

Use of the Unified Parkinson's Disease Rating Scale Activities of Daily Living Subscale to Assess Response to Rasagiline in Early Parkinson's Disease

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Abstract

Various assessment scales are used to measure the severity and rate of progression of Parkinson's disease (PD)—for example, the Unified Parkinson's Disease Rating Scale (UPDRS) and its Activities of Daily Living (ADL) subscale. The relative merits of these scales for accurately determining the degree of disease progression have recently come under scrutiny. Analyses of data from the recent Attenuation of disease progression with Azilect given once daily (ADAGIO) trial demonstrated that patients receiving early-start rasagiline (Azilect®, Teva Neuroscience, North Wales, PA) 1 mg/day experienced slower disease progression, as assessed by their mean total UPDRS score, than patients receiving placebo followed by delayed-start rasagiline treatment. Subsequent secondary analyses showed that 1 and 2 mg/day doses of early-start rasagiline delayed the need for antiparkinsonian drugs and improved other parameters, including ADL scores and fatigue, when compared with placebo followed by delayed-start rasagiline. Furthermore, the analyses highlighted that, over time, the motor and mentation sections of the UPDRS-ADL subscale increasingly reflect the response to treatment of the early- and delayed-start rasagiline 1 mg/day patient groups. The results from the ADAGIO trial suggest that rasagiline has potential disease-modifying effects, but more clinical data are required to confirm their effect on PD progression.

Keywords

Early Parkinson's disease, Unified Parkinson's Disease Rating Scale, Activities of Daily Living subscale, rasagiline, ADAGIO trial

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Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, affecting 1–2 % of people aged more than 60 years.¹ It is a complex disorder that affects the motor, cognitive, behavioral, and autonomic systems.² PD can be hard to diagnose early because mild parkinsonian signs are often detected in elderly patients who are not known to have neurological disease.³ Many patients who have parkinsonian signs, such as gait and balance changes, rigidity, bradykinesia, and tremor do not technically fulfill the stringent diagnostic criteria for confirmed PD.^{3–5} These patients have a predisposition to develop PD, but not all will go on to develop clinically manifest PD.⁵

Many of the signs of PD are associated with the age-related decline of dopamine-producing neurons in the *substantia nigra*. It is thought that approximately 50 to 80 % of dopaminergic neurons are lost prior to the emergence of the typical motor signs of PD.⁶ More recent studies have suggested that motor symptoms may emerge when as few as 30 % of dopaminergic neurons in the *substantia nigra* are lost.⁷

Levodopa, in combination with a dopa decarboxylase inhibitor, is well established for the treatment of PD. Long-term use, however, is associated with the development of motor fluctuations and dyskinesias.^{8–12} Furthermore, dopamine replacement often does not alleviate non-motor symptoms, including sleep disturbances, depression, orthostatic hypotension, and dementia.¹³ It is, therefore, important to explore alternative treatment options, including potential disease-modifying drugs.

Assessing the Clinical Severity of Parkinson's Disease

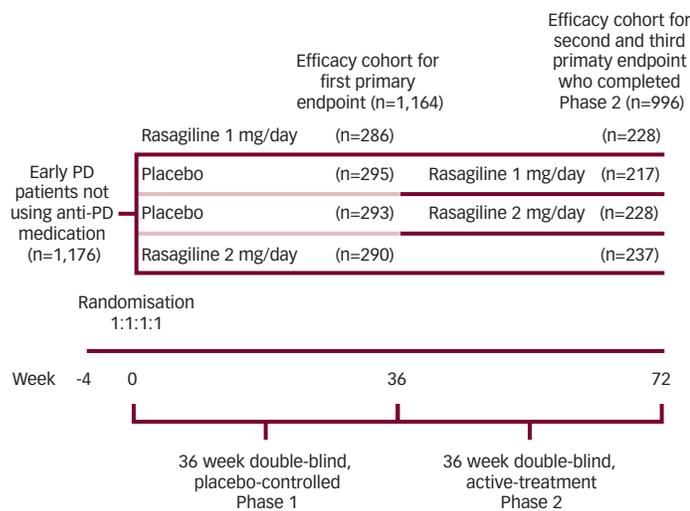
The evaluation of PD requires sensitive and accurate rating scales to assess clinical severity and treatment-related changes.¹⁴ Observer-rated scales have been used to evaluate the clinical severity of PD, including the Hoehn and Yahr scale, the Columbia University Rating Scale, the Webster Scale, the Hamilton Depression Rating Scale, and the mini-mental state examination.^{15–17} A number of limitations and issues arise regarding the use of these scales for the assessment of PD.¹⁸ For example, some

Table 1: Mentation, Behavior, and Mood Parameters in the Unified Parkinson's Disease Rating Scale

	0	1	2	3	4
Intellectual impairment	None	Mild. Consistent forgetfulness with partial recollection of events but no other difficulties	Moderate memory loss, disorientation, and difficulty handling complex problems	Severe memory loss, with disorientation in time and space and impaired handling	Severe memory loss. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone
Thought disorder	None	Vivid dreaming	'Benign' hallucinations with insight retained	Occasional to frequent hallucinations or delusions without insight. Could interfere with daily activities	Persistent hallucinations, delusions, or florid psychosis. Not able to care for oneself
Depression	None	Periods of sadness or guilt greater than normal, but never sustained for days or weeks	Sustained depression (one week or more)	Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest)	Sustained depression with vegetative symptoms and suicidal thoughts or intent
Motivation/initiative	Normal	Less assertive than usual, more passive	Loss of initiative or disinterest in elective (non-routine) activities	Loss of initiative or disinterest in day-to-day (routine activities)	Withdrawn, complete loss of motivation

Source: Movement Disorder Virtual University, 2008.²²

Figure 1: Schematic Diagram of the Attenuation of Disease Progression with Azilect Given Once Daily Trial Design



PD = Parkinson's disease. Source = adapted from Olanow et al., 2008,²⁹ and Olanow et al., 2009.³²

components of these scales depend on subjective rather than objective judgments by the clinician, which may lead to poor inter-rater reliability.^{18,19} Rating scales and questionnaires should offer inter-observer reliability, test-retest consistency, and internal coherence.²⁰ Disability scales often measure more constant variables, and have been found to be a more reliable indicator of disability, than clinical rating scales.^{18,19}

As PD is a multidimensional disorder, disease progression and treatment efficacy should be assessed not only through motor symptoms but also through psychopathological and autonomic symptoms. The Unified Parkinson's Disease Rating Scale (UPDRS) was developed as a brief, valid, and reliable scale for the assessment of activities in PD and has replaced many of the older assessment scales. Furthermore, it includes the patient self-reported Activities of Daily Living (ADL) subscale.^{21,22} The UPDRS is the most commonly used subscale for assessing Parkinsonian motor impairment and disability in clinical trials and within clinical settings.²³ It

has four subsections, derived from pre-existing scales:²²

- subsection I: mentation, behavior, and mood (see Table 1);
- subsection II: Activities of Daily Living (ADL) (see Table 2);
- subsection III: motor (see Table 3); and
- subsection IV: complications.

The UPDRS motor examination parameters are given in Table 3. There are 14 of them: speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility, arising from a chair, posture, gait, postural stability, and body bradykinesia and hypokinesia.

The UPDRS has the advantage of wide use, is applicable across the PD spectrum, and has an almost comprehensive coverage of motor symptoms.²² It has been shown to have good-to-excellent inter-rater reliability for speeded repeated movements, resting tremor, rising from a chair, and gait.²⁴ To improve inter-rater reliability, training materials, including a video, have been developed by the Movement Disorder Society.²⁵ There is a significant correlation between the UPDRS motor subscale and many neuropsychological tests of cognitive domains.²⁶ Moreover, the UPDRS has been subjected to extensive clinimetric analyses, giving it scientific and clinical credibility.²²

Although the widely adopted UPDRS has been reported to have good internal consistency, reliability, and inter-rater reliability,^{21,27} concerns have been raised about reproducibility on a large scale.^{22,28} Specifically, some items in the motor section, including speech and facial expression, have been shown to have a relatively poor inter-rater reliability, while posture, body bradykinesia, action or postural tremor hands, and rigidity have been shown to have moderate inter-rater reliability.^{24,27}

Using the Unified Parkinson's Disease Rating Scale—Activities of Daily Living Subscale to Assess Parkinson's Disease

More recently, it has been shown that the UPDRS-ADL subscale may be more sensitive when assessing disease progression over time

Table 2: Activities of Daily Living Subscale in the Unified Parkinson's Disease Rating Scale

	0	1	2	3	4
Speech	Normal	Mildly affected. No difficulty being understood	Moderately affected. Sometimes asked to repeat statements	Severely affected. Frequently asked to repeat statements	Unintelligible most of the time
Salivation	Normal	Slight but definite excess of saliva in mouth, may have night-time drooling	Moderately excessive saliva, may have minimal drooling	Marked excess of saliva with some drooling	Marked drooling, requires constant tissue or handkerchief
Swallowing	Normal	Rare choking	Occasional choking	Requires soft food	Requires nasogastric tube or gastrostomy feeding
Handwriting	Normal	Slightly slow or small	Moderately slow or small, all words are legible	Severely affected, not all words are legible	The majority of words are not legible
Cutting food and handling utensils	Normal	Somewhat slow, but no help needed	Can cut most foods, although clumsy and slow. May need some help	Food must be cut by someone else, can only feed slowly	Needs to be fed
Dressing	Normal	Somewhat slow, but no help needed	Occasional assistance with buttoning and getting arms into sleeves	Considerable help required, can only do a few things alone	Helpless
Hygiene	Normal	Somewhat slow but no help required	Help required to bath or shower. Very slow in hygienic care	Requires assistance for washing, brushing teeth, combing hair, and going to the bathroom	Foley catheter or other mechanical aids
Turning in bed and adjusting bed clothes	Normal	Somewhat slow and clumsy, but no help required	Can turn alone or adjust sheets, but with great difficulty	Can initiate, but not turn or adjust sheets alone	Helpless
Falling	None	Rare falling	Occasionally falls (less than once a day)	Falls on average once daily	Falls more often than once daily
Freezing when walking	None	Rare freezing when walking, may have start hesitation	Occasional freezing when walking	Frequent freezing when walking. Occasionally falls from freezing	Frequent falls from freezing when walking
Walking	Normal	Mild difficulty. May not swing arms, or may drag a leg	Moderate difficulty, but requires no or little assistance	Severe disturbance of walking, requires assistance	Cannot walk at all, even with assistance
Tremor	Absent	Slight and infrequently present	Moderate, bothersome to patient	Severe, interferes with many activities	Marked, interferes with most activities
Sensory complaints related to parkinsonism	None	Occasionally has numbness, tingling, or mild aching	Frequently has numbness, tingling, or aching. Not distressing	Frequent painful sensations	Excruciating pain

Source: Movement Disorder Virtual University, 2008.⁷²

than the UPDRS motor subscale.²⁹ Furthermore, it has been suggested that the UPDRS-ADL subscale is a better marker of disease progression and non-motor symptoms, less influenced by variability in drug cycle and motor fluctuations than subsections of other tests used in PD. Also, ADL subscales might be more sensitive to subtle functional changes affecting the patient (e.g., in hygiene, dressing, or eating) than motor subscales, which do not necessarily capture these changes.^{30,31} The UPDRS-ADL subscale does not appear to be susceptible to placebo response, whereas a placebo response was observed with the UPDRS motor subscale.³² Indeed, the UPDRS-ADL subscale appears to be insensitive to the transient but objectively demonstrable motor changes that often occur in older subjects with higher motor impairment at baseline. Furthermore, the UPDRS-ADL subscale does not identify placebo-treated patients showing objectively defined improvement.³²

In early PD, in the absence of overt motor symptoms, the analysis of non-motor symptoms is an important approach to detecting disease. There is, however, a lack of information available to help us understand

the relationship between different non-motor symptoms with a view to initiate earlier treatment for PD patients. The UPDRS-ADL subscale assesses motor and non-motor symptoms and, as such, may be more sensitive in detecting early disease, thus aiding diagnosis.

In addition to the UPDRS-ADL subscale, there are various other ADL scales, which are less commonly used in clinical trials, including the Alzheimer's Disease Cooperative Study-ADL scale (which includes 23 parameters), the Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's Disease, the Parkinson's Disease Quality of Life Questionnaire, and the Parkinson's Disease Activities of Daily Living Scale.³³⁻³⁵ ADL questionnaires have also been used to assess pramipexole treatment: they showed that improvements were significantly greater with pramipexole treatment than with placebo, regardless of whether post-L-dopa rescue scores were included or not.³⁶

In this article, the merits of the UPDRS and UPDRS-ADL subscale are discussed in the context of the beneficial effects of rasagiline (Azilect®,

Table 3: Motor Examination Parameters in the Unified Parkinson's Disease Rating Scale

	0	1	2	3	4
Speech	Normal	Slight loss of expression, diction, and/or volume	Monotone, slurred but understandable. Moderately impaired	Marked impairment, difficult to understand	Unintelligible
Facial expression	Normal	Minimal hypomimia, could be normal 'poker face'	Slight but definitely diminution of facial expression	Moderate hypomimia. Lips parted some of the time	Masked or fixed face with severe or complete loss of facial expression. Lips parted 1/4 inch or more
Tremor at rest ¹	Absent	Slight and infrequently present	Mild in amplitude and persistent, or moderate in amplitude but only intermittently present	Moderate in amplitude and present most of the time	Marked in amplitude and present most of the time
Action or postural tremor of hands	Absent	Slight, present with action	Moderate in amplitude, present with action	Moderate in amplitude, present with posture holding as well as action	Marked in amplitude. Interferes with feeding
Rigidity ²	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficulty
Finger taps ³	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements	Severely impaired. Frequent hesitations in initiating movements or arrests in ongoing movements	Can barely perform the task
Hand movements ⁴	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements	Severely impaired. Frequent hesitations in initiating movements or arrests in ongoing movements	Can barely perform the task
Rapid alternating movements of hands ⁵	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements	Severely impaired. Frequent hesitations in initiating movements or arrests in ongoing movements	Can barely perform the task
Leg agility ⁶	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movements	Severely impaired. Frequent hesitations in initiating movements or arrests in ongoing movements	Can barely perform the task
Arising from chair ⁷	Normal	Slow or may need more than one attempt	Pushes oneself up from arms of seat	Tends to fall back and may have to try more than one time, but can get up without help	Unable to arise without help
Posture	Normal erect	Not quite erect, slightly stooped posture. Could be normal for older person	Moderately stooped posture, definitely abnormal. Can be slightly leaning to one side	Severely stooped posture with kyphosis. Can be moderately leaning to one side	Marked flexion with extreme abnormality of posture
Gait	Normal	Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion	Walks with difficulty, but requires little or no assistance. May have some festination, short steps, or propulsion	Severe disturbance of gait, requiring assistance	Cannot walk at all, even with assistance
Postural stability ⁸	Normal	Retropulsion, but recovers unaided	Absence of postural response. Would fall if not caught by examiner	Very unstable, tends to lose balance spontaneously	Unable to stand without assistance
Body bradykinesia and hypokinesia ⁹	None	Minimal slowness, giving movement a deliberate character. Could be normal for some persons. Possibly reduced amplitude	Mild degree of slowness and poverty of movement that is definitely abnormal. Alternatively, some reduced amplitude	Moderate slowness, poverty or small amplitude of movement	Marked slowness, poverty or small amplitude of movement

1 = head and upper and lower extremities; 2 = judged on passive movement of major joints with patient relaxed in sitting position; cogwheeling to be ignored; 3 = patient taps thumb with index finger in rapid succession; 4 = patient opens and closes hands in rapid succession; 5 = pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously; 6 = patient taps heel on the ground in rapid succession, picking up entire leg; amplitude should be at least 3 inches; 7 = patient attempts to rise from a straightbacked chair, with arms folded across chest; 8 = response to sudden, strong posterior displacement produced by pull on shoulders while patient is erect with eyes open and feet slightly apart; patient is prepared; 9 = combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.
 Source: Movement Disorder Virtual University, 2008.⁷²

Teva Neuroscience, North Wales, PA) on early PD patients as demonstrated in the Attenuation of disease progression with Azilect given once daily (ADAGIO) trial.

Using Activities of Daily Living to Assess the Efficacy of Rasagiline in a Delayed-start Trial

Currently, there are no established disease-modifying drugs for the treatment of PD. Available pharmacologic options treat symptoms, but do not have clinically proven neuroprotective properties. A major limitation in defining a disease-modifying therapy has been the lack of an outcome measure that accurately reflects the underlying disease state and is not confounded by symptomatic or pharmacologic effects of the study intervention. Some early drug studies have suggested potential mechanisms addressing underlying pathophysiology and prevention of cell loss, but subsequent clinical trials show confounding results, with difficulties in separating symptomatic improvement and neuroprotective effects.^{13,37} The development of a delayed-start trial design has helped overcome these confounding effects.^{38,39}

Rasagiline—A Second-generation Monoamine Oxidase Type B Inhibitor

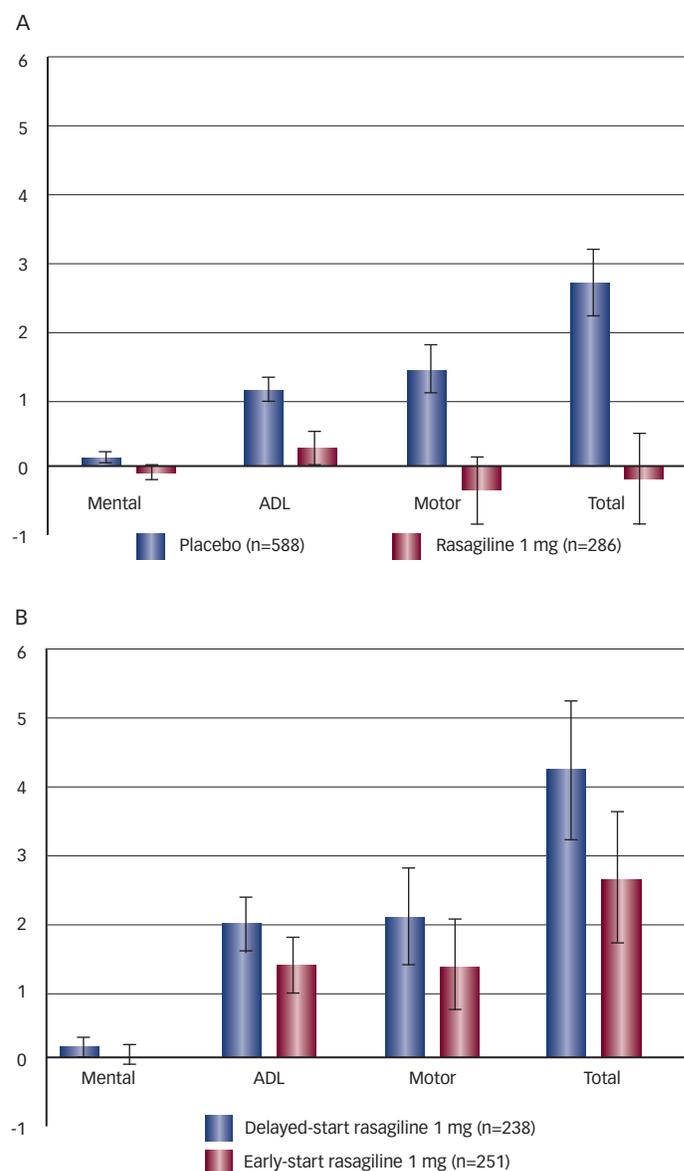
Rasagiline (N-propargyl-[1R]-aminoindan) is a highly selective, irreversible inhibitor of monoamine oxidase type B (MAOB) and is approved for the symptomatic treatment of PD as initial monotherapy and as adjunct therapy to L-dopa.⁴⁰⁻⁴² Early studies have shown that rasagiline protects dopamine neurons *in vitro*⁴³⁻⁴⁶ and *in vivo*.^{47,48} In primates, rasagiline has been shown to increase striatal extracellular dopamine concentrations.⁴⁹ Unlike first-generation propargylamines, rasagiline does not have an amphetamine-like structure and thus does not generate amphetamine or methamphetamine metabolites that may cause adverse effects.⁵⁰ Rasagiline is metabolized by cytochrome P-450 into its active metabolite, 1R-aminoindan, which also has *in vitro* and *in vivo* neuroprotective effects.⁵¹

The Attenuation of Disease Progression with Azilect Given Once Daily Trial Design

Some retrospective analyses have tried to determine potential disease-modifying activity by comparing data from typical placebo-controlled, double-blind trials with data from the open-label, long-term extension periods in which all patients receive the study drug. Long-term extensions to clinical trials are common so that additional safety data can be collected. Any analyses that attempt to compare patients who have received the study drug throughout the double-blind and open-label phases with patients who originally received placebo and then the study drug should be interpreted with caution. For example, drop-out rates are often higher in the placebo group than in the treatment group and therefore, by the time the open-label phase begins, the two groups may be different than at the very beginning of the trial.

To determine whether rasagiline has disease-modifying potential in patients with PD, a delayed-start trial design was implemented in the prospective, double-blind, placebo-controlled ADAGIO trial using the UPDRS to evaluate patients with PD.^{31,39,52} The rationale for the ADAGIO trial came from the TEMPO (Rasagiline mesylate [TVP-1012] in early monotherapy for Parkinson's disease outpatients) trial, in which

Figure 2: Effects of Treatment on Mean Unified Parkinson's Disease Rating Scale Subscores and Total Scores at Week 36 (A) and Week 72 (B) in the Attenuation of Disease Progression with Azilect Given Once Daily Trial



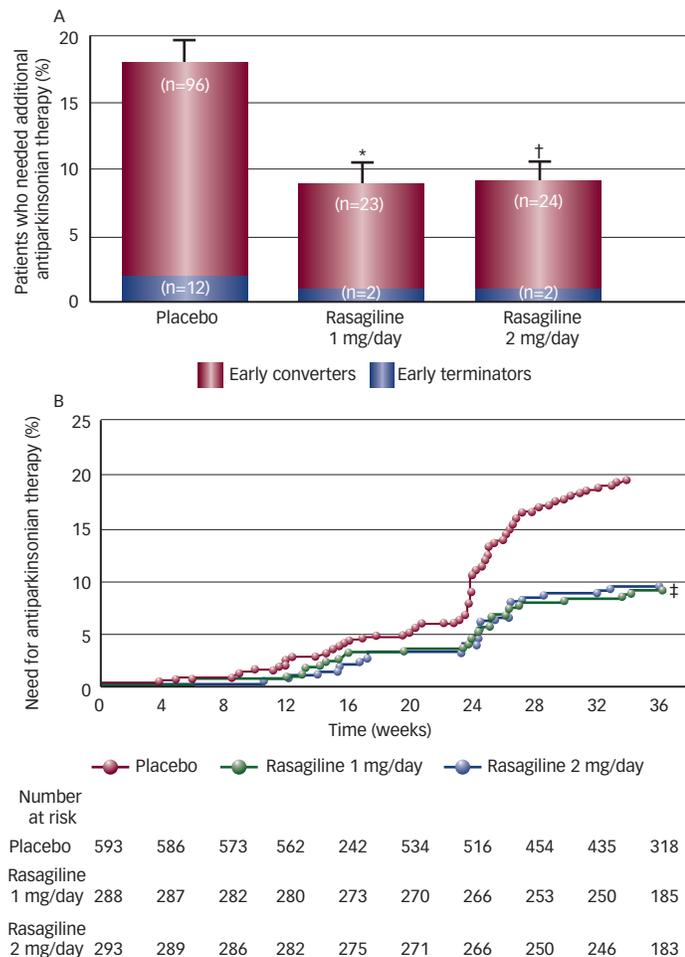
Error bars are 95 % confidence intervals. The mean was estimated by using a mixed model repeated use. The data concerning the 2 mg/day rasagiline doses are not reproduced here. ADAGIO = Attenuation of disease progression with Azilect given once daily; ADL = Activities of Daily Living; UPDRS = Unified Parkinson's Disease Rating Scale. Source: Rascol, et al., 2011.³¹

rasagiline had been shown to improve symptoms in PD patients as assessed using the UPDRS.⁴⁰⁻⁴²

Primary Efficacy Results from the Attenuation of Disease Progression with Azilect Given Once Daily Trial

A total of 1,176 treatment-naive patients with early, very mild PD were enrolled in the ADAGIO trial. They were randomly assigned to receive rasagiline (1 or 2 mg/day) for 72 weeks, or placebo for 36 weeks followed by rasagiline (1 or 2 mg/day) for 36 weeks. The 18-month

Figure 3: Rasagiline Reduces the Need for Additional Antiparkinsonian Treatment in the Placebo-controlled Phase of the Attenuation of Disease Progression with Azilect Given Once Daily Trial



Source: adapted from Rascol, et al., 2011,³¹ with permission from publisher.

ADAGIO trial continued to use a double-blind methodology after patients on placebo switched to rasagiline at week 36 (see Figure 1).

At baseline, patients had a mean total UPDRS score of 20.4.⁵² Results showed that, compared with delayed-start rasagiline 1 mg/day treatment, early-start rasagiline 1 mg/day treatment provided benefits that indicated potential disease-modifying activity.⁵² Rasagiline 1 mg/day met all three primary endpoints:

- superiority of slope suggesting a slower rate of disease worsening, as measured by a smaller change in mean UPDRS scores between week 12 and week 36 (0.09 and 0.14 with rasagiline and placebo, respectively; p=0.01);
- a difference in UPDRS scores between baseline and week 72 (2.82 and 4.52 with early- and delayed-start rasagiline, respectively; p=0.02); and
- non-inferiority of slope between the early- and delayed-start groups between week 48 and week 72, as measured by the rate of change in UPDRS scores (0.085 points/week for both groups; p<0.001).⁵²

These endpoints were not met in the early- versus delayed-start rasagiline 2 mg/day comparison. A *post hoc* subgroup analysis of the patients with the highest quartile of UPDRS scores at baseline (UPDRS >25.5) i.e. patients more affected by the disease, however showed different results. Patients in this population who were treated with 2 mg/day early start rasagiline showed significant differences for all three primary endpoints compared with those who received 2 mg/day delayed start rasagiline (p<0.001, p=0.04 and p<0.001, respectively). Therefore, 2 mg/day delayed start rasagiline treatment achieved results consistent with disease modification in that population. It is possible that 2 mg/day rasagiline has a greater symptomatic effect, thus masking any potential disease-modifying effects in the more modestly affected cohort of patients studied in the ADAGIO trial. More data are required before any conclusions can be made. The different results for the two doses have been extensively discussed elsewhere.^{2,53-55}

Analyses of Unified Parkinson's Disease Rating Scale-Activities of Daily Living Subscores in the Attenuation of Disease Progression with Azilect Given Once Daily Trial

In light of the recent evidence that the UPDRS-ADL subscale may be more sensitive in assessing disease progression in early PD,^{29,30,56} *post hoc* analyses have been conducted using data from the ADAGIO trial.³¹ UPDRS-ADL subscores are derived from patients' reports of function over the past week, and may therefore be less sensitive to short-term variability driven by environment or investigators.

The changes in UPDRS-ADL subscores from baseline to weeks 36 and 72, respectively, were assessed for each of the treatment groups. At week 36, estimated changes from baseline in UPDRS-ADL subscores were +1.13 (95 % confidence interval [CI] 0.95–1.31), +0.27 (95 % CI 0.02–0.52), and +0.33 (95 % CI 0.08–0.59) for placebo (n=588), rasagiline 1 mg/day (n=286), and rasagiline 2 mg/day (n=290), respectively. Rasagiline 1 mg/day also improved non-motor symptoms of the UPDRS-ADL subscale compared with placebo (mean difference -0.33; p=0.049).³¹ At week 72, estimated changes from baseline in UPDRS-ADL subscores were +1.45 (95 % CI 1.04–1.85) and +2.07 (95 % CI 1.64–2.50) for early-start rasagiline 1 mg/day (n=251) and delayed-start rasagiline 1 mg/day (n=238), respectively, and +1.44 (95 % CI 1.08–1.80) and +1.66 (95 % CI 1.30–2.03) for early-start rasagiline 2 mg/day (n=258) and delayed-start rasagiline 2 mg/day (n=249), respectively (see Figure 2—which only shows data for the 1 mg/day rasagiline doses).³¹

In *post hoc* analyses, the effects of treatment on ADL subscores at week 36 and week 72 were compared with the effects of treatment on the other UPDRS subscores, in order to establish whether the UPDRS-ADL subscale is a responsive measure of disease progression over time. The percentage contribution of each UPDRS subscale was calculated by dividing the treatment effect recorded in each subscale by the sum of the three subscales (mentation, ADL, and motor).

Between baseline and week 36, rasagiline 1 mg/day significantly improved scores on each of the UPDRS subscales compared with placebo. During that period, the changes were likely to be the result of the combined effect of the short-term symptomatic and the putative long-term disease-modifying actions of the drug. At week 72, however,

only the ADL subscale showed a significant difference between the early- and delayed-start groups (see *Figure 2*). By that time, all patients had been receiving the same drug for at least nine months and, therefore, any difference between the two groups at this stage was likely to indicate only the disease-modifying effects of the drug. At week 36, the contribution of the motor subscale was approximately twice that of the ADL subscale (64 and 29 %, respectively, with rasagiline 1 mg/day). However, at week 72, the contribution of the ADL subscale to treatment effect had increased to 41 %, whereas the motor component had decreased to 51 %. Furthermore, the ADL subscale was the only one to show a statistically significant between-group difference (early- versus delayed-start rasagiline 1 mg/day).

The ADAGIO cohort (i.e., patients with early, very mild PD) showed a low rate of progression on the UPDRS, an effect previously observed in the Neuroprotection exploratory trials in PD (NET-PD) study. Analysis of data from the ADAGIO trial using the UPDRS-ADL subscale supports the notion that it may be a more appropriate measure to assess disease progression than the UPDRS motor subscale.^{57,58}

Use of Additional Antiparkinsonian Medication in the Attenuation of Disease Progression with Azilect Given Once Daily Trial

During the placebo-controlled phase of the ADAGIO trial, it was also shown that significantly fewer patients receiving rasagiline required additional antiparkinsonian medication (levodopa or dopamine agonists) compared with those receiving placebo (9, 9, and 18 % with rasagiline 1 and 2 mg/day and placebo, respectively; odds ratios 0.41 [95 % CI 0.25–0.65] $p=0.0002$ for rasagiline 1 mg/day versus placebo and 0.41 [95 % CI 0.26–0.64] $p=0.0001$ for rasagiline 2 mg/day versus placebo), indicating that the probability of requiring additional antiparkinsonian medication was approximately 60 % lower in the early-start groups than in the pooled placebo group.³¹ The percentages of patients who needed additional antiparkinsonian medication and the time to receiving that medication are given in *Figure 3*.

Assessment of Fatigue in the Attenuation of Disease Progression with Azilect Given Once Daily Trial

Fatigue is a common and consistent problem in PD and often pre-dates the onset of motor symptoms,⁵⁹ which makes the Parkinson Fatigue Scale (PFS) another useful tool in assessing PD.⁶⁰ The ADAGIO trial assessment using the PFS showed that rasagiline 1 mg/day was beneficial on fatigue. Patients in the placebo groups had a significantly greater worsening in PFS scores from baseline to the last observed value than patients in the groups receiving rasagiline 1 mg/day (treatment difference -0.14 [standard error; SE 0.05]; $p=0.0032$) and 2 mg/day (treatment difference -0.19 [SE 0.05]; $p<0.0001$).³¹

Other Delayed-start Trials

To date, few trials have employed delayed-start methodology and have assessed ADL as a measure of disease progression in PD. The previous rasagiline trial TEMPO demonstrated that, during its placebo-controlled, double-blind six month phase (Phase 1), rasagiline was safe and efficacious compared with placebo for

patients with early PD.⁴⁰ At baseline, patients enrolled in the TEMPO trial had a significantly higher mean total UPDRS score than those enrolled in the ADAGIO trial (24.5–25.9 versus 20.4, respectively).^{40,52} From month seven to month 12 of the TEMPO trial, early- and delayed-start rasagiline treatment were compared: in patients who received rasagiline 1 mg/day treatment for 12 months (early-start treatment), the functional decline was less pronounced than in patients who received placebo for six months followed by rasagiline for six months (delayed-start treatment).^{40,61} After 52 weeks, the mean changes in total UPDRS scores from baseline for the three different treatment groups were: +3.01 (with rasagiline 1 mg/day), +1.97 (with rasagiline 2 mg/day), and +4.17 (with delayed-start rasagiline 2 mg/day). During the entire 6.5-year follow-up period, this change was 2.5 units (or 16 %) in favor of the early-start versus delayed-start rasagiline group. However, it is difficult, from these results, to draw firm conclusions regarding the disease-modifying effect of rasagiline due to the high drop-out rate of patients during the extension study.⁶²

In the TEMPO trial, rasagiline 1 and 2 mg/day (early-start rasagiline) were both superior to delayed-start rasagiline in terms of changes in UPDRS scores in patients who had high UPDRS scores at baseline.⁶¹ Similar results were observed in the ADAGIO trial patients with the highest quartile of UPDRS scores, suggesting that the effect of rasagiline 2 mg/day on symptoms may have masked a benefit in terms of functional decline with early-start treatment in patients with very mild disease.⁵² During its comparison phase (month seven to month 12), the TEMPO study showed a mean difference of 39.1 % in ADL subscore changes from baseline, and a mean difference of 11.9 % in motor subscore changes from baseline, between the early-start and delayed-start rasagiline groups;⁶² this supports the concept that on-motor symptoms assessed by the ADL subscale may be more stable markers of disease progression.⁵⁶ The UPDRS in its entirety may be less sensitive to changes in early PD and may not capture improvements in non-motor areas.^{63–65} Improvements of ADL subscores in rasagiline-treated patients are consistent with significant benefits in non-motor symptoms compared with placebo.⁶⁶

A delayed-start design also was used to assess a potential disease-modifying effect of the dopamine agonist pramipexole. The Pramipexole on underlying disease (PROUD) study enrolled approximately 500 patients with early PD. During Phase 1, patients received 1.5 mg/day pramipexole or placebo for 6–9 months. During Phase 2 (i.e., until study end at month 15), those receiving placebo during Phase 1 received pramipexole. The primary endpoint was the change in total UPDRS score (sections 1–3) at month 15 from baseline. The PROUD study results have been reported as negative by preliminary presentations.^{13,67}

Potential Limitations of Delayed-start Trial Designs

There are a number of concerns regarding delayed-start study designs that may affect the quality of results. The delayed-start group (i.e., patients who receive placebo during Phase 1) foregoes symptomatic therapy for the first half of the study. In clinical trials assessing the treatment of slowly progressing diseases such as PD, the first half of the study normally lasts 6–9 months, which is a long time for a patient to be without symptomatic therapy. Moreover, most patients, when newly diagnosed with PD, already require treatment to control symptoms, thus reducing the pool of potential

study recruits. It is possible that such patients would have very slowly progressing disease, making it difficult to apply the study results to patients found in normal clinical practice.⁶⁸ In addition, those patients who receive placebo during Phase 1 are more likely to drop out of the trial as a result of a lack of efficacy, which may cause a divergence in baseline characteristics and invalidate randomization.⁶⁹ As previously mentioned, in ADAGIO patients receiving placebo were allowed proceed to Phase 2 instead of discontinuing treatment.⁵² Another potential concern is that, by using slope estimates for measuring changes in UPDRS score, the data have been assumed to fit into a linear model.⁶⁹ It is, however, not known whether PD progresses in a linear fashion, particularly in early disease when there is a rapid loss of dopaminergic cells.

New Developments in Parkinson's Disease Assessment Scales

The Movement Disorder Society (MDS) has recently revised the UPDRS to include more non-motor measures and to make it less biased toward certain cultural practices.²² The revised scale, the MDS-UPDRS, has four sections:

- section I: non-motor experiences of daily living;
- section II: motor experiences of daily living;
- section III: motor examination; and
- section IV: motor complications.⁶⁶

This scale has been validated for non-motor symptom assessment and correlation with the original UPDRS.^{70,71} In the MDS-UPDRS, motor and non-motor ADL have been separated, so future trials using this scale will improve our understanding of the respective contribution of these parameters. Future rasagiline trials should help us understand how the assessment and subsequent treatment of non-motor symptoms might help improve the quality of life of patients with PD.

Conclusions

The UPDRS-ADL subscale is well known and commonly used to assess disease progression in PD. Moreover, it is quick for patients to self-complete. The ADAGIO trial provided an opportunity to assess the rate of change in UPDRS scores in a large sample of patients with early and untreated PD. Rasagiline treatment showed a potential disease-modifying effect, which supports its early use.^{31,52} During the ADAGIO trial, rasagiline treatment also delayed the need for additional antiparkinsonian drugs and reduced the non-motor symptom fatigue. Disease progression may be more accurately assessed using the UPDRS-ADL subscale than the UPDRS motor subscale, because the former includes both motor and non-motor components. If the non-motor symptoms in PD can be identified, and subsequently decreased through appropriate treatment, this may also slow the clinical progression of the disease.^{30,56} Future studies separating the assessment of motor and non-motor symptoms will help determine treatment success and how these symptoms modulate as the disease progresses. ■

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