Combined Rasagiline and Antidepressant Use in Parkinson Disease in the ADAGIO Study
Effects on Nonmotor Symptoms and Tolerability

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**IMPORTANCE** Depression, cognitive impairment, and other nonmotor symptoms (NMSs) are common early in Parkinson disease (PD) and may be in part due to disease-related dopamine deficiency. Many patients with PD are treated with antidepressants for NMSs, and the effect of the combination of PD medications that enhance dopamine neurotransmission and antidepressants on NMSs has not been studied. We report the effects of the addition of a monoamine oxidase B inhibitor, rasagiline, to antidepressant treatment in PD.

**OBJECTIVE** To evaluate the effect of rasagiline on depression, cognition, and other PD NMSs in patients taking an antidepressant in the Attenuation of Disease Progression With Azilect Given Once Daily (ADAGIO) study.

**DESIGN, SETTING, AND PARTICIPANTS** The ADAGIO study was a double-blind, placebo-controlled, delayed-start trial of rasagiline in de novo PD. In this exploratory post hoc analysis, we analyzed patients taking an antidepressant during the 36-week phase 1 period, in which patients were randomized to rasagiline (1 or 2 mg/d) or placebo.

**MAIN OUTCOMES AND MEASURES** We evaluated the change in NMSs in patients taking an antidepressant and rasagiline compared with those taking placebo. The NMSs were assessed by Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale Nonmotor Experiences of Daily Living, the original Unified Parkinson's Disease Rating Scale, and the Parkinson Fatigue Scale.

**RESULTS** A total of 191 of the 1174 patients (16.3%) were treated with antidepressants during phase 1 and provided efficacy data. Depression and cognition scores revealed significantly less worsening in the rasagiline group compared with the placebo group (differences in Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale item-adjusted means [SEs], −0.19 [0.10], P = .048, and −0.20 [0.05], P < .001, respectively). Parkinson Fatigue Scale (mean [SE] difference, −0.42 [0.09], P < .001) and daytime sleepiness (mean [SE] difference, −0.24 [0.09], P = .006) scores also revealed significantly less worsening in the rasagiline group compared with placebo. There was a nonsignificant trend toward less worsening in apathy and no significant between-group differences in anxiety or sleep. The effect on depression remained significant after controlling for improvement in motor symptoms (mean [SE] difference, −0.23 [0.09], P = .009). There were no serious adverse events in the combined rasagiline-antidepressant group suggestive of serotonin syndrome.

**CONCLUSIONS AND RELEVANCE** The combination of rasagiline and antidepressants in patients with de novo PD is associated with reduced worsening of a range of NMSs in preliminary analyses. Adverse effects appear uncommon with this combination. These findings suggest a role for dopamine-enhancing therapies in NMSs in early PD and encourage further study and confirmation.

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Depression is an important nonmotor symptom (NMS) in Parkinson disease (PD), with approximately 35% of patients having clinically significant depressive symptoms and a higher prevalence of major depression in patients with PD compared with age-matched controls. Patients with PD and depression have a higher co-occurrence of cognitive impairment, worse motor outcomes, and poorer quality of life.

Antidepressant use is common in patients with PD, with one study reporting that 23% of patients with mild PD were taking an antidepressant and 78% had received an antidepressant since their PD diagnosis. Antidepressants were efficacious for PD depression in the largest controlled trial to date, but a meta-analysis reported mixed results.

Monoamine oxidase B (MAO-B) inhibitors are used to treat the motor symptoms of PD but also have been used in the treatment of depression. In the general population, selegiline hydrochloride is effective in treating depression at higher doses that are nonselective for MAO-B, including in refractory geriatric depression.

Depression in PD may be partially related to dopamine deficiency in limbic system pathways, and enhancement of dopaminergic neurotransmission via a selective MAO-B inhibitor could therefore improve depression in PD. There is evidence that frontostriatal dopaminergic deficiency underlies cognitive impairment in early PD, and apathy also appears to be mediated by dopaminergic deficiency and improves with dopamine replacement therapy.

Concerns exist about the safety of combining an MAO-B inhibitor with antidepressants, particularly selective serotonin reuptake inhibitors, because of the risk of potentially fatal serotonin syndrome. However, the frequency of this adverse event has not been evaluated in a controlled clinical trial.

Antidepressant augmentation strategies are common in treating depression in general. We hypothesized that enhancing the dopamine system would improve depression and other NMSs in patients with PD already taking an antidepressant. We evaluated the effects of combined rasagiline and antidepressant use on a range of NMSs in patients with early de novo PD. In addition, we report on the tolerability and safety of this combination.

Methods

Study Design
Written consent was obtained from all participants. The study was approved by participating sites’ institutional review boards for human research. The Attenuation of Disease Progression With Azilect Given Once Daily (ADAGIO) study was a 72-week, double-blind, placebo-controlled, multicenter trial in patients with untreated early PD that used a delayed-start design. There were 2 phases of 36 weeks each. Phase 1, the focus of this article, assigned patients to receive rasagiline (1 or 2 mg/d) or corresponding placebo. No concomitant antiparkinsonian medication was permitted.

Participants
Patients 30 to 80 years of age with idiopathic PD were enrolled. Patients with major psychiatric illness, including major depression based on the impression of site investigators, were excluded. At baseline the following antidepressants (daily dose) were allowed: amitriptyline, 50 mg or less; trazodone hydrochloride, 100 mg or less; citalopram hydrobromide, 20 mg or less; sertraline hydrochloride, 100 mg or less; paroxetine hydrochloride, 30 mg or less; and escitalopram oxalate, 10 mg or less. There was no restriction in tyramine dietary intake. Patients were included in the ADAGIO study antidepressant subpopulation if they were taking an antidepressant at any time during phase 1. One patient of the 192 randomized and taking an antidepressant at some point did not provide postbaseline efficacy data, so the efficacy population presented here includes 191 patients, all of whom were assessed at week 36 or at an early termination visit.

Assessments
Both the original Unified Parkinson’s Disease Rating Scale (UPDRS) movement disorders sponsored revision of the UPDRS were used. Both versions have cognition and depression rater-scored items in the Nonmotor Experiences of Daily Living (nmEDL). The MDS-UPDRS nmEDL at baseline and week 36 or early termination was used to assess severity of depressed mood, cognitive impairment, apathy, anxious mood, sleep problems, and daytime sleepiness (scores of 0-4 for each item, with higher scores indicating greater impairment). The Parkinson Fatigue Scale (PFS) was used to assess fatigue. Adverse events were recorded at each visit.

Statistical Analysis
To increase sensitivity, rasagiline-treated patients were first analyzed as a pooled group; if there was a significant difference between the pooled rasagiline and placebo groups for a given measure, then the 2 dose groups were analyzed separately. The change from baseline to week 36 or early termination in the original UPDRS and MDS-UPDRS item scores for depression, cognition, apathy, fatigue, anxiety, and sleep was calculated. The last observation carried forward was applied for patients who terminated the study early for the MDS-UPDRS because it was measured at baseline and week 36 or termination only. The adjusted mean changes from baseline were estimated using an analysis of covariance model, adjusting for baseline score of the analyzed outcome and site. For the original UPDRS motor and depression scores, a mixed model for repeated measure was applied, adjusting for the respective baseline scores and site. The differences of the adjusted means were calculated comparing the rasagiline and placebo groups. P < .05 was considered significant. Effect sizes for depression and cognition were calculated using the Cohen conventions. To assess the association between changes in motor symptoms and NMSs, Pearson correlation coefficients were calculated for changes over time in depression, cognition, apathy, sleep, and motor scores. We then also controlled for change in UPDRS motor score in the analysis of covariance model comparing the effect of rasagiline and placebo on depression.
Comparison of Study Participants by Antidepressant Treatment Status

In phase 1 of the study, 191 of the 1174 patients (16.3%) were treated with an antidepressant at baseline (144 patients [12.3%]) or after baseline (47 patients [4.0%]) and provided postbaseline efficacy data. These patients likely had clinically significant depression, as evidenced by their significantly higher baseline MDS-UPDRS depression item scores compared with patients not treated with an antidepressant (Table 1). The baseline MDS-UPDRS cognition item score was also higher (ie, worse) in patients taking an antidepressant (mean [SE] between-group difference, 0.15 [0.04] points; \( P < .001 \)). There were no significant group differences in age, sex, baseline UPDRS motor score, or Hoehn and Yahr stage. Patients taking an antidepressant had significantly worse UPDRS activities of daily living scores.

Of antidepressant-treated patients in the phase 1 period, 93 were randomized to rasagiline (1 or 2 mg/d) and 98 to placebo, and 137 (71.4%) completed phase 1 of the study (Figure). Twenty-nine patients (29.6%) in the placebo group and 18 (19.4%) in the pooled rasagiline group were not taking antidepressants at baseline but were prescribed an antidepressant during phase 1 (\( P = .10 \)). Baseline variables were similar for participants taking an antidepressant at baseline and those who began during the study (eTable 1 in the Supplement).

Characteristics of Antidepressant-Treated Participants by Randomization Status

There were no significant differences in baseline variables for antidepressant-treated patients randomized to rasagiline vs placebo (Table 2) or for those randomized to 1 or 2 mg/d (eTable 2 in the Supplement). The antidepressant classes taken by participants were as follows: serotonin reuptake inhibitors, 76.0%; tricyclic antidepressants, 21.4%;
Outcomes for NMSs

Depression
Both the UPDRS and MDS-UPDRS depression item scores worsened between baseline and 36 weeks but significantly less so in the pooled rasagiline group compared with the placebo group. The mean (SE) combined rasagiline-placebo difference was −0.24 (0.11) points (P = .03) for the UPDRS and −0.19 (0.10) points (P = .048) for the MDS-UPDRS depression items (Table 3). There was evidence of a dose-response effect (eTable 4 in the Supplement). The difference between rasagiline and placebo on the MDS-UPDRS depression item score represented a small to medium effect size (Cohen d = 0.36) (eTable 5 in the Supplement).

Cognition
The MDS-UPDRS cognition item revealed significantly less worsening in the pooled rasagiline group compared with placebo. The mean (SE) combined rasagiline-placebo difference was −0.20 (0.05) points (P = .001) (Table 3 and by dose differences in eTable 4 in the Supplement). The difference in the pooled rasagiline group compared with placebo suggested a moderate to large treatment effect on cognition (Cohen d = 0.68) (eTable 5 in the Supplement).

Apathy
The pooled rasagiline group revealed a nonsignificant trend toward reduced worsening in apathy compared with placebo, with a mean (SE) treatment difference of −0.17 (0.09) points (P = .07) (by dose differences in eTable 4 in the Supplement). This likely represents a clinically significant improvement based on the PFS validation study.17

Sleep and Wakefulness
On the daytime sleepiness item, there was significantly less worsening in the pooled rasagiline group, with a mean (SE) difference of −0.24 (0.09) points (P = .006). For the MDS-UPDRS sleep problems item, there was no significant difference between treatment groups (mean [SE] difference, 0.10 [0.09]; P = .30). There was a low but statistically significant correlation between changes in depression and sleep items over time (Table 6 in the Supplement).

Table 3. Changes in Nonmotor Symptoms Over Time in the Pooled Rasagiline and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Change at Week 36a</th>
<th>Mean (SE)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>0.57 (0.07)</td>
<td>0.76 (0.07)</td>
<td>−0.19 (0.10)</td>
<td>−0.38 to −0.002</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.76 (0.07)</td>
<td>0.87 (0.07)</td>
<td>−0.12 (0.10)</td>
<td>−0.31 to 0.08</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.48 (0.07)</td>
<td>0.65 (0.06)</td>
<td>−0.17 (0.09)</td>
<td>−0.35 to 0.02</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.31 (0.04)</td>
<td>0.50 (0.03)</td>
<td>−0.20 (0.05)</td>
<td>−0.30 to −0.10</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>0.43 (0.07)</td>
<td>0.68 (0.06)</td>
<td>−0.24 (0.09)</td>
<td>−0.42 to −0.07</td>
</tr>
<tr>
<td>PFS score</td>
<td>2.41 (0.06)</td>
<td>2.83 (0.06)</td>
<td>−0.42 (0.09)</td>
<td>−0.59 to −0.24</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.75 (0.07)</td>
<td>0.65 (0.06)</td>
<td>0.10 (0.09)</td>
<td>−0.09 to 0.28</td>
</tr>
</tbody>
</table>

Abbreviation: PFS, Parkinson Fatigue Scale.

a Adjusted for baseline score and center.

b All items except the PFS score were Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale Nonmotor Experiences of Daily Living items.
Anxiety
There was no significant difference between treatment groups in the change in the MDS-UPDRS anxiety item (mean [SE] difference, −0.12 [0.10]; \( P = .23 \)).

Association Between Motor and Depression Outcomes
At week 36 there was a significant improvement in the UPDRS motor score in the pooled rasagiline group compared with the placebo group (mean [SE] difference, −2.22 [0.80]; \( P = .006 \)), consistent with the motor treatment effect observed in the entire cohort. To determine whether the rasagiline effect on NMSs was explained simply by its effect on motor symptoms, we determined the association between change in motor symptoms and NMSs in rasagiline-treated patients. No significant correlation was found between the changes in depression (Pearson \( r = 0.16 \), \( P = .12 \)) or cognition (Pearson \( r = 0.03 \), \( P = .80 \)) scores and the change in the UPDRS motor score over time (eTable 7 in the Supplement). In addition, when controlling for change in the UPDRS motor score over time, the UPDRS depression score at baseline, and site, rasagiline-treated patients had an even greater reduction in worsening of depression symptoms over time compared with the placebo group (eTable 8 in the Supplement). This finding indicates that the effect on depression scores with rasagiline was independent of motor improvement.

Tolerability
During phase 1 there was no difference in the number of serious adverse events in the pooled rasagiline group (n = 7) compared with the placebo group (n = 9). There was no clear pattern of any adverse events that were more common and not previously described in the rasagiline groups compared with the placebo group (eTable 9 in the Supplement). There were no serious or nonserious adverse events that could be interpreted as possible serotonin syndrome (Table 4 and eTable 9 in the Supplement).

Discussion
In this post hoc exploratory analysis of the ADAGIO study, participants taking an antidepressant in combination with rasagiline had less worsening of depression, cognition, fatigue, and daytime sleepiness compared with placebo, suggesting a positive effect for rasagiline on NMSs. The aim of the ADAGIO study was to examine a possible disease-modifying effect of rasagiline using a delayed-start design. The large cohort of participants (>1000 participants) had recently diagnosed conditions and were untreated. The placebo-controlled phase 1 period revealed that rasagiline was safe and well tolerated and exerted a symptomatic motor benefit. Primary end points were met for the 1-mg/d but not the 2-mg/d rasagiline group; thus, no clear conclusions could be drawn about a disease-modifying effect.\(^1\)

In this post hoc analysis of those ADAGIO study participants taking an antidepressant during the phase 1 period, we confirmed that rasagiline was safe and well tolerated and improved PD motor symptoms similarly to the overall group. On the basis of the combined patient-rater assessment (MDS-UPDRS) and the PFS, NMSs worsened overall between baseline and 36 weeks but less so in the rasagiline group compared with the placebo group, suggesting a possible treatment effect for rasagiline on NMSs in general. Also similar to the primary ADAGIO study, a consistent dose-response effect was not noted on the NMSs.

Table 4. Frequency of Serious Adverse Events for Antidepressant-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 99)</td>
</tr>
<tr>
<td>All</td>
<td>9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
</tr>
<tr>
<td>Oral paraesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1</td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td>0</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Benign laryngeal neoplasm</td>
<td>0</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Facial hypoesthesia</td>
<td>2</td>
</tr>
<tr>
<td>Knee operation</td>
<td>1</td>
</tr>
</tbody>
</table>
Because rasagiline inhibits metabolism of dopamine and increases synaptic availability, the effects we observed may be due to enhanced dopaminergic neurotransmission. Dopaminergic neurotransmission is affected in non-PD depression, and antidepressants act in part by increasing nucleus accumbens dopamine receptor sensitivity. Dopamine enhancement therapies, including the MAO-B inhibitor selegiline and the D_{2/3} agonist pramipexole, are effective in treating major depressive disorder in the general population. Striatal and extrastriatal dopaminergic pathways have been implicated in the pathogenesis of depression and other NMSs in PD. Our results are consistent with previous work reporting that dopaminergic medications can improve depression and other NMSs in PD. Levodopa may improve depression in PD, although the literature is limited and focused on patients with motor fluctuations. Pramipexole improved depressive symptoms in patients with PD in a placebo-controlled study. Examination of MAO-B inhibitors for the treatment of depression in PD is limited. In the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study, selegiline improved depression compared with placebo on secondary analysis. Rasagiline improved depressive symptoms in patients with de novo PD in a small masked study. Because MAO-B inhibitors also affect other monoamines (eg, phenethylamine), further research is needed to determine the relative roles of dopamine vs other neurotransmitters and their projections in the antidepressant effect of this medication class.

Cognitive impairment is common even in early PD, and executive dysfunction is frequently predominant. Executive dysfunction may involve parallel dopaminergic pathways that connect the cortex and basal ganglia because levodopa can help normalize these deficits. Rasagiline may improve attention and verbal fluency in patients with PD and mild cognitive impairment. In addition, catechol-O-methyltransferase polymorphisms that increase dopamine levels in the prefrontal cortex correlate with better executive abilities, and neuroimaging studies have reported a correlation between nigrocaudate dopamine impairment and executive dysfunction and future cognitive decline. Our results therefore add to the literature that suggests that dopamine-enhancing therapies may improve cognitive symptoms in PD and warrant further study.

We also found that rasagiline in combination with antidepressant treatment reduced worsening of fatigue and daytime sleepiness scores. Sleepiness has been correlated with striatal dopamine loss in early PD, but further research is needed to determine the role of dopamine in PD fatigue.

A significant concern when combining MAO-B inhibitors and antidepressants with serotonergic properties is serotonin syndrome, an acute medical-neurologic condition that can be life-threatening. Previous literature is limited to uncontrolled data and focuses on selegiline rather than rasagiline. Richard et al reported an incidence of 0.04% of possible serotonin syndrome in this population. The package insert for rasagiline reports postmarketing nonfatal cases of serotonin syndrome in patients coprescribed antidepressants. We report on the tolerability and safety of the combination of rasagiline and antidepressants for the first time, to our knowledge, in a controlled trial, and our analysis of serious adverse events did not reveal any events suggestive of serotonin syndrome in almost 100 participants treated for 9 months with this combination. Additional controlled studies with larger sample sizes and longer durations are needed to provide more conclusive data about this risk, and health care professionals should remain vigilant regarding this potential complication.

Selectively analyzing ADAGIO study participants taking antidepressants, who had more NMSs at baseline than those not taking antidepressants, likely increased our ability to detect significant improvement in numerous NMSs in those randomized to receive rasagiline vs placebo. A post hoc analysis that included all ADAGIO study participants found that the total MDS-UPDRS nmEDL scores improved modestly but significantly in the 1-mg/d rasagiline group compared with the placebo group but not in the 2-mg/d rasagiline group. Similarly, the lack of a consistent dosage effect for 1 vs 2 mg/d for NMSs in our study remains a limiting factor in interpretation. In our analysis, this may possibly be due to the relatively small sample size in each active treatment subgroup. There were significant correlations between depression and other NMSs (eg, apathy and sleep), which could explain some of the effects across symptoms that we observed. Future studies would benefit from larger sample size and more detailed instruments to disentangle the “neuropsychiatric” effect that we report here.

Our analysis was additionally limited by several factors. The first limitation was the post hoc (not prespecified) exploratory nature. Second, we were limited to the use of the MDS-UPDRS rather than validated individual NMS assessment instruments for the assessment of NMSs, except for fatigue, for which a dedicated instrument was used. The MDS-UPDRS nmEDL correlates with other validated assessments of NMSs over time, such as the Parkinson’s Disease Questionnaire 39 and the Geriatric Depression Scale, and one benefit of using the MDS-UPDRS nmEDL is its clinical relevance because it is used on routine clinic visits to gauge NMSs. Future studies are needed to determine whether the MDS-UPDRS nmEDL is sensitive to possible nonmotor effects for other PD medication classes. Third, the exclusion of patients with major or severe depression limits the generalizability of our findings, as does the de novo population. However, an advantage of the de novo population is that the confounding effects of concomitant PD medication and fluctuations were excluded.

As outlined above, other dopaminergic therapies may improve NMSs, due to specific antidepressant or more global effects, and it is not clear to what extent the results reported here, if confirmed, are specific to rasagiline. Further research is also required to elucidate the mechanism of action of MAO-B inhibitors and antidepressants on PD NMSs because there is emerging evidence that these compounds may have neuromodulatory or neuroprotective effects in addition to their symptomatic effects.
Conclusions

Rasagline was well tolerated in patients with de novo PD who were taking antidepressants, and this combination reduced worsening of a range of NMSs. These preliminary findings suggest that augmentation with dopamine-enhancing therapies may have a role in the treatment of early PD NMSs, at least in those patients already taking an antidepressant. Given the limitations of the analyses, these findings require confirmation. Additional prospective, controlled studies are warranted to further evaluate the specific nonmotor effects of rasagline, including larger sample sizes and use of standardized NMS scales, before this strategy can be recommended for clinical practice.

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