared with placebo for up to seven years experienced slower motor decline and were less likely to develop freezing of gait but more likely to develop dyskinesias.[26] These findings are also consistent with either a symptomatic or disease-modifying effect as the study was not designed to differentiate between these possibilities. The 2002 American Academy of Neurology (AAN) practice parameter concluded that there was no convincing evidence to suggest a neuroprotective effect of selegiline.[27]

Figure 1: Mean Change in the Unified Parkinson Disease Rating Scale Score for Each Group in TEMPO

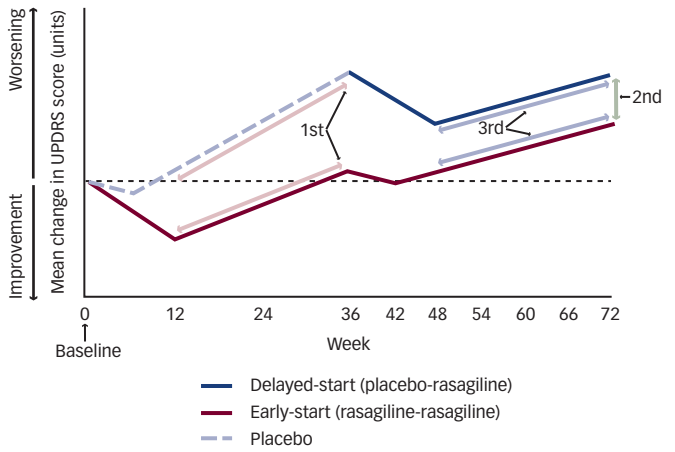


A: Total unadjusted Unified Parkinson Disease Rating Scale (UPDRS) score by visit for each treatment group for the 371 subjects included in the efficacy cohort. For the efficacy cohort, the last observation was carried forward for subjects with missing values for a given visit. B: Unadjusted UPDRS score by visit for each treatment group for the 249 subjects who completed 52 weeks of treatment without starting additional therapy. Figures are mean ± standard error (SE); error bars indicate ± SE. Source: Parkinson Study Group, 2004, adapted with permission.[29]

TEMPO Study

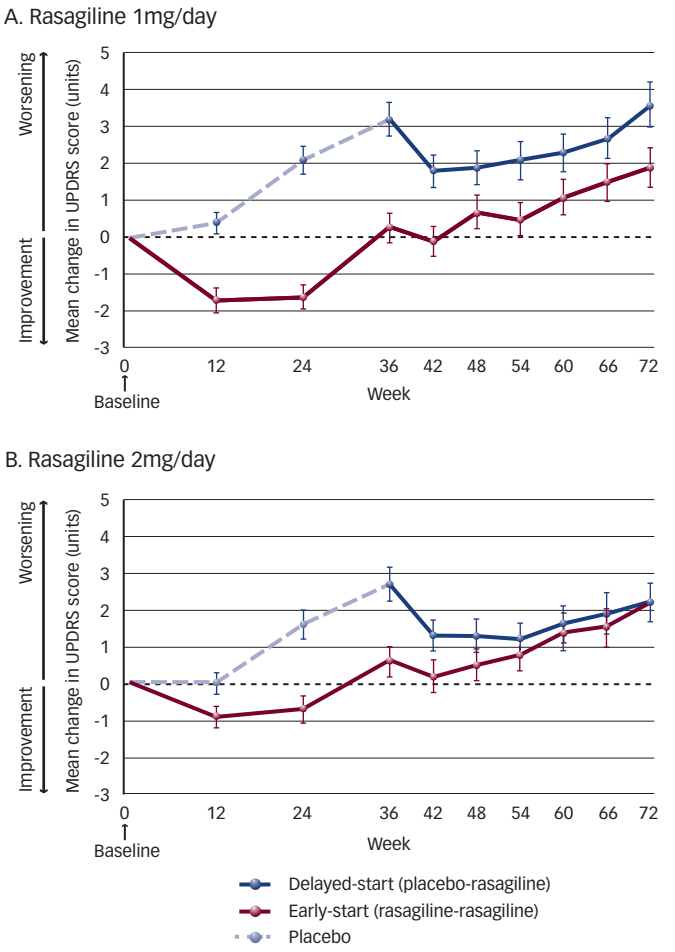
The Rasagiline Mesylate (TVP-1012) in Early Monotherapy for PD Outpatients (TEMPO) study was a one-year study originally designed in two parts: a six-month safety and efficacy study and a 12-month delayed start design study to assess a disease-modifying effect for rasagiline.[28,29] Patients were randomized to treatment with either a placebo, 1mg rasagiline or 2mg rasagiline and were followed for 26 weeks. The primary end-point was the change in total Unified Parkinson Disease Rating Scale (UPDRS) score between baseline and 26 weeks of treatment (see *Figure 1*). The difference in this parameter comparing rasagiline 1 and 2mg versus placebo was -4.20 units ($p<0.001$) and -3.56 units ($p<0.001$), respectively, indicating less symptomatic worsening in both rasagiline groups compared with placebo over six months. The delayed-start study involved switching the placebo group to 2mg rasagiline at the end of 26 weeks, and all groups were followed for the next six months. At the end of one year, the change in the mean adjusted total UPDRS score was -2.3 units ($p=0.01$) comparing rasagiline 2mg with the delayed rasagiline 2mg group, and -1.82 units ($p=0.05$) comparing the rasagiline 1mg group with the delayed rasagiline 2mg group. This showed that the benefits associated with early rasagiline treatment could not be achieved with the later introduction of the same drug.[29] An extension of this study was conducted to compare long-term clinical progression of the disease as assessed by total UPDRS

Figure 2: Schematic Illustration of the Three Primary End-points of ADAGIO



UPDRS = Unified Parkinson Disease Rating Scale.
Source: Olanow et al.; ADAGIO Study Investigators, 2009, adapted with permission.[31]

Figure 3: Change in Unified Parkinson's Disease Rating Scale Score in the Four Study Groups in ADAGIO



UPDRS = Unified Parkinson Disease Rating Scale.
Source: Olanow et al.; ADAGIO Study Investigators, 2009, adapted with permission.[31]

score in the early-start versus delayed-start groups.[30] Initially, all patients were placed on 2mg/day. However, once the initial TEMPO results showed that there was no difference in efficacy between 1 and 2mg/day, the dose given was decreased to 1mg/day. Three hundred and six subjects (85% of the 360 subjects who completed the double-blind portion of the trial) chose to participate in the open-label extension study. The average (± standard deviation [SD]) duration in the study was 3.6±2.1 years while 177 subjects received rasagiline for over five years. For the intent-to-treat analysis including all 306 subjects entering the extension study, the mean difference in change from baseline in total UPDRS score between early- and delayed-start subjects was 2.5 units (p=0.021), corresponding to a mean relative difference of 16% (p=0.006), indicating that the early-start group had less symptomatic worsening. Similarly, for subjects who continued in the study up to database lock (n=177), the adjusted mean difference in change in total UPDRS score was 2.4 units, corresponding to a mean relative difference of 17% (p=0.002) in favor of the early-start rasagiline group. Significantly less worsening (percent change) in total UPDRS score was observed in the early-start group at 0.5, 1.5, 2.0, 3.0, 4.5, 5.0, and 5.5 years ($p<0.05$).[27] This suggests that the clinical benefits noted in the initial study persisted through the years even as patients were being treated with other antiparkinsonian medications.

ADAGIO Study

Recently, rasagiline has been tested in a large, prospective, multicenter trial using a delayed-start design—the Effect of Rasagiline Mesylate in Early PD patients (ADAGIO) study—to further assess its potential effects on disease progression.[31] Both the 1 and 2mg/day doses were tested using a double-blind, placebo-controlled, delayed-start study design. The primary end-point included three hierarchal analyses that had to be met in order to declare the study positive (see *Figure 2*). The first end-point compared the slope of symptom progression in active drug versus placebo groups in the first nine months of the study. An assumption of the study planners was that by 12 weeks the full symptomatic effect of rasagiline would be established. A disease-modifying agent would be expected to have a shallower slope compared with placebo. The second end-point was the difference in UPDRS score at the end of 72 weeks. To demonstrate disease modification, any benefit in the form of slower progression present in the early-start group in phase 1 had to persist until the end of the study. The third end-point evaluated the slope in the second nine months, when all patients were on active drug. A disease-modifying drug should show no difference in slope in this phase since both groups would be receiving any such disease-modifying benefit. Rasagiline 1mg/day met all three primary end-points, consistent with the possibility that the drug has a disease-modifying effect (see *Figure 3*). However, rasagiline 2mg/day failed to meet the second end-point, and some have suggested that this may be due to the very early stage of patients enrolled; in this population, the symptomatic effect of the 2mg dose might have masked any disease-modifying effect. In an effort to explore this possibility, a *post hoc* analysis was performed in all subjects. Considering end-point two (change in total UPDRS score from baseline to end of study) for the 1mg dose, the difference between early and delayed start was -1.68±0.75 UPDRS units in the whole cohort, while for the quartile with the highest baseline UPDRS score it was -3.40±1.66. For 2mg, the change was 0.36±0.68 in the whole cohort and -3.63±1.72 in the highest quartile.[32] Both doses met all three hierarchical end-points when tested in subjects whose baseline UPDRS scores fell into the highest quartile. That these results for the highest quartile analysis were statistically significant is remarkable since the number of patients included in this analysis was much smaller than that in

the prospectively identified cohorts, which accordingly reduced the statistical power of the analysis to find a difference (see *Figure 3*).

Discussion

Given the current limitations in technology and the lack of a validated biomarker, neuroprotection has not and cannot be demonstrated in patients with PD. This is true because we cannot directly observe and quantify the number of viable dopaminergic neurons in the living human brain. The DATATOP trial showed beneficial effects for selegiline, but short- and long-term open-label extensions produced inconclusive results and failed to establish the mechanism of clinical benefit (symptomatic or disease-modifying, or both). The TEMPO trial showed positive results in favor of the early-start group for both 1 and 2mg rasagiline, but it has been suggested that early administration of any symptomatic drug may in part prevent the loss of compensatory mechanisms, which once lost cannot be restored. The recent presentation of the results of the Assessment of Potential Impact of Pramipexole On Underlying Disease (PROUD) study shed some light on this question.[33] This was a delayed-start trial involving 535 patients that evaluated pramipexole 1.5mg/day as a possible disease-modifying agent. The initial placebo-controlled phase was six months, followed by active drug treatment in all subjects for the balance of 15 months. The primary end-point was change in UPDRS score from baseline to the end of the study, and the group difference in adjusted means was -0.4 UPDRS units (95% confidence interval [CI] -2.2–1.4; p=0.65). These results suggest either that pramipexole did not have a disease-modifying effect, or that such an effect was masked by the high level of symptomatic effect of this agent.

The long-term open-label extension that followed the TEMPO trial is of interest, but there are concerns with this study design, including the possibility of rating bias after the blind was broken and the fact that the long-term extension assessed only the 1mg strength. Additionally, there were high drop-out rates in the extension: by 1.5 years approximately 20% of the original 404 subjects were lost, and by three years this had jumped to 37%, with 59% lost by 5.5 years. Finally, interpretation of the results is made more difficult by the fact that most patients were taking other symptomatic drugs for PD. Although the early-start group was receiving numerically more levodopa dose equivalents (except at year six), no significant statistical difference was seen in levodopa dose equivalents between the early- and later-start groups. The ADAGIO trial surprised many by providing a positive result only for the 1mg dose. The difference between the early- and delayed-start groups in the 1mg arm was 1.7 UPDRS units (which some have suggested is not clinically significant), but this represents a 38% reduction in the rate of decline, and reflects the impact of only nine months of differential treatment. While statistically significant, long-term studies assessing cumulative disability would be needed to address the question of whether this difference proves clinically significant in the long run. *Post hoc* analysis of the quartile with the highest baseline UPDRS scores showed positive results for both the 1 and 2mg strengths, while it was negative for both doses when considering the lower three quartiles. This analysis supported the argument that a greater effect of the 2mg dose on symptoms might have masked a disease-modifying benefit associated with early-start treatment in patients with very mild disease. Nevertheless, interpretation of *post hoc* analyses is difficult due to the greater risk for bias.

While these studies do not establish a neuroprotective effect of rasagiline in humans, the results of TEMPO and ADAGIO demonstrate that earlier initiation of rasagiline 1mg results in less symptomatic worsening of UPDRS scores over a 12–18 month period compared with later initiation of the same drug. As such, early use of rasagiline may enable physicians to delay initiation of more potent agents in Parkinson's disease. As monotherapy MAO-B inhibitors have mild symptomatic effects on motor symptoms and generally do not require dose titration. They have minimal side effects and few deleterious drug interactions. Rasagiline may be preferred to oral selegiline by some physicians and patients as it can be given once daily compared with twice daily for selegiline and because it has no amphetamine metabolites. Other options for initial monotherapy for PD include levodopa and dopamine agonists. Levodopa is the most effective dopaminergic drug, and if symptoms are severe at presentation, if a rapid response is required, or if the patient is elderly with cognitive deficits, this agent is preferred. Disadvantages of levodopa initiation include the risk for motor fluctuations and dyskinesias, the latter being sometimes severe when used in younger patients. Dopamine agonists often exert a robust symptomatic effect and when used as initial monotherapy have been shown to delay motor fluctuations and dyskinesias. The disadvantages of this class include side effects of hallucinations, impulse-control disorders, excessive daytime sleepiness, nausea and vomiting, and orthostatic hypotension. Based on the best available evidence, MAO-B inhibitors produce a symptomatic effect without inducing motor complications and, in the case of rasagiline, may offer the potential for disease modification. We believe that patients with early PD whose symptoms are mild enough that they do not require levodopa or a dopamine agonist should be offered a trial of rasagiline treatment unless contraindicated by concomitant drugs. ■

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Richard B Dewey, Jr, MD, is a Professor of Neurology and Director of the Clinical Center for Movement Disorders at the University of Texas Southwestern Medical Center. His primary research interests are in therapeutics of Parkinson's disease, and he is now involved in a study aimed at finding a drug that will halt or slow the progression of this disorder. He is a Fellow of the American Academy of Neurology (AAN) and a member of the American Neurological Association (ANA). Professor Dewey trained in neurology and movement disorders at the Mayo Clinic in Rochester, and received his MD from Baylor College of Medicine in Houston.

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