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CLINICAL TRIALS

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Time course of physical and psychological responses to selegiline monotherapy in newly diagnosed, idiopathic parkinsonism

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Abstract. *Rationale*: Poor specificity of face-value endpoints and the poor sensitivity of gross clinical examination may have militated against demonstrating prophylaxis by selegiline.
Methods: Objective measures of the four cardinal signs were used as primary outcome criteria in a randomised, double-blind, placebo-controlled, parallel group study of selegiline monotherapy in 25 newly diagnosed elderly sufferers from idiopathic parkinsonism, stratified for sex and Hoehn and Yahr functional staging.
Results: There was a significant interaction between time and nature of treatment with respect to rigidity. The effect of time during active treatment was highly significant: rigidity decreased by 1.3 % per week. The worsening of rigidity on placebo was not statistically significant. Neuronal rescue is a possible explanation for the long term, progressive improvement produced by selegiline.
No significant treatment effect was seen on the other cardinal signs. However, there was a significant quadratic time trend for arousal on active treatment suggesting tolerance to this effect.
Conclusion: The difference in time course between the psychostimulant and physical effects suggests more than one mode of action.

Key words Selegiline, Parkinsonian; monotherapy; placebo; newly diagnosed elderly; objective assessment

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Selegiline was developed in Hungary by Knoll in 1964 as a monoaminoxidase-inhibitor antidepressant [1]: he described it as "a psychic energizer". Its pharmacology is still being unveiled [2, 3] and new therapeutic uses explored [4–6]. Questions arise as to whether selegiline could be of use, not only in diseases akin to accelerated ageing [7, 8], but also in aspects of normal ageing related to a decline in dopaminergic function [9].

Current indications for selegiline are for "Parkinson's disease or symptomatic parkinsonism, either used alone (in early disease) or as an adjuvant to levodopa therapy" [10]. When used alone, it has benefit on face-value endpoints, such as the time to requiring levodopa therapy, and on global subjective assessments [11–16], but whether these coincide with an objectively measurable effect on the cardinal signs, or can be explained by cognitive effects [1, 15, 17–20], is unclear. If specificity for one or more of the cardinal signs can be demonstrated, it would then be appropriate to consider whether the efficacy of selegiline monotherapy lies in treatment effect(s), neuroprotection [21–27] or neuronal rescue [2, 3], or a combination of these. We present an efficacy study of the time course of physical and psychological responses to selegiline monotherapy in newly diagnosed sufferers from idiopathic Parkinsonism, whose mean age coincided with that of presentation of the condition [28]. The approach, with its restrictive entry criteria, precise and, wherever possible, objective outcomes, and intent on achieving high compliance, is explanatory, not pragmatic: it is intended to generate hypotheses.

Methods

Patients recruited

Consecutively presenting outpatients aged 65 years or over, with newly diagnosed, untreated clinical idiopathic Parkinsonism (functional rating I, II or III on the I–V Hoehn and Yahr [29] scale) were asked to participate in the trial, which had local ethical committee approval. Parkinsonism was diagnosed on the presence of two or more of the cardinal signs, brady/hypokinesia, rigidity, tremor and postural abnormality. Clear-cut, non-idiopathic Parkinsonism was excluded [30], as were patients in whom there were reservations about the diagnosis. Also excluded were patients with progressive or resolving disorders that affect physical ability or performance, those having physical or mental incapacity severe enough to prevent evaluation (including a Modified Tooting Bec [31] mental test score < 8/16), and those receiving any medication which might have an anti-Parkinsonian, hypnotic or sedative effect.

Objective assessment

Interruptions and distractions were strictly avoided during the assessment.

Brady/hypokinesia

Distance/time measurements of gait were obtained using the gait-assessment trolley [32], a computerized method, based on infra-red telemetry, which allows free walking in a non-laboratory environment. Rested subjects walked for 40 m in a 2.5 m wide empty corridor, "at your own speed", following the command "go".

Rigidity

The torque needed to move the forearm of the relaxed limb, at a controlled velocity, through a fixed angle in a horizontal plane about the pivotal axis at the elbow (Fig. 1) was recorded as a hysteresis loop. A horizontal plane was used to eliminate the effect of gravity on the measurement. Flexion/extension was studied in the elbow for reproducibility (a simple hinge movement), and because the sitting position was comfortable and convenient. Whereas Webster [33] used the largest practical arc of 100 (60 to 160)°, 40 (115 to 155)° was found to be optimal for comfort in elderly Parkinsonians. At high frequencies of oscillation, measurement of torque is confounded by increasing inertia [34], whilst at low frequencies, subjects attempt to assist the motor [34, 35]: a frequency of 0.5 Hz was selected. The area of each hysteresis loop was quantified using a graphics pad and commercially available software (Graphic Master, Numonics corp., Pennsylvania; Design CAD 2-D, American small business computers, Oklahoma, USA), and the mean work required per unit displacement (area of the loop divided by angular displacement) calculated.

Activation [36] (an increase in rigidity in the test limb, evoked by voluntary movement of the contralateral limb) was produced by squeezing a paediatric sphygmomanometer cuff, with the opposite hand, to a pressure of one third of that hand's maximum grip pressure at that assessment plus 20 mm Hg. The protocol consisted of 2 min acclimatisation to the passive arm movement, six baseline recordings of the hysteresis loop at 10 s intervals, achievement of the predetermined grip pressure, five recordings at 15 s intervals during activation, and four "recovery" recordings at 15 s intervals after release of the grip. Recordings under baseline, activation and recovery conditions were then repeated directly. The arm judged to be the more rigid at the initial visit, or, if both sides were equal, the non-dominant arm (i.e. the arm expected to have the smaller muscle mass [36]), was studied at this and subsequent assessments.

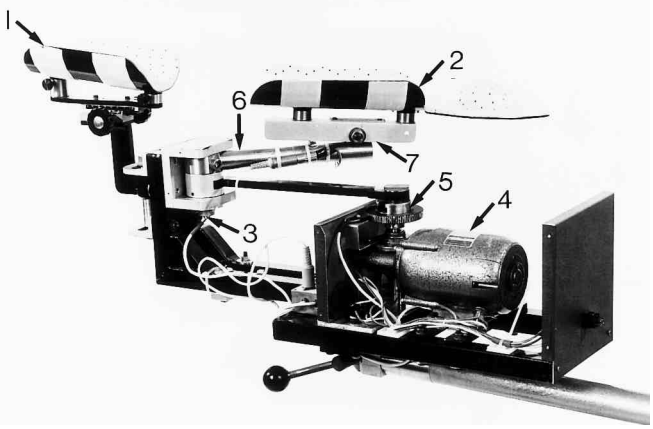

Fig. 1 Apparatus for measuring rigidity. The subject sits with his/her upper arm and forearm resting horizontally in the padded cradles (1 and 2), such that the humero-ulnar joint is positioned directly above the pivotal point of the apparatus (3), and the hand supported in the prone position. The adjustable height of the apparatus and position of the cradles allowed this to be achieved in comfort, and light strapping with velcro strips discouraged active movement. The geared motor (4), encased in practice, drives the crankshaft (5) back and forth, which moves the driven arm (6). The motor speed is controlled electronically, and monitored by an optical tachometer. Torque is measured using a semiconductor strain gauge (7), and the angular position of the armrest using a high quality potentiometer mounted on the rotation axis (3). The signals representing torque and angular position are amplified and charted on an xy recorder. (There was no drift in calibration between start and end of study.)

Tremor

Unlike accelerometry, the method used [37] gives a direct measure of amplitude and avoids attaching transducers to the patient, which might either induce or inhibit tremor. The relaxed hand of the seated patient hangs within the optimal field of view of two pairs of differentially-connected infra-red detectors, mounted on the opposite, vertical faces of a perspex box (23×23 cm $\times 36$ cm deep). The height of the latter above the ground is adjustable. A continuous recording of the voltage output in each of the two planes, monitored by the sensors, was made using a magnetic tape recorder: the mean for the two planes was converted into mm of tremor using a calibration curve. Provocation of tremor was attempted by asking the subject to repeat, in reverse order, a series of random numbers read out by the investigator. The length of a sequence of digits needed to stretch the recall capability of the patient was determined at each visit. The protocol consisted of five one minute periods: rest, provocation, rest, provocation and rest. The hand judged to be the more tremulous at the initial visit or, if both hands were equal, the non-dominant hand was used at all assessments.

Postural abnormality

Body sway, standing at ease, was measured as total angular movement in the sagittal plane [38] during three consecutive minutes.

Psychomotor and psychometric disability

Reaction times were measured as the time taken to lift the left or right index finger from its touch-sensitive support. Prior to the imperative signal, an alerting signal appeared on the computer screen, such that the subject either did not (unwarned condition) or

did (warned) know in advance whether the instruction would be to lift left or right index [39]. The delay between the alerting and the imperative signal varied randomly between 1 and 3 s, with a mean of 2 s. The difference between unwarned and warned reaction time was used as a measure of efficiency of cognitive processing [39].

Standardisation of measurements

Numerical values, or categories, for relevant [32, 39–41] covariates were recorded. At the initial visit, height, weight, leg length, arm length (shoulder to elbow and elbow to wrist), forearm girth (maximum), skin fold thickness over triceps (at junction of proximal 1/3 and distal 2/3 of upper arm), and hand volume were measured. Blood pressure was recorded on the occasion of each assessment of gait, and room, body and hand temperature on that of tremor.

Protocol

Run-in

At the initial visit, a clinical examination was made, with functional [29] and Webster [36] severity ratings of parkinsonism. Arterial blood pressure was measured, supine (after 5 min) and erect (3 min). This was followed by a physiotherapy session, where exercises, to be carried out daily at home, were first performed. As a practice run for the trial, the above objective assessments were then carried out, and subjective ratings made of affect on a 20 point scale [42], stress on a 19 point and arousal on a 15 point [43]. The subsequent weekly visits were for supervision of exercises and gait assessment.

Criteria for entering trial

Patients whose walking had improved to a plateau in a minimum of five visits, or had remained stable, were allocated to a treatment group. Values for mean (SD) stride length (two walks on the initial and one on each subsequent run-in visit) were entered into a commercially available computer program (PCNONLIN, Statistical Consultants Inc., Kentucky, USA). The achievement of values within 10% of the plateau predicted by the program was acceptable. Those whose performance had not plateaued within the 4 week period were reassessed after one and, if necessary, two further weeks of exercises.

Trial

This was a randomised, double-blind, placebo controlled, parallel group study of selegiline monotherapy, stratified for sex and Hoehn & Yahr [29] staging at entry to the trial. One group received active selegiline, 5 mg twice daily, the later dose of the day to be taken at 14.00 h, and the other group matched placebo tablets (Orion Corporation Farmos). Compliance with trial medication was measured, by tablet counts, at each visit, thus allowing for targeted counselling.

In order to minimise any confounding effect of variability in physical training on outcome, the regimen of standard daily exercises was continued throughout the trial, with backup from supervised sessions at the start of each formal assessment visit.

Primary outcome criteria were the objective measurements of the four cardinal signs. Secondary outcome criteria were the psychomotor and psychometric disability associated with Parkinsonism and the ratings of affect, stress and arousal. Assessments were made of the outcome criteria, covariates (see Standardisation of measurements) and the Webster score (see Interpretation of primary outcome criteria), at entry into the trial proper (pre-treatment) and at six weekly intervals during treatment, for a period of 54 weeks, or until they were discontinued in accordance with the "temporal end point" or other exit criteria, or because of drop out.

The temporal endpoint was reaching stage IV on the Hoehn & Yahr rating: this was a set indication for levodopa replacement therapy. Other exit criteria were as follows:- current life style threatened by the progression of the disease; falls with serious injury or fracture; putative adverse effects of trial medication; other medical conditions needing specialist attention; anti-Parkinsonian medication prescribed by another source. Judgements had patient safety as the final arbiter. They were made "blind" to treatment, by the physician responsible for the day to day running of the trial, in consultation with two other physicians. Adverse events were recorded by a questionnaire, relating to symptomatology and drug reactions, and by spontaneous, intercurrent reporting. The questionnaire was administered at entry and with the six weekly assessments. Reasons for any patient-initiated drop out were recorded Table 1.

Statistical methods

Calculation of sample size

The calculation was based on brady/hypokinesia as measured by mean stride length [44]. This was the primary outcome criterion for which estimates of the between-patient variance could be made. It was performed using commercially available computer software (N handbook, 1988, W.W. Munchen, IDV-Dateanalyse und Versuchsplanung). For a type I error of 0.05 and a type II of 0.2 or 0.3, it was calculated (taking a mean (SD) stride length of 1000 (100) mm to be typical) that a total sample size of 32 or 26 subjects, respectively, would be required to show a 100 mm (i.e. 10%) difference in stride length between treatments.

Hindsight showed that the prior estimate of standard deviation was smaller than that observed for our patients' walks at a given time point (Table 2). However, in the analysis of summary measures (below), it is the standard deviation of the patients' mean performance during treatment that is required, and this will, indeed, be smaller than that observed at a single time point.

Analysis of outcome: summary measures

A summary measure for each outcome criterion, the mean value during treatment for each patient, was used as the dependent variable in an analysis of covariance [45], with the corresponding pre-treatment value as covariate. Initially, the interaction of nature of treatment and pre-treatment value on a dependent variable was examined. If this was not statistically significant, the treatment effect was assessed after removal of the interaction term. Personal and/or environmental characteristics (see Standardisation of measurements), which contributed significantly to explaining the between-patient variance in a dependent variable, were included in the analysis. Where there was more than one test condition, as with rigidity, the within-subject interaction between nature of treatment and condition was considered.

Analysis of outcome: time trends

Linear models were used to assess within-subject time trends in the outcome criteria and to determine whether these trends were different in the two treatment groups. Subject was fitted as a block to enable a within-subject analysis. The predictor variables, time since treatment commenced and nature of treatment, were fitted as a covariate and a binary factor, respectively. Any non-linearity in the time trend was allowed for by the inclusion of a quadratic term in the model. The significance of each term in the model was assessed using an F test on the reduction of the sum of squares when that term was removed from it. The interaction between subject and time since treatment commenced was used to assess whether the trends were parallel on each treatment.

The above approach to the analysis of repeated measures is valid provided the within-patient variance-covariance matrix has a compound symmetric structure. An unbalanced repeated measures analysis of variance was performed [46] using a range of different covariance structures: for all models, the compound symmetric structure was found to be the most appropriate by the maximum Akiake's information criterion.

The sincerity of the description of time trends was tested. A logrank test [47] was performed in order to demonstrate that the duration of assessment was not significantly different between active and placebo groups, and that any interaction found between nature of treatment and time since treatment commenced could not be attributed to uneven attrition. Plots of the time trends of individuals were then examined, to ensure that there was no systematic relationship between trend and length of participation in the trial in either treatment group. In the case of apparently quadratic time trends, those individuals who contributed to fewer than four of the six-weekly time points were excluded from the analysis.

In the case of stride length, run-in data were available. These were incorporated into the model: two separate time trends were fitted, intersecting at the assessment immediately pre-treatment [48].

Allowance for the pre-treatment difference found in rigidity (see Table 2) was made by expressing each value obtained during treatment as a ratio to that patient's value immediately pre-treatment. To illustrate the effect of time on rigidity, the overall trend was displayed for each treatment (as in Fig. 2). The intercept of each regression line was determined by the arbitrary choice of a patient. The 95% confidence intervals correspond to a patient with a median number of assessments for his/her treatment group: they were constructed using 1.98.var(y), based on the residual degrees of freedom (123) from the analysis of covariance, and where the variance in y, the predicted dependent variable, is due to the uncertainty in the estimated regression coefficients.

Validity of assumptions

The assumptions of normally distributed residuals [49] and equality of variance [50] were investigated. To ensure the validity of assumptions, a $\log_e$ transformation was required for measures of rigidity, tremor, sway and reaction time and the affect rating. (For transformed variables, linear time trends are expressed numerically as percentage changes from pre-treatment values.)

Interpretation of primary outcome criteria

Simple linear regression was used to examine the relationship between the mean values during treatment for a primary outcome criterion and those for the corresponding Webster sub-score. Where congruency was limited, it was considered whether the subjective assessment could be based on a different aspect of that cardinal sign, or be a complex judgement, tempered by a global impression. Forward and backward, stepwise multiple linear regression was used to explore how far the subjective rating could be explained in terms of demographic data and the total Webster score. Values for the proportion of the variance explained were adjusted (R_a^2) to take account of the chance contribution made by each variable in the model.

Results

Patients

In view of the attrition expected in an elderly cohort, 35 patients were recruited. Five of these were judged to require levodopa therapy during the run-in period. The remainder met the criteria for entering the trial.

Table 1 Clinical end points in the 30 patients entering the trial

Category	Number of patients active	Placebo
Entered trial	14	16
Early† *exits*		
drop outs	1[a]	2[a]
deaths	0	2[b]
Later exits		
drop outs	0	2[a]
exclusions		
– Hoehn and Yahr Stage IV	4	2
– intercurrent illness††	5	2
Reached end of study	4	6

† before first assessment on treatment
†† not attributable to adverse effects
[a] reason given being perceived adverse effects of trial medication or no perceived benefit
[b] sudden, unexpected cardiovascular event

Progression simply in terms of reaching a clinical end points is detailed in Table 1.

Outcome criteria could be analysed in 25 patients (19 male, 6 female), of mean (SD) age 74.9 (6.3) years: five patients had exited from the trial before their first six-weekly assessment was due. The median (interquartile range) for the number of assessments carried out was 7 (4, 8) for the 13 patients on active and 6 (2, 9) for the 12 on placebo treatments. Four patients perceived adverse effects of trial medication: these were, on placebo, confusion and agitation (2 patients), nausea (2) and headaches (2), and, on active, nausea, vomiting and diarrhoea (1). The mean (s.e. mean), and range, of compliance with active treatment, 94 (10), 65–100%, was similar to that with placebo, 97 (6), 80–105%.

Definition of sample

Table 2 gives the characteristics of the trial patients and contrasts them with subject groups without clinical parkinsonism [39, 40] and with treated idiopathic parkinsonism [39, 41]. Stride length of the trial patients was intermediate between that of the other two groups. Given the improvement obtained by physiotherapy at time of entry (see Effect of time on outcome measures), they were only 13% of the way down the path [23] from health to the established condition. Standing body sway in the trial group was less than in the healthy controls, perhaps reflecting a poverty of compensatory movements in early parkinsonism. It was, however, considerably less than in the parkinsonians receiving treatment. Sway in the latter may reflect impairment of balance (the hallmark of stage III) and, perhaps, hypotension during a prolonged stand. The trial group, unlike the treated parkinsonians, did not have early evidence of depression. The very small deficit in mental test score in the trial group was on a par with that in the established condition. As regards psychomotor performance, the reaction times of the trial group did not

Table 2 Characteristics of the 25 patients formally assessed in the trial, at the time of assignment to active or placebo treatments, in contrast with those of age-matched, treated sufferers and controls without clinical parkinsonism

Characteristic	Mean value (data interval*)			
	Treated Parkinsonians (n** = 59)	Trial active (13)	Trial placebo (12)	Controls (60)
Common physical				
Age (y)	75.4 (63.0, 87.0)	76.9 (66.0, 87.8)	73.8 (60.0, 87.7)	75.5 (62.3, 88.7)
Height (m)	1.62 (1.46, 1.78)	1.68 (1.52, 1.84)	1.64 (1.46, 1.81)	1.62 (1.47, 1.77)
Weight (kg)	63.6 (40.0, 87.2)	70.0 (44.1, 96.0)	75.2 (38.7, 111.7)	64.0 (44.3, 83.7)
Gender***	31M, 28F	11M, 2F	8M, 4F	28 M, 32F
Special physical				
Mean stride length (m)	0.80†† (0.44, 1.17)	1.17 (0.75, 1.59)	1.23 (0.72, 1.74)	1.26† (0.91, 1.61)
Mean‡ rigidity (N.m)****	–	0.55 (0.13, 2.37)	0.30 (0.10, 0.88)	–
Mean‡ tremor (mm)*****	–	0.87 (0.75, 1.74)	0.97 (0.67, 2.38)	–
Mean body sway (°. min^{-1})****	9.9†† (2.0, 48.2)	4.8 (1.7, 13.6)	5.0 (2.4, 10.5)	7.2† (2.7, 19.5)
Rating scale *****				
Hoehn and Yahr	3.0†† (2.0, 4.0)	2.0 (2.0, 3.0)	2.0 (2.0, 2.75)	–
Blood pressure (mm Hg)				
lying	–	115 (84, 147)	109 (70, 149)	–
standing	–	114 (81, 148)	106 (66, 147)	–
Psychometric *****				
Mental test score	14.5 (13.0, 15.5)	14.5 (12.5, 15.5)	14.0 (12.1, 16.0)	15.0† (14.0, 16.0)
Affect	6.0†† (4.0, 9.0)	4.0 (2.0, 6.0)	2.5 (1.25, 3.0)	3.5 (2.25, 5.0)
Arousal	–	10.0 (7.5, 12.0)	13.0 (9.25, 14.0)	–
Stress	–	2.0 (1.0, 6.5)	2.5 (0.00, 8.25)	–
Psychomotor(ms) ****				
Unwarned reaction time	815 (367, 1811)	718 (367, 1402)	688 (341, 1388)	616 (442, 860)
Warned reaction time	695† (291, 1659)	552 (331, 920)	510 (207, 1255)	486 (278, 852)

* 2 s.d., ** number in group, *** M, male; F, female, **** geometric mean and data interval, ***** median (interquartile range).
‡ over all test conditions, – data not available.
† $P < 0.05$, †† $P < 0.001$: significant contrasts of treated Parkinsonians or healthy controls with trial group, after adjustment for relevant covariates [39–41]

differ from those of healthy controls, but the performance of the treated parkinsonians was impaired. Moreover, efficiency of central processing, as measured by unwarned minus warned reaction times, was also unimpaired in the trial group.

Effect of time on outcome measures

Brady/hypokinesia

Those newly diagnosed parkinsonians capable of improving their gait by physiotherapy appeared to have done so during the run-in, where the overall rate of improvement in stride length had a mean (95% confidence interval, C.I.) of 11.8 (8.0, 15.6) mm per week ($P < 0.0001$). During the trial proper, no trend with time was seen, nor was there any interaction between nature of treatment and time. There was no evidence that a response over time was being masked [32] by a hypotensive effect of selegiline. Mean arterial blood pressure did fall with time (-0.86 (-1.56, -0.16) mm Hg lying and -1.33 (-1.99, -0.67) standing per 6 weeks, $P = 0.01$ and 0.0001, respectively), but did so irrespective of the nature of treatment. This may reflect familiarity with the protocol.

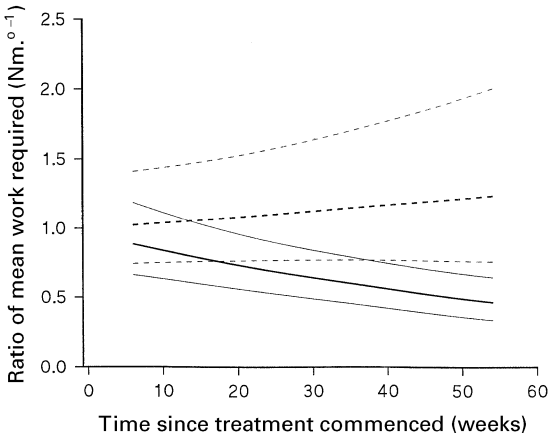

Fig. 2 Comparison of mean time course in baseline rigidity, as measured by the work required for unit angular displacement of the forearm, on active (——) and placebo (-----) treatments. Results are expressed as the ratio of the values during treatment to those pre-treatment. The 95% confidence intervals given about each regression line are based on the completion of six of the six-weekly assessments

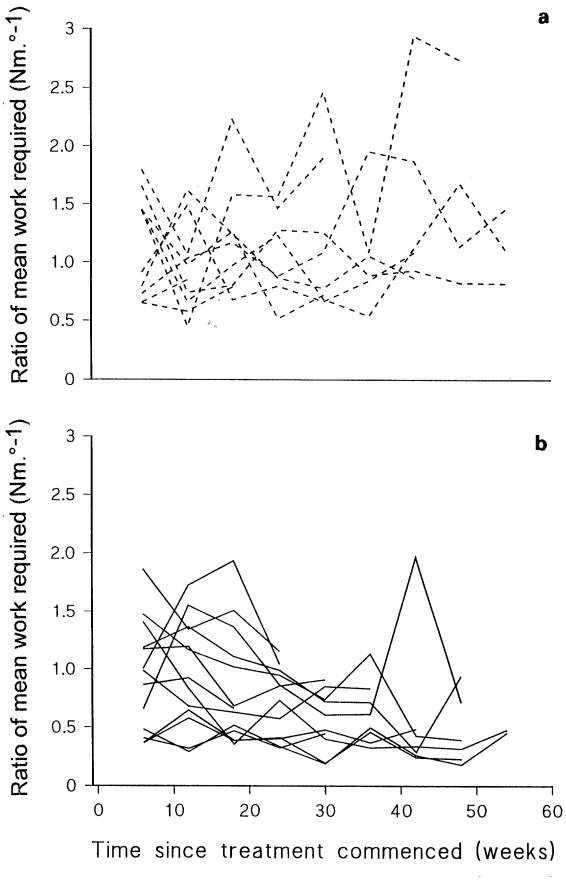

Fig. 3a, b Time course of the mean work required, under baseline test conditions, in individual patients on **(a)** placebo (------) and **(b)** active (——) treatment. The 10 patients in a) and the 13 in b) had a minimum of two 6 weekly assessments. Results are expressed as the ratio of the values during treatment to those pre-treatment

Rigidity

The rigidity measure selected (see Congruency of objective and subjective assessments), the mean work required per unit displacement, showed a significant interaction between nature of treatment and time under all test conditions ($P = 0.0003$ for baseline, $P = 0.01$ for activation and $P = 0.005$ for recovery). Thus, there was no evidence of selectivity with respect to test condition. No within-patient covariate, relevant to standardisation of the measurement, was identified.

Figure 2 compares the mean time course in baseline rigidity on the two treatments, whilst Fig. 3 shows the time trends in individuals. There was a significant ($R_a^2 = 13\%$, $P = 0.0001$) effect of time on active treatment: the work required decreased by 7.9 (C.I., 4.2, 12.0)% per 6 weeks. The apparent increment on placebo treatment, 2.4 (−1.8, 6.6)% per 6 weeks, was not statistically significant. The significant interaction between nature of treatment and time with respect to baseline rigidity could not be explained on the basis of a difference in attrition rates between active and placebo groups ($P = 0.9$). Moreover, there was no apparent relationship, in either treatment group, between rate of change in rigidity and length of participation in the trial.

On active treatment, the magnitude of the decrease in work during activation was 4.3 (0.8, 7.6)% per 6 weeks and during recovery was 5.2 (1.4, 8.7)%, the apparent increments on placebo being 2.7 (−1.3, 6.8)% and 3.4 (−1.0, 8.0)%, respectively.

Could the effect observed be accounted for by regression to the mean? The pre-treatment values for work required were greater ($P = 0.03$) in patients assigned to active than in those allocated to placebo (Table 2). A sub-group analysis was therefore performed on the data obtained under baseline conditions in those on active (8 patients) and placebo (8) treatments who showed no such difference in pre-treatment values. (The subgroup excluded patients assigned to active with pre-treatment values > the maximum in those allocated to placebo, and patients assigned to placebo with values < the minimum in those allocated to active.) The interaction between nature of treatment and time since treatment commenced remained significant ($P = 0.01$).

Tremor

There was a significant effect of time on tremor ($P = 0.03$), irrespective of test condition. Patients were deteriorating by 2.4 (C.I., 0.3, 4.6)% per 6 weeks. However, no significant interaction of nature of treatment with time was seen. In this analysis, adjustment was made for the within-patient covariates, room and hand temperature: the lower the room ($P = 0.02$), or the higher the hand ($P < 0.001$) temperature, the greater the infra-red signal detected.

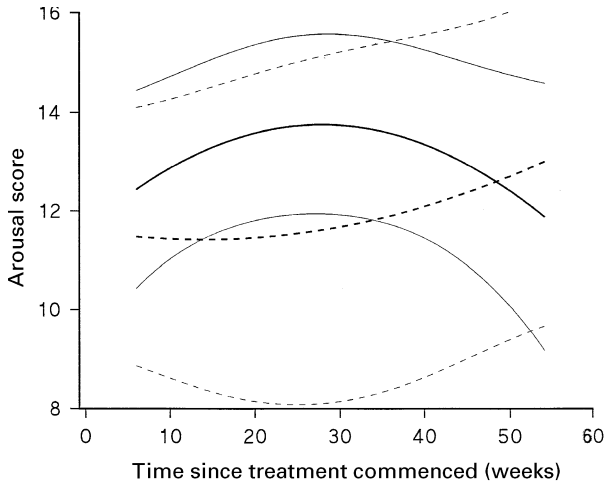

Fig. 4 Overall estimate of within-patient, quadratic time course for arousal, on active (——) and placebo (-----) treatment, in those (10 on active, 8 on placebo) who completed at least four, six-weekly assessments. The 95% confidence intervals are based on six assessments

Postural abnormality

There was no trend with time or interaction between nature of treatment and time for standing body sway.

Secondary outcome criteria

For arousal and stress scores, there was some evidence for an interaction between nature of treatment and a quadratic time trend ($P = 0.07$ and 0.06, respectively, with respect to the quadratic term). Further examination of arousal and stress showed significant quadratic time courses on active treatment only, the proportions of the within-subject variance explained by the quadratic term being small (6.7%, $P = 0.003$, for arousal; 3.4%, $P = 0.02$, for stress). There appeared to be tolerance to beneficial effects (increase in arousal and decrease in stress) of active treatment. However, with exclusion of the five patients who did not have at least four assessments during treatment, this finding withstood only for arousal ($P = 0.05$, Fig. 4).

No interaction between nature of treatment and time since treatment commenced was seen with respect to unwarned or warned reaction time, or the difference between them. Although a significant, albeit small, improvement in the affect score was found with time (0.046 (s.e. mean 0.017) per 6 weeks, $P = 0.007$), there was no evidence that it was specific to the active treatment.

Treatment effect on summary measures of outcome

Table 3 gives an overview.

Gait and posture

There was no significant interaction between nature of treatment and pre-treatment values for the summary measure of gait or body sway, and there was no direct treatment effect. Again no treatment effect was found on lying or standing blood pressure, or on postural fall.

Table 3 Treatment effect on summary measures

Characteristic	Contrast*	95% confidence interval	*P* value
Special physical			
Mean stride length (mm)	2.0	−66.5, 70.5	0.95
Mean[a] rigidity (N.m) **	0.79	0.56, 1.11	0.16
Mean[a] tremor (mm) **	0.84	0.61, 1.15	0.26
Mean body sway (°.min^{-1}) **	0.97	0.75, 1.26	0.82
Blood pressure (mm Hg)			
Lying	6.9	−2.2, 15.9	0.13
Standing	3.5	−5.0, 11.9	0.40
Postural fall	2.1	−2.9, 7.0	0.39
Psychometric			
Affect **	0.93	0.59, 1.48	0.76
Arousal	***	–	0.02
Stress	−1.34	−2.79, 0.12	0.07
Central processing time (ms) [b]**	1.00	0.87, 1.14	0.97
Psychomotor (ms) **			
Unwarned reaction time	***	–	0.01
Warned reaction time	***	–	0.01

* expressed as mean difference (for active treatment minus placebo), except where ** denotes ratio (for subjects receiving active treatment to those receiving placebo) obtained by the antilog of a difference on a log scale. Adjustment for pre-treatment values has been made

*** significant interaction between nature of treatment and pre-treatment value: *P* value relates to interaction.

[a] over all test conditions

[b] unwarned minus warned reaction time

Rigidity and tremor

There was no significant interaction between nature of treatment and pre-treatment values, nor any direct treatment effect, on the values for the summary measure of rigidity or tremor. No personal or environmental characteristics were identified as relevant to the between-subject analysis.

The test conditions did have a significant effect on the mean values, obtained during treatment, for tremor and (Fig. 5) for rigidity ($P < 0.001$ in each case): the response to physiological stimuli corresponded to that typically found on clinical examination. However, there was no significant interaction between nature of treatment and test condition in either case.

Psychometric and psychomotor variables

There was a significant ($P = 0.02$) interaction between nature of treatment and pre-treatment values for arousal: the lower the arousal score before treatment, the greater the effect of active treatment as compared with placebo. Interactions of this nature were also seen for warned and unwarned reaction times ($P = 0.01$ in each case): the longer the reaction time before treatment, the greater the shortening on active treatment. The findings suggest that, although the deficit of some individuals was being redressed by selegiline, a supranormal state was not being evoked. The treatment effect on reaction time was psychomotor rather than purely on the efficiency of cognitive processing: the difference between unwarned and warned reaction time [39] was not similarly affected.

For stress, there was no interaction between nature of treatment and pre-treatment value. Stress did tend to be less on active than placebo treatment, but this just failed to reach significance at the 0.05 level.

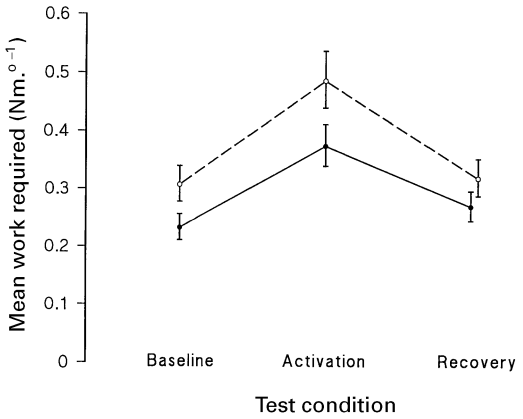

Fig. 5 Effect of test conditions on mean work required per unit angular displacement of the forearm. Mean values during treatment and 95% confidence intervals (based on the variance within-treatment, not that between-treatments) are given for patients on active (——) and placebo (-----) treatments. (There was no significant difference in the results of initial test sequence and repeat: the mean, under each condition, was used in the statistical analysis)

Congruency of objective and subjective assessments?

Brady/hypokinesia

Since stride length is the criterion for Webster's subjective assessment of gait, it is not surprising that objectively measured stride length explained much of the variance ($R_a^2 = 63\%$, $P < 0.001$) in the "gait" subscore.

Rigidity

The Webster sub-score for rigidity refers to activation only as being present or absent, and grades resting rigidity in the mid-line rather than in a limb: congruency between the objective measures of rigidity and the sub-score was, therefore, not suprisingly limited. The work required for unit displacement under baseline test conditions best reflected this sub-score ($R_a^2 = 16\%$, $P = 0.045$).

Physicians probably make a complex judgement on rigidity. In the multiple linear regression modelling for the subjective rating (see *Interpretation of primary outcome criteria*), candidate variables were age, body weight, gender, the Webster total score minus the rigidity sub-score, and work required under baseline conditions. Although, the final model explained (R_a^2) 49% of the variance in the rigidity sub-score, only total Webster score minus the rigidity sub-score ($P < 0.001$) and weight ($P = 0.01$) were selected. Thus, judgement may have been coloured by the global impression of the severity of parkinsonism. Weight, probably acting as a surrogate for muscle mass, did not appear to be adequately compensated for in the subjective assessment of pathological rigidity.

Tremor

The Webster sub-score for tremor, like the objective test, is based on amplitude. The correlation of objective assessment with sub-score was, indeed, significant ($P < 0.001$) for each of the five phases of the objective test. Moreover, when under provocation by the recall task, the objective test best explained ($R_a^2 = 79\%$) the variance in the sub-score: the sub-score specifies the 'maximum' tremor.

Postural abnormality

Standing body sway, a measure of instability, showed no evidence of congruency with the Webster sub-score for anatomical "posture", a quite different aspect of the postural abnormality.

Discussion

On selegiline treatment, rigidity gradually improved over the study period, whereas it tended to worsen on placebo. Rescue from a persistent insult could provide a simple explanation of this. There is evidence in rodents that selegiline might rescue neurones from damage inflicted by a discrete insult. In mice exposed to MPTP, followed by a wash out to allow for its metabolism and excretion, maintenance selegiline treatment resulted in reduction of cell death in the substantia nigra by nearly two-thirds [2]. Following axotomy of the facial nerve in 14 day old rats, those who received maintenance selegiline treatment showed a doubling of the number of motor neurones surviving compared with controls [3]. The authors suggest a neurotrophic factor-like action.

The significant interaction between nature of treatment and time since commencing treatment on rigidity could be interpreted as neuroprotection, but the superimposition of significant improvement with time on active treatment, rather than just attenuation of deterioration, requires an additional mechanism. A drawn out process of learning to relax is unlikely to be responsible, given the inital practice run, the acclimatisation period of each assessment and that the improvement on active treatment applied to activation as well as resting test conditions.

Levodopa therapy appears to have a selective effect on activated rigidity [51]: this suggests that the present findings do not simply represent a dopaminergic treatment effect. Moreover, most of the improvement in brady/hypokinesia, in previously untreated parkinsonians not receiving physiotherapy, appears to occur in the first week of maintenance levodopa therapy [52].

If neuroprotection prevents neuronal damage, rescue prevents damage progressing to clinical manifestations, and treatment masks those clinical manifestations, any rapid deterioration on stopping selegiline would more likely be due to withdrawal of treatment than of rescue, and to withdrawal of rescue than of neuroprotection. In subjects who had received selegiline, changes in tremor and rigidity ratings one month after withdrawal of therapy [13, 16] were worse than in those who had received placebo. Such a time course seems too rapid for loss of neuroprotection to result in clinical manifestations. Objective documentation of withdrawal is needed. Between-observer disagreement, within-observer carryover effect and difficulty dissociating the cardinal sign to be scrutinised from the general condition [35] may make subjective assessment an insensitive tool.

Little is known of the selectivity of medicinal interventions for, and interdependency of, the cardinal signs. A measure of brady/hypokinesia, stride length, is highly discriminant between those with and without Parkinsonism [53]. However, only a small deficit in it was seen in our patients by the end of the run-in: selegiline monotherapy did not reverse this. Body sway does not appear to have a simple, progressive time course from health to established disease, and was unaffected by selegiline. An alternative measure of the postural instability, foot separation during walking [54], may be of more value. All but one of the trial group exhibited the characteristic tremor. No effect of selegiline monotherapy was seen on postural tremor: rest and action tremor need investigation.

Using selegiline, it might be possible to avoid damage from continuing or repeated environmental insults, and interrupt or slow down vicious circles [21, 23, 25, 55, 56, 58–64]. Intervention would be desirable before there is a largely irreversible cycle of neurodegeneration. There is probably a long latency between insult and clinical diagnosis [7, 8, 23, 65, 66]: the 6-hydroxydopamine lesioned rat has a considerable capacity for compensation [67]. A measure of the tendency towards Parkinsonism might provide a marker of when and where to intervene, as well as an outcome criterion in the investigation of prophylaxis. It is feasible to define a pre-clinical state functionally, in terms of objective measures relating to the cardinal signs [53, 68]. A preclinical state might be detectable by brain imaging [23], but this is impractical for widespread screening and follow up. Genetic [69–71] or biochemical [61, 69, 72] markers might indicate susceptibility and complement a functional marker in targeting prophylaxis and investigating the aetiology.

The peak age for the diagnosis of idiopathic Parkinsonism is in the mid-seventies [28]. The small minority with disease of early onset [73] might be closer to an environmental insult and have suffered an intense exposure [73–75]. However, studies in this group might prove misleading as to the potential benefit of prophylactic intervention where there is chronic or episodic exposure [65, 74], and interaction between that exposure and age-related attrition of neurones [7, 8, 65].

The difference in time course between physical and psychometric responses to selegiline, found in the present study, suggests more than one mode of action. The initial increase in arousal, and its decline with time, on monotherapy with selegiline may explain, at least in part, the finding [13, 14, 16, 76, 77] that its benefit wanes in early and de novo Parkinsonism. Indeed, subjective ratings had been found to improve during the first three months only [13, 16], there being a nine month delay in the estimated median time to requiring levodopa. Moreover, could withdrawal from a psychometric action of selegiline explain the deterioration found in motor performance one month after its cessation? Tolerance may develop to a psychostimulant, and depression follow its withdrawal [78].

The psychostimulant effect of selegiline may relate to the parent drug, its metabolites, or to the build up of the “endogenous amphetamine” phenylethylamine, which is normally metabolised by monoamineoxidase B. The latter may have some direct dopaminergic effects, as well as the pre-synaptic, amphetamine-like action

[26]. Selegiline is metabolised to l-desmethyl selegiline and l-methamphetamine, both of which can be converted to l-amphetamine [26]. There is no reported racaemic transformation to the more psychoactive d-isomers, but l-metabolites might accumulate during chronic treatment [79]. The psychostimulant (and any affective or cognitive) effect could be mediated via inhibition of monoamineoxidase, or of neuronal catecholamine uptake, by the parent drug. There is a report [19] of psychological dependence.

Reduction in the serum noradrenaline concentration has been found with selegiline adjuvant therapy [19]: this is in keeping with the tendency to reduced stress in our patients on active treatment.

When selegiline is used alone in Parkinsonism, beneficial effects have been reported in relation to ratings of depression, or their progress with time [15, 20]. However, in depressed patients without Parkinsonism, higher doses are generally required [17, 18, 26]. Our patients were not depressed: no effect of selegiline was seen on the unipolar affect scale used. Using selegiline as adjuvant therapy, one group [80] found that motor performance improved more in depressed Parkinsonians, another [19] ascribed any benefit to an euphoriant effect.

As regards the cognitive deficits in parkinsonism, could intervention in a pre-clinical state be rewarding? Selegiline improves learning and memory defects associated with ageing in rats [6, 25, 26]. However, here the inefficiency of cognitive processing in newly diagnosed parkinsonism [39] was not improved by selegiline. Similarly, in a study of only five sufferers [81], selegiline monotherapy appeared to have no effect on the difference between simple and complex reaction times. Moreover, no difference has been found, between those receiving and not receiving selegiline, in the annual rate of decline in tests of attention, recall and storage [20]. In four Parkinsonian patients with progressive dementia, the results of adjuvant therapy were not encouraging [82].

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