A randomized, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment

The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders*

Artice abstract—Cognitive impairment is a frequent manifestation of advanced human immunodeficiency virus (HIV) infection. The response to antiretroviral medication is often partial and poorly sustained. Recent studies suggest that free radical production within the CNS and neuronal apoptosis may play important roles in the pathogenesis of HIV dementia. We conducted a randomized double-blind, placebo-controlled trial using a parallel group, 2 × 2 factorial design evaluating deprenyl, a monoamine oxidase B inhibitor and putative anti-apoptotic agent, and thioctic acid, an antioxidant, in 36 patients with HIV-associated cognitive impairment. Both deprenyl and thioctic acid were well tolerated with few adverse events. Deprenyl recipients showed significant improvement on tests of verbal memory compared with patients not taking deprenyl. Thioctic acid treatment did not improve cognitive function. These results suggest that deprenyl treatment is associated with cognitive improvement in subjects with mild HIV-associated cognitive impairment, whereas thioctic acid has no benefit. A larger efficacy trial is needed to assess the long-term effect of deprenyl on cognitive performance in patients with HIV infection.

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Human immunodeficiency virus type 1 (HIV-1)-associated dementia complex (HIV dementia) occurs in 15 to 20% of acquired immunodeficiency syndrome (AIDS) patients and is characterized by cognitive impairment, motor dysfunction, and behavioral changes.[1-5] The cognitive impairment includes mental slowing, forgetfulness, and poor concentration. Motor symptoms include loss of fine motor control, clumsiness, unsteady gait, and tremor. Behavioral changes include apathy, lethargy, and depression.[2,3,6] HIV dementia is usually a rapidly progressive disorder with a mean survival of about 6 months,[2] although recently, patients with slower progression or a stable course have been identified.[7] HIV-1-associated minor cognitive motor disorder, a milder syndrome, is estimated to occur in 25% of patients with symptomatic HIV infection.[8]

Few available antiretroviral agents have been studied for the treatment of HIV dementia. Open label studies with zidovudine (ZDV) in demented patients showed improvements in clinical functioning, neuropsychological performance, and neuroimaging studies.[9] ZDV, in a placebo-controlled blinded study, also improved neuropsychological function in AIDS or AIDS-related complex patients without dementia.[10] The only placebo-controlled trial of ZDV in HIV dementia demonstrated the greatest neurocognitive improvement only with very high dosages (i.e., 2,000 mg/day).[11] Unfortunately, the response to ZDV treatment may be short-lived or associated with intolerable side effects and therefore often unsatisfactory. There is very limited information about the therapeutic effects of other antiretroviral medications (e.g., dideoxynucleosides)[12] or protease inhibitors.

Neurotoxins from HIV-infected activated macrophages or microglia interacting with astrocytes may play a central pathogenetic role in HIV dementia.[13,14] Putative neurotoxins include cytokines (tumor necrosis factor alpha [TNF-α]) and oxygen radicals.[2,15] Both TNF-α and hydroxyl free radicals may stimulate apoptosis (programmed cell death), and apoptotic neurons have been demonstrated in the cerebral cortex and basal ganglia of both children and adults with HIV encephalitis.[16,17]

We hypothesized that these indirect mechanisms of neuronal injury could be modified by deprenyl and thioctic acid to improve or even prevent HIV-associated cognitive impairment. Deprenyl, a selective monoamine oxidase type B inhibitor, at very low dosages in in vitro and in vivo systems has a trophic

*Members of the Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders and their affiliations are listed in the Appendix on page 650.

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effect on injured neurons.[18-21] Thioctic acid is a naturally occurring enzymatic cofactor for pyruvate dehydrogenase and alpha oxoglutarate dehydrogenase and scavenges harmful hydroxyl radicals and other reactive oxygen species.[22,23]

We conducted a randomized, double-blind, placebo-controlled clinical trial of deprenyl and thioctic acid to assess their safety and tolerability and to assess their impact on HIV-associated cognitive impairment in HIV seropositive (HIV+) patients.

Methods. *Organization.* This multicenter study was organized by the Charles A. Dana Foundation Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders (Columbia University, Johns Hopkins University, University of Rochester) and was sponsored by the Charles A. Dana Foundation (New York, New York). The study was approved by the institutional review board at each center. An independent safety monitoring committee periodically reviewed the safety of the study.

Recruitment and enrollment. Thirty-six eligible subjects were enrolled in the trial. Inclusion criteria were HIV infection (confirmed by ELISA or Western blot), evidence of cognitive impairment (defined as performing at or below 1 SD from the mean on at least two neuropsychological tests or 2 SD below the mean on at least one test), a stable antiretroviral regimen for 6 weeks before randomization, an age of 18 years or older, and capability of giving informed consent. Neuropsychological test scores for subjects with 12 years of education or less were compared with norms established by the AIDS Link to Intravenous Experience study.[24] For subjects with more than 12 years of education, norms established by the Multicenter AIDS Cohort Study[25] were used. Patients were excluded if they had a past or present history of opportunistic CNS infection or CNS neoplasm, severe premorbid psychiatric illness likely to interfere with protocol compliance, history of chronic neurologic disorder unrelated to HIV infection, any clinically significant condition or laboratory abnormality that in the investigator's opinion would interfere with the subject's ability to participate in the study, or use of meperidine or any monoamine oxidase inhibitor within 14 days before the baseline visit. Active use of illicit drugs was not exclusionary. However, individuals were screened for the stability of drug use and the likelihood that such use would continue throughout the study.

Study design and randomization. A randomized, double-blind, placebo-controlled, 2 × 2 factorial design was used. Subjects were randomly assigned to one of four treatment groups: placebo, deprenyl alone, thioctic acid alone, or both deprenyl and thioctic acid. The computer-generated randomization plan included stratification by center and blocking to ensure an approximately equal distribution of subjects among the four treatment combinations within each center. Assignment to treatment was performed through a call-in computer enrollment module that maintained the blindness of treatment assignment for all subjects and staff involved in the study.

Therapy and follow-up. Subjects in either of the two deprenyl groups (deprenyl alone or deprenyl and thioctic acid) took 2.5 mg orally three times a week. Subjects in either of the two thioctic acid groups (thioctic acid alone or thioctic acid and deprenyl) took 600 mg orally twice daily (Asta Medica AG, Dresden, Germany). Subjects in the placebo group took the same number of matching placebo tablets as the active treatment groups. The thioctic acid was taken in the morning and evening with 8 ounces of water approximately 1 hour before meals. Deprenyl was taken in the morning on Monday, Wednesday, and Friday.

After randomization, subjects were reevaluated at 2, 4, and 10 weeks. At each visit, subjects were assessed for adverse clinical experiences. A battery of safety surveillance laboratory tests was performed and included urinalysis, hematology (CBC and differential), and serum chemistry profiles (routine electrolytes, calcium, phosphate, liver function tests, albumin, total protein, and uric acid). Clinical assessments included vital signs, Karnofsky Performance scale,[26] and pill counting to assess compliance. Neuropsychological evaluation included the Rey Auditory Verbal Learning Test,[27] Digit Symbol Test,[28] Grooved Pegboard (dominant and nondominant hands),[29] timed gait, and California Computerized Assessment Package (Cal Cap) reaction time test[30] and was performed at baseline and at 4 and 10 weeks. The Cal Cap reaction time test, a measure of psychomotor speed, has two portions: choice and sequential. In the choice part, the subject is shown a series of numbers on a computer screen and is asked to press a button when the number "7" is displayed. In the sequential part, the subject is again shown a series of numbers on a computer screen, and the subject is asked to press a button when the next sequential number is the same as the previous number. An overall clinical impression of cognitive functioning was also graded as normal, mild, moderate, or severe. A functional assessment, including activities of daily living (ADLs) on the Personal Self Maintenance Scale,[31] instrumental ADLs of Lawton and Brody,[32] and the role functioning and physical function scales of the Medical Outcomes Study,[33] was performed at baseline and at 4 and 10 weeks. An assessment of mood using the Center for Epidemiologic Studies Depression Scale (CES-D)[34] was also performed at these three visits. A neurologic examination, including the motor component of the Unified Parkinson's Disease Rating Scale,[35] CD4+ lymphocyte count, and a serum beta-2 microglobulin level, was performed at baseline and at 10 weeks.

The investigator was permitted to suspend the experimental medications if the subject developed persistent or recurrent adverse experiences with an intensity rated as moderate (sign or symptom intense enough to interfere with usual activity) or severe (sign or symptom interferes significantly with ability to do work or usual activity). If the adverse experience improved, the subject was rechallenged at one-half of the dosage before returning to the full dosage. If an adverse experience was judged to be severe and persistent, the subject was withdrawn from the study.

Outcome measures. The primary outcome measure of the study was whether or not the subject completed the study on the originally assigned dosage of experimental medications, regardless of whether or not a dosage suspension occurred during the study. Secondary measures included whether or not the subject completed the study without a dosage suspension and whether or not the subject completed the study. Measures of safety included frequencies of adverse experiences and abnormal results on laboratory tests and changes over time in laboratory tests and vital signs. Measures of efficacy included 4- and 10-

Table 1 *Subject characteristics at baseline*

	Placebo (n = 9)	Deprenyl (n = 9)	Thioctic acid (n = 9)	Both (n = 9)
Age* (y)	38.5 ± 6.7	40.6 ± 7.0	43.7 ± 11.6	42.1 ± 10.1
Education* (y)	13.7 ± 3.8	12.7 ± 3.3	15.0 ± 3.7	12.0 ± 1.8
Male gender (%)	77.8	66.7	66.7	77.8
Race (%), white/black/hispanic	44/33/22	55/33/11	44/44/11	78/22/0
Overall clinical impression (no. of patients), normal/mild/moderate/severe	0/2/6/1	1/6/2/0	2/5/1/1	0/9/0/0
Years since HIV+ test*	4.6 ± 3.5	5.3 ± 3.0	6.6 ± 3.3	6.3 ± 2.4
CD4+ count*	244.3 ± 304.4	221.7 ± 136.3	197.4 ± 118.2	168.0 ± 149.5

* Values are means ± SD.

week changes from baseline in neuropsychological test results, neurologic examination results, and measures of function and mood.

Sample size considerations. The sample size of 18 subjects per treatment group (e.g., deprenyl versus no deprenyl) was chosen to provide approximately 88% power to detect a 45% difference in tolerability (95% versus 50%) between the two groups, using a one-sided Fisher's exact test at the 5% level of significance. The same applies to the comparison of the thioctic acid and no thioctic acid groups. It was thought that if approximately 50% of the subjects assigned to an active treatment group could tolerate the assigned dosage, then this medication would be considered a reasonable candidate for further investigation, given the inexorable progression of HIV dementia and the lack of any available effective long-term treatment. These calculations assumed no statistical interaction between deprenyl and thioctic acid with regard to the primary tolerability measure, an assumption supported by the minimal side-effect profiles of the two drugs.

Statistical methods. In accordance with the intention-to-treat principle, all 36 subjects were included in the primary statistical analyses. The proportion of subjects unable to tolerate the experimental medications was compared among the groups (deprenyl versus no deprenyl; thioctic acid versus no thioctic acid) using one-sided Fisher's exact tests, modified using the mid probability value.[36] Similar analyses were performed for the secondary tolerability measures and for the incidences of adverse experiences and abnormal laboratory tests.

Analyses of the efficacy variables used a three-way ANOVA model, with 10-week change from baseline in the variable of interest as the dependent variable, deprenyl (yes/no) and thioctic acid (yes/no) as the factors of interest, and investigator as the stratification factor. F tests were performed for significance of each of the main treatment effects, and 95% CIs for these effects were also computed. The assumption of no statistical interaction between deprenyl and thioctic acid was checked descriptively by examining group means and formally by adding the interaction term to the above model and testing for its significance. All analyses were repeated considering the 4-week change from baseline as the dependent variable. Similar analyses were performed for changes in laboratory test results, vital signs, and HIV markers. Variables that seriously violated the assumption of normality (e.g., CD4+ count) were transformed using the natural logarithm for purposes of statistical analysis.

Analyses of efficacy variables were repeated using an ANCOVA model similar to the ANOVA model above, except that the baseline value of the variable of interest was included as an additional covariate.

For subjects who prematurely dropped out of the study, the last available observation recorded for the subject was carried forward for all subsequent visits for purposes of the primary statistical analyses. Separate additional analyses were performed that included only subjects who did not prematurely drop out of the study. However, the results of these analyses did not differ substantially from those of the primary analyses and hence are not reported here.

Results. *Comparability of treatment groups at baseline.* The four treatment combinations were very similar in terms of age, education, gender, race, estimated duration of HIV infection, and CD4+ count as shown in table 1. Despite the randomization for treatment assignment, most subjects in the placebo group had a moderate neuropsychological deficit according to the overall clinical impression, whereas most subjects in each of the three active treatment groups had a mild cognitive deficit. The overall clinical impression ratings of mild impairment corresponds with HIV dementia stage 0.5 and of moderate impairment with HIV dementia stage 1.[37] The placebo group tended to perform more poorly than the three active treatment groups for each of the neuropsychological tests. Neurologic examination, depression, and functional measures were distributed similarly among the four treatment groups.

Tolerability and safety measures. Both deprenyl and thioctic acid were well tolerated. There were no significant differences among the four treatment groups regarding the primary and secondary measures of tolerability. Three of nine subjects in the placebo group did not complete the study (one subject was withdrawn from the study by the investigator because of noncompliance and illicit drug use, one subject refused any treatment immediately after randomization, and one subject was lost to follow-up after baseline). In the deprenyl-alone group, only one of nine subjects did not complete the study (lost to follow-up after 4 weeks). One subject in the deprenyl-alone group completed the study on a reduced dosage. For subjects in the thioctic acid-alone group, only one of nine subjects did not complete the study (secondary to a geographic move). All

Table 2 *Mean changes from baseline to 10 weeks in neuropsychological test scores*

	Placebo (n = 9)	Deprenyl (n = 9)	Thioctic acid (n = 9)	Both (n = 9)
Rey Auditory Verbal Learning				
Total number correct	5.0 ± 5.1	7.8 ± 5.5	−6.0 ± 5.6	2.4 ± 6.4
Trial 5 recall	−0.1 ± 2.0	1.7 ± 1.3	−0.7 ± 2.2	0.9 ± 1.3
Delayed recall	0.4 ± 2.3	2.3 ± 1.6	−1.2 ± 2.0	−0.6 ± 3.4
Recall after interference	0.0 ± 1.2	0.7 ± 2.5	−1.2 ± 2.1	0.1 ± 1.9
Correct recognition	0.0 ± 1.9	1.3 ± 1.8	−0.6 ± 0.7	−0.1 ± 1.7
Symbol Digit (number correct)	2.3 ± 5.3	8.2 ± 7.4	2.0 ± 9.9	2.9 ± 6.3
Grooved Pegboard (sec)				
Dominant	4.7 ± 14.4	−5.3 ± 12.3	5.4 ± 17.8	−6.1 ± 19.9
Nondominant	−10.5 ± 18.5	−7.4 ± 15.8	2.8 ± 12.9	−5.8 ± 18.8
Cal Cap				
Mean choice reaction time	−8.6 ± 66.9	−11.4 ± 46.2	−9.1 ± 46.1	−12.9 ± 49.6
Mean sequential reaction time	−7.1 ± 65.0	17.3 ± 49.2	63.6 ± 61.7	−12.3 ± 19.7

Values are means ± SD; positive values for Rey Auditory Verbal Learning and Symbol Digit indicate improvement. Negative values for Grooved Pegboard and Cal Cap indicate improvement.

subjects in the combined group completed the study on their assigned dosage. Adverse experiences were not the cause of any study termination.

Severe adverse events developed in three subjects. One subject on deprenyl developed bacterial pneumonia and meningitis. Another subject taking deprenyl developed flu symptoms with fatigue, shortness of breath, and sinusitis. One subject in the combined treatment group developed neutropenia, and after a drug suspension and rechallenge at full dose, neutrophil levels normalized and remained stable. No subjects in the thioctic acid or placebo groups had severe adverse events.

Fifty-three different adverse experiences were reported among the study subjects. There were no significant differences among the groups regarding the incidences of adverse events. The most common adverse experiences were headache (one placebo, two deprenyl, one thioctic acid, two both) and nausea (none placebo, two deprenyl, none thioctic acid, two both).

Six of 18 patients on deprenyl (either alone or combined treatment) had clinically insignificant increases in blood levels of phosphate (compared with 1 of 18 patients not on deprenyl). There were no other significant differences among the treatment groups regarding changes in laboratory tests.

Efficacy measures. The changes in the measures of efficacy from baseline to week 10 for all four treatment combinations and the estimated treatment effects for deprenyl and thioctic acid are given in tables 2 and 3. Because of the observed differences among the treatment groups at baseline with regard to the neuropsychological test results, the analyses adjusting for the baseline values using ANCOVA are reported, although these results did not differ substantially from those of the unadjusted analyses. Subjects receiving deprenyl performed significantly better on the Rey Auditory Verbal Learning Test total score ($p = 0.002$) and trial 5 ($p = 0.007$) than subjects not receiving deprenyl. As shown in the figure, this improvement gradually increased over time. No other statistically significant effects of deprenyl were apparent after adjustment for multiple comparisons, although the direction of the treatment effects on other tests of recall (delayed recall, recall after interference, correct recognition) and psychomotor processing (Cal Cap mean choice and mean sequential reaction times, Symbol Digit, and Grooved Pegboard) consistently favored deprenyl.

Subjects receiving thioctic acid performed worse on the Rey Auditory Verbal Learning Test total score ($p = 0.005$) and delayed recall ($p = 0.02$) than subjects not receiving thioctic acid. In contrast to deprenyl, the direction of the effects of thioctic acid on all other neuropsychological test results was consistently negative, although not statistically significant.

Neither deprenyl nor thioctic acid had a significant impact on mood, neurologic examination performance, or functional status. Subjects receiving thioctic acid demonstrated a reduction in mean CD4+ lymphocyte count compared with subjects not receiving thioctic acid ($p = 0.01$). However, the magnitude of this effect (−0.23 units on the natural log scale) did not appear to be of any clinical consequence. Neither treatment had an impact on levels of beta-2 microglobulin.

Discussion. This study demonstrates that both deprenyl and thioctic acid are well tolerated in immunosuppressed HIV+ patients with cognitive impairment and suggests that deprenyl may improve verbal memory function. The improvement in memory performance was seen on the Rey Auditory Verbal Learning Test (total score and trial 5) with trends for improvement in other components (delayed recall, recall after interference, correct recognition).

Tests of psychomotor speed (Cal Cap mean reaction time, Digit Symbol, Grooved Pegboard) did not significantly improve, although trends for improvement were noted with deprenyl. Given that the study

Table 3 Effects of deprenyl and thioctic acid on mean changes from baseline to 10 weeks in neuropsychological test scores

	Deprenyl treatment effect	95% CI	*p* Value	Thioctic acid treatment effect	95% CI	*p* Value
Rey Auditory Verbal Learning						
Total number correct	5.9	(2.3,9.5)	0.002	−5.8	(−9.7,−1.9)	0.005
Trial 5 recall	1.6	(0.5,2.7)	0.007	−0.5	(−1.6,0.7)	0.41
Delayed recall	1.0	(−0.7,2.6)	0.24	−1.9	(−3.6,−0.3)	0.02
Recall after interference	1.0	(−0.6,2.7)	0.21	−0.6	(−2.3,1.1)	0.48
Correct recognition	0.8	(−0.2,1.7)	0.11	−0.6	(−1.6,0.4)	0.26
Symbol Digit (number correct)	2.5	(−2.6,7.6)	0.32	−2.9	(−7.9,2.1)	0.25
Grooved Pegboard (sec)						
Dominant	−6.4	(−18.3,5.6)	0.28	3.5	(−8.3,15.3)	0.55
Nondominant	−4.5	(−16.3,7.3)	0.44	5.2	(−6.5,17.0)	0.37
Cal Cap						
Mean choice reaction time	−27.7	(−58.8,3.5)	0.08	−16.6	(−46.6,13.4)	0.26
Mean sequential reaction time	−45.3	(−88.1,−2.5)	0.04	16.8	(−23.0,56.6)	0.39

Treatment effect for deprenyl is the difference in mean change between the group taking deprenyl (n = 18) and the group not taking deprenyl (n = 18) adjusted for investigator effects and the baseline value of the neuropsychological test in an ANCOVA model. The treatment effect for thioctic acid is similarly defined. See text for details.

was designed as a tolerability trial rather than an efficacy trial, the neuropsychological test performance improvement seen with the small number of subjects taking deprenyl is encouraging.

The trial used a 2 × 2 factorial design, permitting the evaluation of two therapies without requiring a major increase in sample size. The use of this parallel group design assumes no negative statistical interaction between deprenyl and thioctic acid on the tolerability and efficacy measures. It assumes, for example, that the effect of deprenyl on cognition is the same regardless of whether or not a patient is taking thioctic acid. Because of the small sample sizes used in our trial, this assumption is difficult to verify.

Subjects randomly assigned to the placebo group tended to have more cognitive impairment compared with subjects in the active treatment groups and hence may have more rapid HIV dementia progression. However, even after adjustment for the baseline values of the neuropsychological tests, using ANCOVA, the effects of deprenyl on memory remained significant.

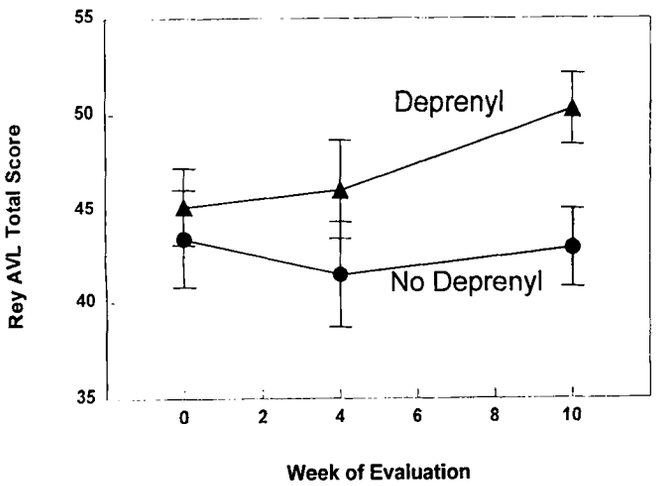

Figure. Effect of deprenyl treatment on the Rey Auditory Verbal Learning (AVL) Total Score. Points represent means and error bars represent SEs.

As shown in the figure, the improvement in memory scores is seen at 4 weeks of treatment with deprenyl and the disparity between the deprenyl and no-deprenyl groups continues to increase at 10 weeks. This finding suggests that the potential therapeutic efficacy of deprenyl may increase with a longer period of treatment. Further investigation of the efficacy of deprenyl in HIV-associated cognitive impairment using a larger number of patients and a longer duration of treatment is warranted.

During this 10-week trial, no functional improvement in everyday activities was noted with either treatment. However, the duration of the trial may have been too short to detect improvement in daily functioning.

Our study is unlike many previous trials of patients with HIV dementia[9-12] in that there was a high proportion of women (28%) and ethnic minorities (44%).

One previous trial by the Dana Consortium has evaluated antioxidant treatment for HIV dementia, using a similar patient population. A double-blind, placebo-controlled trial of OPC-14117, a lipophilic compound with structural homology to vitamin E that acts to scavenge superoxide anion radicals, showed that this compound was well tolerated and may have exerted a mild beneficial effect on neuropsychological test performance in patients with HIV-associated cognitive impairment.[38] It is unclear why OPC-14117 would exert such an effect, whereas another antioxidant, thioctic acid, does not appear to improve cognitive performance.

Deprenyl has been used previously in patients with Parkinson's disease and Alzheimer's disease.[39-41] A large, prospective, multicenter, double-blind, placebo-controlled trial (the DATATOP study) demonstrated that deprenyl delayed the onset of disability associated with early otherwise untreated Parkinson's disease[39] but that deprenyl did not have a significant effect on cognitive test performance.[42] In a 6-month, double-blind, randomized, crossover study of deprenyl versus placebo in 19 patients with Alzheimer's disease, deprenyl improved verbal memory on the Rey Auditory Verbal Learning Test.[40] In a recent double-blind, randomized, placebo-controlled trial of 341 patients with Alzheimer's disease of moderate severity, the authors concluded that treatment with either deprenyl or alpha-tocopherol slowed the progression of Alzheimer's disease.[41] However, these previous studies used a deprenyl dosage of 10 mg/day, which inhibits monoamine oxidase type B, blocking the degradation of dopamine in glial cells and neurons and blocking the reuptake of dopamine by neurons.[43] The current study used a deprenyl dosage that does not completely inhibit monoamine oxidase type B.[18]

The precise mechanism underlying the beneficial effect of deprenyl is not known.[44] Deprenyl, at the low dosages used in this trial, may have had a trophic effect on injured neurons.[18,21,44] The mechanism of this trophic effect may be through stimulation of antiapoptotic factors.[19,21] In particular, low-dosage deprenyl induces synthesis of the neuronal antiapoptotic gene, *bcl-2*, in PC12 cells.[45] In addition, deprenyl may provide neuroprotection through stimulation or synthesis of growth factors such as ciliary neurotrophic factor and basic fibroblast growth factor in reactive astrocytes.[44,46,47] Deprenyl may also suppress the formation of hydroxyl free radicals by upregulating the activities of the brain antioxidant enzymes, catalase, and superoxide dismutase.[48-51]

The potential efficacy of deprenyl in this trial may strengthen the significance of the role of neuronal apoptosis in the pathogenesis of HIV dementia. The improvement with deprenyl treatment suggests a reversible component to HIV-associated cognitive impairment. However, we cannot be certain of the mechanism of this effect. It seems unlikely that an apoptotic effect would be measurable in 10 weeks, a relatively short time period, and neuronal death should not be reversible. Another possibility is that deprenyl produces clinical improvement through nonspecific mechanisms. Low dosages of deprenyl, like its metabolites L-methamphetamine and L-amphetamine, may increase catecholaminergic activity in the brain.[52] A procatecholaminergic effect of deprenyl may increase patients' attention, thus improving neuropsychological performance. Further studies are needed to substantiate the efficacy of deprenyl in HIV dementia and to elucidate the precise mechanism of deprenyl response in HIV dementia.

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Appendix

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Disclosure

ASTA Medica provided thioctic acid and matching placebo, and Ira Shoulson, MD, donated deprenyl and matching placebo. Dr. Karl Kieburtz received research support from Somerset Pharmeceuticals for trials in Parkinson's disease in accord with Parkinson Study Group conflict of interest guidelines.

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