L-deprenyl in Alzheimer's disease

Cognitive and behavioral effects

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Article abstract—*Background:* Short-term studies of L-deprenyl in Alzheimer's disease (AD) suggest a beneficial effect, whereas longer-term studies are less convincing. Accordingly, we undertook a 6-month, randomized, double-blind, placebo-controlled clinical trial to assess the potential benefit of L-deprenyl in AD. *Methods:* Sixty subjects were assigned to L-deprenyl (10 mg daily) or placebo. After 4 weeks of single-blind placebo, 51 subjects entered the double-blind phase. The Brief Psychiatric Rating Scale (BPRS) was the primary outcome measure. Secondary outcome measures were the Mini-Mental State Examination, Global Deterioration Scale, Alzheimer's Disease Assessment Scale (noncognitive), Cornell Scale for Depression in Dementia, Buschke Selective Reminding Test (BSRT), Relative's Assessment of Global Symptomatology-Elderly (RAGS-E), Controlled Oral Word Association Test, and Modified Continuous Performance Test. In addition, several exploratory tasks were included for future hypothesis testing. *Results:* We found no significant differences between the L-deprenyl and placebo groups on the primary or secondary measures. However, several measures appeared to be sensitive to change over time, including the total score on the BPRS and some of its components as well as parts of the BSRT and the RAGS-E. *Conclusion:* Oral L-deprenyl provides no detectable benefit on general behavior, neuropsychiatric symptoms, or cognitive function in AD after 6 months of treatment. Protocols for future drug studies should utilize measures that are sensitive to change over time such as the BPRS.

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A beneficial effect of L-deprenyl, a selective irreversible inhibitor of monoamine oxidase B (MAO-B) at doses up to 10 mg daily in humans,[1,2] has been reported in several studies in Alzheimer's disease (AD).[3-18] Mechanisms for possible therapeutic effects in AD include (1) enhancement of central monoamine systems through inhibition of MAO-B,[14] an enzyme that has increased activity in AD[19-23]; (2) stimulant effects of L-deprenyl and its metabolites, amphetamine and methamphetamine, on mood and arousal[12]; (3) neuronal protection caused by decreased production of oxidative free radicals by MAO-B inhibition[24]; and (4) neuronal rescue from cell death.[25]

Although eight of the studies reporting a beneficial effect of L-deprenyl in AD were double-blind, randomized controlled trials,[4,5,9,13-17] only three of these eight extended for more than 3 months. Burke et al.[15] studied 39 subjects over 15 months and found questionable improvement on one item of the Brief Psychiatric Rating Scale (BPRS). Koivisto et al.[16] and Riekkinen et al.[17] presented preliminary 18-month data from 67 subjects showing significant slowing of cognitive decline in patients on active treatment. The Mini-Mental State Examination (MMSE) scores in patients treated with L-deprenyl decreased 3.7 points, whereas scores in patients treated with placebo decreased 4.2 points. A 0.5-point difference on the MMSE is, however, of questionable clinical relevance. More recently, Sano et al.,[18] in a 2-year study of 341 patients, reported that treatment with selegiline (L-deprenyl) slowed functional deterioration but had no effect on cognitive measures.

We undertook a 6-month, randomized, double-blind, placebo-controlled trial to assess the benefit of L-deprenyl in AD. We selected the BPRS as the major outcome measure based upon reported improvement on BPRS factors related to mood and agitation.[5,12] Tariot et al.[5] reported a decrease in the total BPRS score from 40 to 35, which represented a 12.5% change after 4 weeks of treatment. We set a 20% change as our criterion for the effectiveness of treatment with L-deprenyl on the grounds that there might be either additional improvement in the L-deprenyl group when the treatment period is extended to 6 months, or there might be some deterioration in the placebo group during this period as the illness progressed. In addition to the BPRS, we in-

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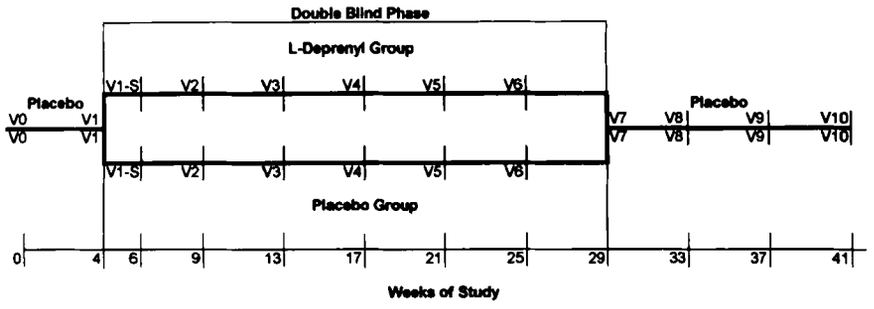

Figure. Schedule of follow-up visits. V = visit.

cluded measures of cognitive function, including the MMSE,[26] to provide a broad assessment of the effects of L-deprenyl. The results are reported here.

Methods. *Design.* This study was a single-center, randomized, placebo-controlled, double-blind clinical trial. The recruitment goal was 52 participants with a fixed follow-up period of 6 months. This sample size was expected to provide 90% power to detect a 20% change in total BPRS score for participants assigned to the L-deprenyl group compared with the placebo control group. The estimate of the variance of the difference in the means was obtained by imputation from information contained in the paper by Tariot et al.[5] following the procedure described by Midgley et al.[27] The study was approved by the Research Ethics Committee at Baycrest Centre for Geriatric Care, and informed consent was obtained in all cases.

Eligibility and randomization. Study subjects were recruited from the Behavioural Neurology Clinic at Baycrest Centre for Geriatric Care and from the practices of community- and university hospital-based physicians. Subjects were between the ages of 50 and 80 years and met NINCDS-ADRDA criteria[28] for probable AD. To determine eligibility of potential subjects, initial evaluation included a medical history, physical examination, CT, EEG, ECG, blood and urine tests, modified Hachinski Ischemic Scale,[29] Global Deterioration Scale (GDS) of Reisberg,[30] and MMSE. Screening blood tests consisted of CBC, ESR, blood urea nitrogen, liver function tests, VDRL, thyroid function tests, red blood cell folate, vitamin B_{12}, and serum electrolytes, creatinine, and calcium. There was no history of alcoholism, head injury, or psychiatric disorder. Multi-infarct dementia was excluded by a score of greater than 2 on the modified Hachinski Ischemic Scale.[29] CT of the head was normal or showed atrophy. EEG was normal or showed nonspecific slowing. Severity of dementia was rated with the MMSE[26] and the GDS.[30] MMSE inclusion criterion was a score of 10 to 23 inclusive, and GDS inclusion criterion was a score of 3 to 5 inclusive. All subjects spoke English fluently. The caregiver supervised administration of medication and acted as historian.

Upon completion of the admission procedure, which took up to 4 weeks, subjects were randomized to active drug or placebo group. A random-number table was used to generate an unpredictable assignment of sequences in blocks of six, with each block containing three series of L-deprenyl and three series of placebo. Randomization was stratified by gender. Draxis Health Inc. (formerly Deprenyl Research Ltd.) prepared 48 concealed, pre-randomized medication series labeled 1 to 48. The L-deprenyl tablets (5 mg) and placebo were identical in appearance. Subjects were assigned medication series in consecutive order from 1 to 24 (men) and 25 to 48 (women). Additional medication series were supplied to accommodate new recruitment due to dropouts and were labeled 49 to 54 for women and 55 to 60 for men. Patients, caregivers, and outcome evaluators were blinded to treatment assignment throughout the trial. Information about each randomization series was stored in separate opaque envelopes in the Baycrest pharmacy in case the code had to be broken.

Intervention procedure. All subjects who met the inclusion criteria completed cognitive and behavioral measures at baseline (visit 0, figure). They received placebo in single-blind fashion for the first 4 weeks and then entered the double-blind phase at visit 1. The active treatment group received L-deprenyl (5 mg) after breakfast for 7 days, followed by 10 mg after breakfast. There were 11 follow-up assessment visits, 28 days apart, except for supplementary visit 1 (1-S), which was at a 2-week interval and visit 2, which was at a 3-week interval. At visit 1-S, subjects were given a brief physical examination and assessed for adverse events. Upon completion of the 25-week double-blind phase, all subjects were placed single blinded on placebo until the end of the study (visit 10, week 41). Cognitive and behavioral measures were administered at each follow-up visit except 1-S. Blood and urine tests were carried out at visits 1-S, 4, 7, and 10. At each visit subjects returned their used bottles of medication, were interviewed for possible adverse events, and received new bottles of assigned tablets containing either active drug or placebo. Pill counts for returned bottles were recorded by the pharmacist. Subjects who withdrew before the beginning of the double-blind phase of the trial were replaced by patients of the same gender and were allocated the same medication series and identification number. Dropouts after the double-blind phase were not replaced.

Experienced research assistants administered the cognitive and behavioral measures. Although there were different raters throughout the study, all were trained and received ongoing supervision by the neuropsychologist on our team (D.R.).

Outcome measures. Primary outcome measure. The primary outcome measure was the change in the BPRS[31] score from baseline to end of treatment. The BPRS measures psychopathology and was selected as the major efficacy variable based on previous findings.[5,12] Higher scores indicate worse function.

Secondary outcome measures. Secondary behavioral and cognitive outcome measures were selected to assess mood, general behavior, memory, verbal fluency, attention, and functional capacity.

Behavioral measures. The Alzheimer's Disease Assessment Scale (ADAS) (noncognitive section)[32] evaluates depression, concentration, cooperation, psychotic disturbances, and motor activity. The Cornell Scale for Depression in Dementia (CSDD)[33] measures depression. The Relative's Assessment of Global Symptomatology-Elderly (RAGS-E)[34] samples psychiatric symptoms and behavior.

Cognitive measures. The Buschke Selective Reminding Test (BSRT)[35,36] evaluates short- and long-term memory as well as rate of learning.[37] Three different forms[38] were administered sequentially across successive test sessions. The order was the same across subjects. The Controlled Oral Word Association Test (COWAT)[39] measures verbal fluency for generating words beginning with a given letter or belonging to a category within 60 seconds. The Modified Continuous Performance Test (MCPT)[40,41] measures sustained attention or vigilance. A total of 300 letters were presented at a rate of one per second. Subjects were instructed to tap the table each time they heard the letter A. The MMSE[26] is a general measure of cognitive function. The GDS[30] stages cognitive and functional capacity.

Exploratory measures. We also incorporated additional exploratory measures for future hypothesis testing. These were not part of the pre-planned comparisons but were carried out to assist with future study designs related to L-deprenyl, and for other potential therapies in AD, by identifying tasks that are sensitive to mental status changes over relatively short time intervals. The variables included subcomponents of the primary and secondary measures, as well as the following measures: The Boston Naming Test (BNT)[42] measures naming ability. The Rey-Osterrieth Complex Figure Test (REY)[43,44] measures visuoconstructional ability and recall. The Digit Symbol (DS) is a subtest of the Wechsler Adult Intelligence Scale-Revised.[45] Subjects were required to fill in blank spaces under a number with the appropriate symbol. Incidental recall of digit-symbol pairs was also evaluated. The Recurring Faces Task (RFT) was designed by the study authors. Subjects were required to judge whether each of eight target faces was old or young. Fifty-four faces were then presented in three blocks of 18, each block containing the 8 target faces and 10 distracter faces. Subjects were asked whether they had seen the faces previously. A delayed recognition trial was also included.

Statistical analyses. Entry measures for age, education, the MMSE, time post-onset (TPO), and the GDS, as well as gender distribution, were compared between the two groups using unpaired *t*-tests for continuous variables and chi-square tests for discrete variables. For the outcome measures, baseline values represented the average of the variables assessed at visits 0 and 1, and the post-treatment values represented the average at visits 6 and 7. The change in total BPRS score from baseline was assessed using the paired *t*-test. The effect of L-deprenyl on the change was estimated using the *t*-test for independent samples. Thus the primary outcome analysis was the difference in the BPRS change between the two groups from baseline to the end of the double-blind phase of the study. The secondary and exploratory outcome measures were assessed using the repeated-measures analysis of variance (ANOVA) for appropriately distributed variables with mean performance scores across each of the visits 0 to 1, 2 to 3, 4 to 5, and 6 to 7, respectively, as dependent variables. The mean scores for pairs of consecutive visits were used to reduce the occurrence of missing data and the effects of day-to-day variability that characterize patients with AD. The post-treatment score for the REY was taken from visit 5 because this test was not administered at visit 6 or 7. Data of subjects who missed both visits 2 and 3 or visits 4 and 5 or variables not appropriately distributed for an ANOVA were analyzed using the unpaired *t*-test or Wilcoxon's rank sum test to compare the difference in group performance scores at visits 0 to 1 and 6 to 7. The data for men and women were pooled because there were no between-sex differences in performance scores. A p value of <0.05 indicated statistical significance for the primary outcome measure, and the Bonferroni convention was employed to correct for multiple comparisons for the secondary outcome measures ($p < 0.05 \div 8 = 0.00625$). Values in the report are expressed as mean ± SD unless otherwise stated.

***Table 1** Profile of subjects*

	Age (y)	Education (y)	TPO (y)	Initial MMSE	Initial GDS
L-deprenyl group (M = 13, F = 13)					
Mean	70.7	11.2	2.9	17.8	4.2
SD	6.5	3.4	1.6	3.5	0.7
Placebo group (M = 11, F = 14)					
Mean	70.0	10.9	2.7	18.5	3.9
SD	7.8	3.4	1.6	4.0	0.8

TPO = time post-onset; MMSE = Mini-Mental State Examination; GDS = Global Deterioration Scale; M = male; F = female.

Results. A total of 101 potential subjects from the community were assessed in the Behavioural Neurology Clinic, Baycrest Centre for Geriatric Care, Toronto, from 1990 to 1994. Thirty-six did not meet inclusion criteria. Sixty-five were offered entry, and 5 declined participation. Of the 60 subjects entered, 2 were subsequently removed. One subject's admission MMSE had been scored incorrectly, placing him above the cutoff, and the other had unreported alcoholism. Seven additional subjects terminated or withdrew while in the single-blind phase. Of these, six had been randomized to L-deprenyl and one to placebo.

Fifty-one subjects (24 men, 27 women) entered the double-blind phase. Eight withdrew during the double-blind phase (L-deprenyl, n = 7; placebo, n = 1). Two additional placebo subjects withdrew during the single-blind washout period in the final 12 weeks. Age, education, gender distribution, TPO of disease, and baseline MMSE and GDS scores were comparable in the L-deprenyl and placebo groups (table 1). Mean baseline and post-treatment performance scores on behavioral and cognitive measures are shown in tables 2 and 3. Missing data reflected withdrawal/termination or inability to complete tests.

Seven of the eight dropouts in the double-blind phase were from the L-deprenyl group ($p = 0.05$, Fisher's exact test). For all dropouts, the caregiver gave a plausible reason for withdrawal that was unrelated to any adverse effect of medication.

Table 2 *Performance scores on primary and secondary measures*

	L-deprenyl			Placebo		
	n*	Baseline mean (SD)	Post-treatment mean (SD)	n*	Baseline mean (SD)	Post-treatment mean (SD)
BPRS	21	23.8 (3.5)	24.8 (4.0)	24	24.0 (3.3)	25.8 (6.0)
MMSE	21	17.3 (3.7)	17.3 (5.1)	24	18.4 (4.4)	18.5 (6.2)
GDS	21	4.3 (0.8)	4.4 (0.9)	24	3.9 (0.8)	4.0 (0.8)
BSRT†	20	20.4 (9.4)	20.4 (10.5)	22	24.5 (11.7)	23.2 (12.6)
COWAT	21	26.6 (17.2)	22.4 (15.8)	22	28.4 (15.3)	28.0 (18.4)
MCPT	16	23.4 (4.4)	24.6 (2.0)	18	24.6 (3.0)	24.6 (1.8)
CSDD	21	3.1 (1.9)	2.6 (1.9)	24	3.3 (2.3)	3.2 (3.0)
ADAS	21	3.4 (2.3)	2.7 (2.3)	24	3.7 (3.1)	4.3 (4.0)
RAGS-E	21	38.1 (7.9)	37.6 (9.6)	24	39.3 (8.8)	39.0 (11.1)

* Missing values due to dropouts or inability to complete task.
† Free recall, trials 1–8.

BPRS = Brief Psychiatric Rating Scale; MMSE = Mini-Mental State Examination; GDS = Global Deterioration Scale; BSRT = Buschke Selective Reminding Test; COWAT = Controlled Oral Word Association Test; MCPT = Modified Continuous Performance Test; CSDD = Cornell Scale for Depression in Dementia; ADAS = Alzheimer's Disease Assessment Scale; RAGS-E = Relative's Assessment of Global Symptomatology-Elderly.

Primary outcome measure. The difference in the BPRS change between post-treatment and baseline scores was 1.02 ± 2.9 (mean ± SD) in the L-deprenyl group and 1.79 ± 4.5 in the control group. Because the difference was not normally distributed, logarithmic transformation of the data was undertaken for statistical inference testing. This revealed no significant difference between groups ($p = 0.6$), and the 95% confidence interval (for the untransformed data) was −3.02, 1.48.

Secondary outcome measures. Repeated-measures ANOVA showed no significant group × time interaction on the RAGS-E, ADAS, MMSE, CSDD, BSRT, or COWAT. On the BSRT and COWAT, the ANOVA excluded some subjects who had missing values due to an inability to complete the task between visits 2 to 5. To compare the difference in group performance between visits 6 to 7 and 0 to 1, *t*-tests were also performed for these variables. No significant differences were found. For the GDS and MCPT, there was no significant group difference (Wilcoxon's rank sum test).

Exploratory outcome measures. Analyses related to the primary outcome measure (BPRS) will be presented separately from analyses related to the other measures. Because of multiple comparisons, a p value <0.05 for the exploratory analyses must be interpreted with caution.

General results. There were no significant group effects on any exploratory measure except for a difference on the delayed recall condition of the BSRT favoring the L-deprenyl group ($p = 0.003$, Wilcoxon). However, the total number of words recalled on the BSRT was one or less at baseline and after treatment in the L-deprenyl and the placebo groups (baseline/post-treatment: 0.25/0.45 [L-deprenyl]; 1.0/0.69 [placebo]).

There was a suggestion of a group × time interaction on the delayed recognition of the BSRT ($p = 0.04$) and on verbal fluency for generating words beginning with the letter L ($p = 0.03$) (repeated-measures ANOVA). A polynomial transformation, however, showed that the linear effect was not significant for either measure. For delayed recognition on the BSRT, there was a cubic effect ($p = 0.01$), and for verbal fluency for generating words beginning with the letter L there was a quadratic effect ($p = 0.003$).

Factor analyses of the BPRS, CSDD, and RAGS-E. *BPRS.* In previous studies, the effects of L-deprenyl on factors comprising the BPRS[5,12,15] using one of two factor structures[46,47] were examined. We analyzed the performance on the BPRS using both sets of factors and found only a borderline group difference favoring the L-deprenyl group at 5 to 6 months on an Anxiety-Depression factor[47] ($p < 0.05$) and on Item 1 (somatic concern) ($p = 0.05$). Because of multiple comparisons, these differences were not considered important.

CSDD and RAGS-E. There were no significant group differences on factors of the RAGS-E or CSDD.

Sensitivity of measures to change over time. *BPRS.* Data from the L-deprenyl and placebo groups were collapsed because there was no significant difference between the two groups on the BPRS. A paired *t*-test was used (on the logarithmically transformed data) to compare the mean performance scores at visits 6 to 7 with those at visits 0 to 1 ($p < 0.05$). The mean change in scores over the course of the study was 1.43 ± 3.8, and the 95% confidence interval was 0.29, 2.58 (untransformed data). Each of the factors on the BPRS were analyzed separately to determine whether there was any deterioration in scores on these measures during the study (table 4). There was a significant deterioration over time (Wilcoxon's signed rank test) on two factors using the classification by Guy et al.[47]—Anergia and Thought Disturbance. Using the classification by Overall and Beller,[46] the Cognitive Dysfunction factor showed a significant deterioration over time. Individual item scores that changed over time were Item 4 (conceptual disorganization) and Item 18 (disorientation). Item 2 (anxiety) showed borderline improvement.

Table 3 *Performance scores on exploratory measures*

	L-deprenyl			Placebo		
	n*	Baseline mean (SD)	Post-treatment mean (SD)	n*	Baseline mean (SD)	Post-treatment mean (SD)
Facial recognition						
Immediate	14	14.0 (4.9)	12.9 (6.5)	19	14.8 (6.9)	13.8 (8.4)
Delayed	14	4.1 (2.8)	3.9 (2.6)	17	5.2 (2.3)	4.8 (2.6)
REY figure						
Copy	16	14.0 (9.6)	14.3 (10.8)	11	21.7 (9.2)	19.4 (9.5)
Immediate	16	2.4 (2.9)	4.0 (4.9)	10	2.8 (2.9)	4.7 (6.2)
Delayed	16	1.0 (2.6)	1.6 (3.9)	10	0.3 (0.5)	0.8 (1.4)
Digit symbol						
Score 90 sec	5	27.6† (16.9)	28.4† (18.6)	9	20.8† (10.3)	20.6† (11.5)
Incidental Learning	3	2.0† (2.0)	1.7† (2.9)	7	0.6† (1.5)	1.6† (3.4)
BNT	16	26.1 (15.0)	24.2 (14.5)	23	30.1 (15.4)	27.3 (16.7)
BSRT						
Trials 1–4	21	8.8 (3.8)	8.5 (4.6)	24	10.0 (5.7)	10.0 (6.5)
Trials 5–8	20	11.6 (5.8)	11.3 (6.4)	22	13.6 (6.5)	12.2 (7.0)
Immediate storage	20	18.3 (8.5)	18.6 (9.5)	22	20.9 (9.5)	19.3 (10.1)
Long-term storage	20	2.1 (2.4)	1.8 (1.9)	22	3.6 (3.3)	3.9 (3.3)
BSRT delay condition						
Delayed recall	20	0.3 (0.4)	0.5 (0.7)	21	1.0 (1.5)	0.7 (1.0)
Intrusions	20	0.2 (0.5)	0.3 (0.6)	21	0.7 (1.3)	0.6 (1.0)
Recognition	19	6.7 (2.7)	7.0 (2.4)	21	7.3 (2.4)	7.1 (2.5)
COWAT						
C, L (total)	21	12.5 (9.3)	11.5 (8.8)	23	12.4 (8.8)	12.7 (9.0)
Animals	21	6.2 (4.3)	4.8 (3.6)	23	7.2 (3.5)	6.9 (5.0)
First names	21	7.8 (4.9)	6.2 (4.6)	24	7.9 (5.0)	7.4 (5.6)

* Missing values due to dropouts or inability to complete task.
† Too few observations for analysis.

REY = Rey-Osterrieth Complex Figure Test; BNT = Boston Naming Test; BSRT = Buschke Selective Reminding Test; COWAT = Controlled Oral Word Association Test; C, L (total) = total number of words generated beginning with the letters C and L.

The Agitation factor, which included Item 2, also showed a borderline improvement.

Secondary and exploratory measures. The sensitivity of the measures to change over time was analyzed using repeated-measures ANOVA across visits 0 to 1, 2 to 3, 4 to 5, and 6 to 7 for appropriately distributed variables. For other variables we used a *t*-test or Wilcoxon's signed rank test to compare the mean performance scores at visits 6 to 7 with those at visits 0 to 1. Because there were no clearly significant differences between the L-deprenyl and placebo groups on any measures after taking into account the multiple comparisons, we merged the groups for the *t*-tests and signed rank tests.

There was a significant main effect for time on delayed recall on the RFT ($p = 0.004$) and a borderline effect on recall on the BSRT for trials 5 to 8 ($p = 0.05$). A polynomial comparison showed a linear effect for the BSRT ($p = 0.02$) as well as a cubic effect ($p = 0.04$). There was a quadratic effect for the RFT ($p = 0.001$). There were also suggestive main effects for time on the BSRT-immediate storage ($p = 0.02$), RAGS-E ($p = 0.04$), and verbal fluency for the letter C ($p = 0.03$), but these effects were nonlinear. The effect was cubic for the BSRT-immediate storage ($p = 0.04$), quadratic for the RAGS-E ($p = 0.006$), and cubic for verbal fluency for the letter C ($p = 0.006$). There was a suggestion of improvement over time on the delayed recall of the REY ($p = 0.02$; Wilcoxon).

On the RAGS-E, each item reflects a factor.[34] Only Item 1, which is related to needing help for personal care and appearance, suggested deterioration ($p = 0.02$, Wilcoxon). We analyzed the CSDD using five factors as well as individual items.[33] None of the factors showed a significant change, whereas the item related to anxiety suggested improvement ($p = 0.01$, Wilcoxon).

Missing data. Missing data at post-treatment assessment were due to withdrawal/termination or inability of subjects to complete the tests. The proportion of patients in these categories did not differ significantly between the L-deprenyl and placebo groups. Because these patients were not represented in the above analyses, we carried out the following two additional analyses to capture data from these subjects:

Table 4 BPRS factors and items showing sensitivity to change over time

	Sample size	Mean change*	SD	*p* Value
Factor				
Anergia	45	0.81	1.73	0.003
Thought disturbance	45	0.79	1.12	0.0001
Cognitive dysfunction	45	1.39	2.04	0.0001
Agitation	45	−0.31	1.05	0.05
Items				
Conceptual disorganization	45	0.76	1.15	0.0001
Disorientation	45	0.63	1.15	0.0004
Anxiety	45	−0.27	0.92	0.05

*Positive indicates deterioration; negative indicates improvement.

(1) Post-treatment outcome was taken as mean performance scores across visits 3 to 7 and compared with mean baseline scores across visits 0 to 1. This analysis assessed the effects of L-deprenyl at 2 or more months of treatment. There were no significant differences between the L-deprenyl and placebo groups on any behavioral or cognitive measures.

(2) Patients who became untestable on selected cognitive measures during the study were assigned a score of 0 on these tests. This procedure was applied to cognitive measures on which low scores indicated a poorer performance and where 0 was the worst possible score.

There were no significant differences between the L-deprenyl and the placebo groups on any cognitive measure except for delayed recall on the BSRT ($p = 0.006$, Wilcoxon). The mean number of words recalled was less than one at baseline and after treatment in the L-deprenyl and the placebo groups (baseline/post-treatment: 0.29/0.43 [L-deprenyl]; 0.96/0.60 [placebo]).

Adverse events. Table 5 shows the percentage of patients in the L-deprenyl and placebo groups who experienced adverse events. No subject was withdrawn from the study because of adverse events.

Compliance. The average percentage of scheduled pills taken by the subjects in each group was greater than 95% at each visit.

Discussion. The design of our study was aimed primarily at assessing the effects of L-deprenyl on the BPRS after 6 months of treatment. The sample size at completion of the double-blind treatment phase was sufficient to detect a 20% change in the total BPRS score with a power of 85%. By this criterion, we did not detect a benefit of L-deprenyl on the BPRS. In addition, we did not demonstrate a difference in any of the secondary outcome measures of mood, general behavior, functional capacity, memory, attention, and verbal fluency.

For the BPRS, exploratory analyses revealed a borderline effect of L-deprenyl on the Anxiety-Depression factor (Items 1, 2, 5, 9)[47] and on Item 1, which deals with somatic concern. Because of multiple statistical comparisons, we do not attribute importance to these findings. In their 15-month trial, Burke et al.[15] found a slight effect of L-deprenyl on the BPRS. They were reluctant to attach much significance to this finding because of a small effect size, a possible chance association due to multiple comparisons, and because improvement was found only on a single item of the BPRS (disorientation) and not on any factors of this test. In support of their conclusion, the performance scores on the disorientation item in our study failed to show any effect of L-deprenyl. In contrast, short-term studies by Schneider et al.[12] and Tariot et al.[5] found a significant improvement on the BPRS after 4 weeks of treatment with L-deprenyl. The latter study was a double-blind placebo-controlled serial trial.[5] The subjects in both studies were less impaired on the BPRS than those in our sample. In addition, the patients studied by Schneider et al.[12] were more impaired than our subjects on the MMSE (mean MMSE score 9.4 ± 7.4 versus 17.2 ± 4.0). The discrepancy between our results on the BPRS and previous short-term studies[5,12] may be due to differences in profile of the patients studied.

In the exploratory analyses, there was a slight difference between the L-deprenyl and the placebo groups on delayed verbal recall on the BSRT. This difference, however, represented an average of less than one word recalled. Moreover, the total number of words recalled was one or less in both groups. The effect is therefore not clinically meaningful. In addition, caution must be applied in interpreting the statistical significance in this case because of the multiple comparisons. Also, there was a suggestion of a group difference on delayed recognition on the

Table 5 Percentage of subjects with adverse events during double-blind phase

Event	L-deprenyl group (n = 26)	Placebo group (n = 25)
Dizziness	30	20
Irritability	23	16
Insomnia	15	16
Restlessness	19	12
Mood changes	19	16
Hallucinations	8	20
Confusion	50	52
Shakiness	4	8
Headaches	12	20
Palpitations	4	4
Bowel problems	15	8
Dry mouth	27	12
Change in appetite	8	8
Weight loss	8	12
Rash	4	4
Impotence	4	4
Other problems	0	12

BSRT and verbal fluency for the letter L, but the effects for these measures were not linear. Again, caution must be applied in interpreting the statistical significance of these exploratory analyses because of multiple comparisons.

Delivery route of L-deprenyl. L-deprenyl promotes neuronal rescue from cell death caused by apoptosis,[48,49] a process that may be important in AD.[50-52] L-deprenyl is metabolized mainly in the liver to L-desmethyldeprenyl, L-methamphetamine, and L-amphetamine.[53-56] Recent data from Tatton et al.[48] suggest that L-desmethyldeprenyl is the active molecule that induces a decrease in apoptosis. The action of L-deprenyl is, however, antagonized by L-methamphetamine and L-amphetamine.[48,57,58] This antagonism is reduced by subcutaneous, as compared with oral, administration in animal models.[59] This is presumably due to first-pass delivery[60] of L-deprenyl to the brain instead of initially passing through the liver. We cannot rule out the possibility that oral administration of L-deprenyl in our study was a factor in producing negative results. Further research will be required to address this issue, including possible studies of transdermal L-deprenyl in AD.

Measures for future studies. Many subjects were too impaired for several cognitive tests, especially toward the end of the study. These included the MCPT, REY, RFT, BNT, and DS. Although these measures provide useful information in clinical settings, they are too difficult for drug studies using the MMSE entry criterion of 10 to 23 inclusive and GDS entry criterion of 3 to 5 inclusive. In contrast, most subjects could complete the BSRT and COWAT, suggesting that these measures are appropriate for trials with more severely impaired patients. However, attention should be paid to length of test administration when designing future protocols. The BSRT and COWAT required up to 10 to 20 minutes each to administer, and subjects required more coaxing and rest breaks. These measures should not be scheduled for the same visit.

Measures of cognition, mood, and behavior should be sensitive to change over short time periods for drug trials in AD, especially those focusing on slowing progression of disease. Although sensitivity of measures to change depends upon severity of dementia,[61] the majority of measures in our study did not show significant change over the 6-month treatment phase. The exceptions were the total score on the BPRS, as well as some of its components. There was also a suggestion of change on free recall on trials 5 to 8 of the BSRT and Item 1 of the RAGS-E dealing with help caring for personal needs and appearance. The BPRS, BSRT, and first item of the RAGS-E may be useful for short-term drug studies designed to slow progression of disease. The MMSE, ADAS (noncognitive section), GDS, CSDD, MCPT, BNT, REY, and DS may not be suitable for detecting progression of disease in trials extending only 6 months with subjects comparable with our patients.

In addition, there was a suggestion of change on delayed recall on the RFT, BSRT-immediate storage, RAGS-E, and verbal fluency for the letter C. However, these effects were nonlinear and difficult to interpret, especially in view of the multiple statistical comparisons.

Dropout rate. More subjects in the L-deprenyl, as compared with the placebo group, withdrew from the study. Because of the small number of subjects, the level of significance ($p = 0.05$) should be considered borderline because even one additional dropout in the placebo group would have affected the level of significance. Caution should be exercised in drawing conclusions related to the role of active drug in the dropout rate. Moreover, in each case the caregiver gave a plausible reason for withdrawal that was unrelated to any adverse effect of medication, suggesting a play of chance.

Adverse events. Comparison of the percentage of patients reporting adverse events on L-deprenyl compared with placebo showed the greatest between-group difference for dry mouth. This supports the finding of the DATATOP study in Parkinson's disease[62] in which the adverse experience of dry mouth was significantly different between subjects receiving L-deprenyl and those not receiving this drug.

Conclusion. Oral L-deprenyl provided no detectable benefit on general behavior, neuropsychiatric symptoms, or cognitive function in our population with AD after 6 months. In the course of the study, we gained insights that might improve selection of measures for assessing efficacy of drug treatment in dementia. These measures should apply to a broad range of cognitive impairment, allowing for deterioration of subjects during the trial, be sensitive to change over short periods of time, and be simple enough for most subjects to complete. Although the BPRS and parts of the BSRT and RAGS-E may be sensitive, few measures satisfied all three criteria. Protocols for future drug studies in AD should focus on measures that are sensitive to change, can be carried out by patients undergoing progressive cognitive decline, or depend upon caregiver reports.

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