
A Preliminary Placebo-Controlled Trial of Selegiline Hydrochloride for Smoking Cessation

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Background: *Since dopaminergic mechanisms appear to be involved in nicotine dependence, we studied the safety and efficacy of the monoamine oxidase B inhibitor selegiline hydrochloride compared with placebo for smoking cessation in nicotine-dependent cigarette smokers.*

Methods: *Forty subjects with DSM-IV nicotine dependence were randomized to: 1) selegiline hydrochloride (5 mg p.o. twice daily) or 2) placebo in an 8-week trial. Outcome measures included smoking cessation rates, treatment retention, and medication side effects.*

Results: *Selegiline hydrochloride increased trial end point (week 8) 7-day point prevalence smoking cessation rates (selegiline hydrochloride, 9/20 [45.0%]; placebo, 3/20 [15.0%], odds ratio = 4.64, 95% CI, 1.02–21.00, $p < .05$), and smoking cessation rates during the last 4 weeks of the trial (selegiline hydrochloride, 6/20 [30.0%]; placebo, 1/20 [5.0%], odds ratio = 8.14, 95% CI, 0.88–75.48, $p = .07$) in comparison with placebo. Six-month follow-up 7-day point prevalence smoking cessation rates were reduced compared with trial end point (selegiline hydrochloride, 4/20 [20.0%]; placebo, 1/20 [5.0%], odds ratio = 4.75, 95% CI, 0.48–46.91, $p = .18$). Treatment retention was similar between drug and placebo groups ($p = .13$), and selegiline hydrochloride was well tolerated in cigarette smokers.*

Conclusions: *This preliminary study suggests that selegiline (10 mg/day) is safe for use and enhances smoking cessation rates compared with placebo in nicotine-dependent cigarette smokers. Biol Psychiatry 2003;53:136–143 © 2003 Society of Biological Psychiatry*

Key Words: Selegiline hydrochloride, placebo-controlled trial, nicotine dependence, smoking cessation, smoking cessation counseling, depression

Introduction

The prevalence of cigarette smoking in the United States is approximately 25%, but smoking prevalence has been reduced substantially since the 1960s when it approached 45%, possibly because of increased awareness about the deleterious health consequences of habitual tobacco use (Vocci and DeWit 1999). However, the decline in rates of tobacco use appears to be slowing, and may have reached a nadir, possibly due to the fact that the subset of the population that continues to smoke cigarettes may have comorbid disorders which preclude them from successfully achieving smoking cessation, such as psychiatric and alcohol/drug use disorders which are associated with high rates of smoking (Hughes et al 1986; Lasser et al 2000; George and Vessicchio 2001). While the treatment of nicotine dependence has been greatly improved with the widespread availability of nicotine replacement therapies and sustained-release bupropion (Hurt et al 1997; Jorenby et al 1999), not all tobacco users respond to these treatments. Thus, the development of novel and more efficacious pharmacotherapies for the treatment of nicotine dependence is of great importance, especially given that over 450,000 Americans continue to die each year from smoking-related medical illnesses (Hughes 1998; Hughes et al 1999).

There is increasing evidence for a role of dopamine (DA) systems in the neurobiology of nicotine dependence. In animal studies, nicotine administration increases mesolimbic DA release and metabolism (Pontieri et al 1996; George et al 1998; George et al 2000b), and nicotine withdrawal leads to a decrease in DA and norepinephrine (NE) function (Ward et al 1991; Fung et al 1996; Pontieri et al 1996; George et al 1998). Several treatments for nicotine dependence including the FDA-approved agent sustained-release (SR) bupropion (Zyban®) (Hurt et al 1997), the $\alpha 2$ adrenergic agonist clonidine (Glassman et al 1988; Glassman 1993), and the tricyclic antidepressants doxepin (Edwards et al 1989) and nortriptyline (Hall et al 1998) may exert their actions through modulation of central DA and/or other monoamine systems (Ascher et al 1995; Hughes et al 1999). A promising class of medications for the treatment of nicotine dependence, which augment

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central DA systems through inhibition of DA metabolism, are the monoamine oxidase-B (MAO-B) inhibitors. This class includes available agents such as selegiline hydrochloride (SEL; L-Deprenyl; Eldepryl®), a drug that has been used in the treatment of Parkinson's disease (Larsen et al 1999), and explored as a potential treatment for depression (Bodkin and Kwon 2001) and cocaine dependence (Bartzokis et al 1999). Monoamine oxidase-B is located primarily in brain and preferentially metabolizes DA as compared with NE and serotonin (5-HT). It has been shown that an as-yet-unidentified component of tobacco smoke (not nicotine) inhibits MAO-A (Fowler et al 1996b) and MAO-B (Fowler et al 1996a), suggesting that non-nicotinic receptor mechanisms may be involved in the psychoactive properties of tobacco. Irreversible MAO-A inhibitors such as phenelzine (Nardil®) and tranylcypromine (Parnate®), which have been used in the treatment of atypical depression, preferentially inhibit the metabolism of 5-HT and NE as compared with DA. In particular, these agents are associated with "hypertensive" crises, due to their blockade of the metabolism of the dietary pressor tyramine, since MAO-A is primarily localized in the gastrointestinal tract (Kuhn and Muller 1996; Mahmood 1997). This property is not associated with irreversible MAO-B inhibitors like selegiline at the conventional dose range of 5–10 mg/day since inhibition of MAO-B is selective; at higher doses (≥ 15 mg/day), selegiline also inhibits MAO-A (Mahmood 1997) and the metabolism of tyramine. Interestingly, Berlin and colleagues (Berlin et al 1995) demonstrated that the reversible MAO-A inhibitor and novel antidepressant moclobemide (400 mg/day) increased smoking cessation rates (moclobemide, 41%; placebo, 25% at the 12-week trial end point; $p = .13$) and was well tolerated in $n = 88$ nicotine-dependent cigarette smokers, suggesting a role for NE and 5-HT mechanisms in nicotine dependence.

Accordingly, we have studied the safety and efficacy of the MAO-B inhibitor SEL versus placebo for the treatment of nicotine dependent cigarette smokers during the course of an 8-week smoking cessation trial. The results of this preliminary trial suggest that SEL is both safe for use and efficacious for smoking cessation in nicotine-dependent cigarette smokers, and further implicate DA mechanisms in the nicotine dependence state.

Methods and Materials

A total of 64 outpatient cigarette smoking subjects who met DSM-IV criteria for nicotine dependence were screened for this study. Subjects were recruited through advertisements in local newspapers and by word of mouth. After complete description of the study to subjects, written informed consent from forty eligible subjects was obtained, and these subjects were randomized into the trial. The protocol was approved by the Human Investigation Committee of Yale University School of Medicine and conducted in

the outpatient smoking research clinic of The Program for Research in Smokers with Mental Illness (PRISM) at The Connecticut Mental Health Center (CMHC) in New Haven, CT.

All subjects were evaluated at baseline with the Structured Clinical Interview for DSM-IV (SCID-I), Beck Depression Inventory (BDI; total scale score of 0–63) (Beck and Steer 1987), Tiffany Questionnaire for Smoking Urges (T-QSU; total subscale scores of 1–7) (Tiffany and Drobes 1991), Fagerstrom Test for Nicotine Dependence (FTND; scale score of 0–10) (Heatherton et al 1991), plasma and urine cotinine using high-performance liquid chromatography, and an expired breath carbon monoxide (CO) level (Bedfont EC50 Microsmokerlyzer II, Kent, UK). The BDI and T-QSU were also used at monthly intervals during the trial (weeks 1, 4, and 8) to assess depressive symptoms and tobacco craving respectively. Subjects required an FTND score of 5 or higher, and an expired CO level ≥ 10 ppm and plasma cotinine level ≥ 150 ng/mL at baseline evaluation for study inclusion. Subjects with a lifetime history of schizophrenia, bipolar disorder, panic disorder, and posttraumatic stress disorder were excluded from the trial. Consistent with previous smoking cessation trials (Hurt et al 1997; Jorenby et al 1999), subjects with a past history of major depression were included in this sample, but were excluded if they had BDI scores > 30 at baseline evaluation (which is consistent with severe depression [Beck and Steer 1987]) or were prescribed antidepressant medications or sympathomimetic agents (e.g., phenylephrine, methylphenidate), due to concerns about potential interactions with selegiline hydrochloride (Siderowf and Kurlan 1999). Subjects prescribed opioids (e.g., meperidine, oxycodone, and methadone) or with a history of alcohol/drug abuse or dependence (except nicotine or caffeine) in the 6 months before study enrollment were also excluded.

Eligible subjects ($n = 40$) were randomly assigned to either selegiline hydrochloride ($n = 20$, 5 mg p.o. bid) or matching placebo (PLA; $n = 20$, one capsule p.o. bid). Study medications were prepared by research pharmacists at CMHC by encapsulation of selegiline hydrochloride (Eldepryl) capsules using blue 00 opaque capsules; matching placebo capsules contained only a dextrose matrix. Both subjects and raters (JCV, AT) were blinded to study medication assignment. Study medication was begun during the first week of treatment at 5 mg p.o. once daily for the first 7 days, and the dose was increased to 5 mg p.o. twice daily on the eighth study day. The smoking "quit date" occurred at the beginning of week 3 (Day 15) of the study, during the third individual smoking cessation counseling therapy session. The smoking cessation counseling program was based on the smoking cessation guidelines of The Agency for Health Care Policy and Research (AHCPR) (Fiore 1996) and included 3 weeks of motivational enhancement therapy (weeks 1 through 3), and relapse-prevention strategies in weeks 4 through 8. These sessions were conducted by Master's or Doctoral level therapists, and were of 30-min duration. Subjects attended individual smoking counseling therapy appointments and weekly research assessments on separate days. After completion of trial assessments, study medication was tapered to 5 mg (or one placebo capsule) p.o. once daily during week 9 of the trial for 1 week before discontinuation of study medications. Compliance with study medications was assessed using the EMIT d.a.u.™. We performed the Amphetamine Class

assay (Syva Co., Cupertino, CA) on urine samples from subjects collected at weeks 4 and 8 of the trial to detect the major urinary metabolites of selegiline (l-amphetamine and l-methamphetamine). This is a homogenous enzyme immunoassay that employs a polyclonal antibody preparation with good cross-reactivity for the l-isomers of amphetamine and methamphetamine. A solution containing 150 ng/mL each of l-amphetamine and l-methamphetamine was used for the “cut-off” control. Although the procedure provides semi-quantitative data, results were reported as positive or negative.

Trial end point (week 8) 7-day point-prevalence smoking abstinence (no smoking reported in the 7 days up to and including the day of assessment) and last 4 weeks of trial continuous smoking abstinence (smoking abstinence for four continuous weeks up to and including the day of assessment) was determined by an absence of self-reported cigarette smoking (using the weekly time-line follow-back method which assesses cigarette smoking during the previous 7 days; [Sobell et al 1988]), and verified by an expired breath CO level < 10 parts per million (ppm). Research assessments, including CO level determinations, were generally conducted between 11:00AM and 2:00 PM on the day of assessment. Finally, subjects were followed up at 6 months after trial completion with a clinic visit to determine 7-day point-prevalence smoking abstinence rates, and confirm smoking status with a CO level determination.

STATISTICAL ANALYSIS. Kaplan-Meier survival analysis (Bland and Altman 1998) was used to determine differences in subject retention rate between the two medication treatment groups. Smoking cessation outcome data (trial end point 7-day point prevalence and last 4 weeks of trial continuous smoking abstinence) was analyzed using Pearson Chi square analysis, and odds ratio (OR) with a 95% confidence interval (CI). Bivariate logistic regression analysis was used to determine if the presence of baseline depressive symptoms or a past history of major depression predicted smoking cessation failure with study medication treatment. For determination of smoking abstinence rates, an “intention-to-treat” analysis was utilized. As is the convention in published smoking cessation studies (Hall et al 2001), subjects who were lost during the trial or at the 6-month follow-up were counted as smokers. Hierarchical linear modeling (HLM) (Bryk and Raudenbush 1987) was used to determine whether the linear rate of change across the course of the study in continuous outcome measures (e.g., CO levels) varied as a function of medication treatment group (George et al 2000a; George et al 2002b). The majority of the statistical analyses were done using SPSS version 11.0; MIXREG software was used for HLM analyses. Post hoc differences were considered significant when $p < .05$.

Results

Demographic and Clinical Characteristics

A comparison of various demographic and clinical characteristics of the study sample is presented in Table 1. There were no significant differences between SEL and PLA groups on demographic characteristics, smoking history, or baseline clinical characteristics. Participants were

Table 1. Demographic and Baseline Clinical Characteristics of Cigarette Smokers Prescribed Selegiline Hydrochloride Versus Placebo ($n = 40$)

	Selegiline ($n = 20$)	Placebo ($n = 20$)
Age	49.7 ± 7.0	48.3 ± 10.3
Gender	8 M/12 F	7 M/13 F
Race	15 W/5 B	15 W/3 B/2 O
Education (yrs)	13.5 ± 1.6	14.4 ± 3.2
Cigarettes/Day	23.0 ± 10.0	22.4 ± 8.1
Smoking Pack/Years ^a	38.2 ± 22.1	32.9 ± 16.2
Previous Quit Attempts	9.4 ± 21.7	4.7 ± 2.7
Baseline CO Level (ppm)	21.7 ± 7.3	22.6 ± 9.9
FTND Score	6.6 ± 1.4	6.6 ± 1.8
Plasma Cotinine (ng/mL)	294 ± 99	241 ± 84
Urine Cotinine (ng/mL)	1705 ± 772	1673 ± 770
Motivation to Quit (0–4)	3.7 ± .8	3.8 ± .6
History of MDD	3/20 (15%)	7/20 (35%)
BDI Score	7.4 ± 5.9	8.4 ± 7.3

M, male; F, female; W, white; B, black; O, other race; CO, carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; MDD, major depressive disorder; BDI, Beck Depression Inventory.

^a $p > 0.05$, all comparisons

^aSmoking pack/years was calculated as average daily smoking multiplied by number of years smoking.

mostly Caucasian (75%), female (63%), were heavy and chronic smokers with a moderate to high level of nicotine dependence, had a history of several previous quit attempts, had a high level of motivation to quit smoking at the beginning of the trial, and overall had depressive symptomatology in the nondepressed range (Beck scores < 10) (Beck and Steer 1987).

Retention of Subjects in the Trial

The proportion of subjects remaining in the study during each week of the treatment trial (based on weekly individual smoking cessation counseling session attendance) is depicted in the survival curve in Figure 1. Kaplan-Meier survival curve analysis suggested that subject retention was not significantly different in the SEL compared with the PLA treatment group (Log Rank Test; $\chi^2 = 2.27$, $df = 1$, $p = .13$), though there was a selective attrition of subjects in the PLA group after week 4. Total weeks in treatment during the trial in the SEL versus the PLA group were not significantly different (SEL, 7.3 ± 1.8 ; PLA, 6.2 ± 2.1 weeks, $p = .06$), as was the proportion of subjects remaining at trial end point (week 8; SEL, 18/20; PLA, 14/20, $\chi^2 = 2.50$, $df = 1$, $p = .11$).

Smoking Cessation Rates in Selegiline Hydrochloride Versus Placebo Study Groups

Smoking cessation rates, as assessed by: 1) 7-day point prevalence (trial end point; week 8) smoking abstinence; 2) continuous abstinence during the last 4 weeks (weeks 5 through 8) of the treatment trial; and 3) 7-day point prevalence smoking abstinence at 6-month follow-up assessment

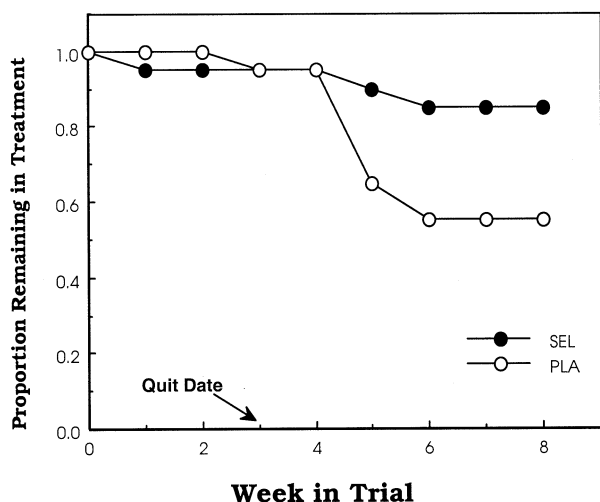
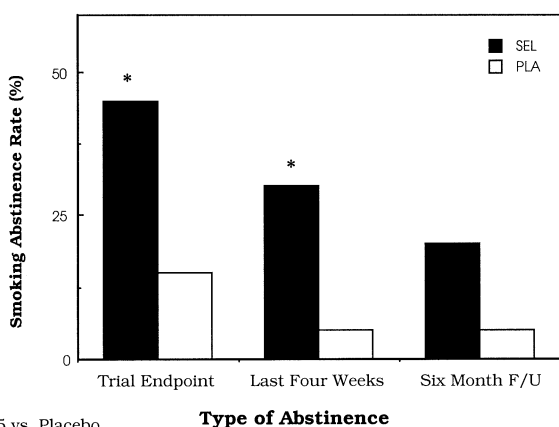


Figure 1. Treatment retention in selegiline versus placebo study groups during the 8-week trial. Data were analyzed using the Kaplan-Meier survival curve method (Bland and Altman 1998). SEL, selegiline hydrochloride; PLA, placebo.

(all biochemically verified by CO level < 10 ppm), are presented in Figure 2. Endpoint point prevalence smoking abstinence rates were significantly higher in the SEL versus the PLA group (SEL, 9/20 [45.0%]; PLA, 3/20 (15.0%), $\chi^2 = 4.29$, $df = 1$, $p < .05$; OR = 4.64, CI, 1.02–21.00, $p < .05$). Logistic regression analysis demonstrated that treatment with SEL significantly predicted smoking cessation ($B = 1.65$, $SE = 0.81$, Wald Statistic = 4.12, $df = 1$, $p < .05$). For continuous abstinence during the last 4 weeks of the trial, a significant difference between the SEL and PLA groups was also observed



* $p < 0.05$ vs. Placebo

Figure 2. Smoking cessation rates as assessed by: 1) 7-day point-prevalence smoking abstinence at trial end point (week 8); 2) continuous smoking abstinence during the last 4 weeks of the trial (weeks 5–8); 3) 7-day point-prevalence smoking abstinence at 6-month follow-up (F/unit). * $p < .05$ versus placebo group using the χ^2 Test. SEL, selegiline hydrochloride; PLA, placebo.

(SEL, 6/20 [30.0%]; PLA, 1/20 [5.0%], $\chi^2 = 4.33$, $df = 1$, $p < .05$; OR = 8.14, CI, 0.88–75.48, $p = .07$). Point prevalence 7-day smoking abstinence rates at the 6-month follow-up assessment were: SEL, 4/20 (20.0%); PLA, 1/20 (5.0%) ($\chi^2 = 2.06$, $df = 1$, $p = .15$; OR = 4.75, CI, 0.48–46.91, $p = .18$). Only 11 of 40 smokers were reassessed at the 6-month follow-up; no shows were assumed to be smoking. All smokers who met criteria for smoking cessation in this study (12/40) were retained for the complete 8-week trial.

Smoking Cessation Rates as a Function of Past History of Major Depression and Current Depression Status

There is considerable evidence that a history of major depression leads to smoking cessation failure, as had been shown with other psychiatric disorders (Glassman 1993; Lasser et al 2000). Accordingly, in this trial we also examined how a past history of major depressive disorder (MDD) and current depressive symptoms influenced smoking cessation outcomes. Although we observed a higher proportion of subjects in the PLA group with a history of major depression (Table 1), there was no significant influence of a past history of major depression on smoking cessation outcomes ($B = -0.49$, $SE = 0.90$, Wald Statistic = 0.29, $df = 1$, $p = .59$), and when past history of major depression was entered into the logistic regression model as a covariate, it did not predict treatment failure with SEL study medication (medication \times past history of depression status interaction: $B = -0.02$, $SE = 1.03$, Wald statistic = 0.00, $df = 1$, $p = .98$). Similar results from logistic regression analyses were obtained on the last 4 weeks of treatment continuous abstinence measure.

When subjects were stratified by current depression scores (BDI score ≤ 9 [$n = 28$], or 10–30 [$n = 12$], corresponding to the absence of clinically significant depression or mild to moderate depressive symptoms respectively [Beck and Steer 1987]), after collapsing across the study medication groups, there was no significant difference between the nondepressed versus depressed groups on trial end point (week 8) 7-day point prevalence smoking abstinence rates (nondepressed, 9/28 [32.1%], depressed, 3/12 [25.0%], $\chi^2 = 0.20$, $df = 1$, $p = .65$; OR = 0.36, CI, 0.07–1.98, $p = .24$); however, on achievement of continuous smoking abstinence during the last 4 weeks of the trial, the depressed group did considerably worse than the nondepressed group; however, this difference did not reach statistical significance (nondepressed, 7/28 [25.0%], depressed, 0/12 [0.0%], $\chi^2 = 3.64$, $df = 1$, $p = .06$). For the purposes of these comparisons, there were no differences between these groups on the proportions of subjects randomized to SEL versus PLA study medications (non-

depressed: SEL/PLA, 15/13; depressed: SEL/PLA, 5/7, $\chi^2 = 0.48$, $df = 1$, $p = .49$). The average (\pm SD) baseline BDI scores in the depressed ($n = 12$) versus nondepressed ($n = 28$) groups were 15.5 ± 6.1 and 4.6 ± 3.1 , respectively. The changes in depressive symptoms during the 8-week trial in depressed versus nondepressed groups as a function of study medication treatment status were analyzed using a two-factor repeated measures analysis of variance (ANOVA). This analysis revealed a significant main effect of time ($F = 5.99$, $df = 3,34$, $p < .05$), depression status ($F = 3.75$, $df = 3$, $p < .05$) and medication status ($F = 4.00$, $df = 3,34$, $p < .05$), and a nearly significant medication \times depression status \times time interaction ($F = 2.51$, $df = 3,34$, $p = .08$); however, it did not appear that active selegiline at 10 mg/day altered depressive symptoms compared with placebo in the depressed sample. In fact, active selegiline at this dose may have worsened depressive symptoms (data not shown). Furthermore, bivariate logistic regression analysis confirmed that having depressive symptoms at baseline negatively predicted smoking cessation outcomes with SEL on this continuous abstinence measure ($B = 18.9$, $SE = 0.58$, Wald statistic = 1048.9, $df = 1$, $p < .01$).

Effects of Selegiline Hydrochloride Versus Placebo on Expired Breath Carbon Monoxide Levels and Cigarette Consumption

As an objective measure of smoking reduction in the two study groups, we determined the effects of study medications on weekly expired breath CO levels during the course of the 8-week smoking cessation trial. There was a significant effect of Time on CO levels in both groups ($F = 16.03$, $df = 1,38$, $p < .01$). A decrease in CO levels in the SEL compared with the PLA group appeared during the fourth week of the trial and was sustained during the remainder of the trial, but the medication \times time interaction was nonsignificant ($F = 2.78$, $df = 1,38$, $p = .10$; data not shown). Since subject retention was not significantly different between the study groups, we used Hierarchical Linear Modeling (HLM) procedures to account for missing data in the trial and further evaluate medication \times time interactions for expired breath CO levels. A similar nonsignificant medication \times time interaction ($Z = 1.63$, $SE = 0.34$, $p = .10$) was found using HLM procedures. Furthermore, SEL nonsignificantly reduced self-reported weekly cigarette consumption during the 8-week trial (medication \times time interaction: $F = 1.51$, $df = 1,38$, $p = .23$).

Effects on Selegiline Hydrochloride Versus Placebo on Cigarette Craving

There were no significant effects of SEL versus PLA on the positive effects of smoking (factor 1; intention to smoke and anticipation of positive effects; week 1: SEL, 4.30 ± 1.40 ; PLA, 4.41 ± 1.20 ; week 4: SEL, 3.82 ± 1.15 ; PLA, $3.30 \pm$

Table 2. Number (Percentage) of Cigarette-Smoking Subjects Reporting Adverse Events who were Prescribed Selegiline Hydrochloride and Placebo During the Trial ($n = 40$)

Adverse Event	Selegiline ($n = 20$)	Placebo ($n = 20$)
Headache	8 (40)	9 (45)
Anorexia	3 (15)	2 (10)
Constipation	5 (25)	3 (15)
Nausea/Vomiting	5 (25)	4 (20)
Difficulty Falling Asleep	4 (20)	6 (30)
Frequent Night Awakenings	6 (30)	4 (20)
Early Morning Awakenings	4 (20)	5 (25)
Memory Problems	6 (30)	5 (25)
Anxiety/Agitation	7 (35)	8 (40)
Psychotic Symptoms	0 (0)	1 (5)
Dyskinesias	0 (0)	0 (0)

$p > .05$, all comparisons

1.17; week 8: SEL, 3.03 ± 1.24 ; PLA, 3.77 ± 1.01 ; medication \times time interaction: $F = 2.51$, $df = 2,52$, $p = .09$) or the negative effects of smoking (factor 2; anticipation of relief from withdrawal and negative affect; week 1: SEL, 3.35 ± 1.42 ; PLA, 2.49 ± 0.98 ; week 4: SEL, 2.60 ± 1.16 ; PLA, 2.08 ± 1.03 ; week 8: SEL, 2.06 ± 1.28 ; PLA, 2.09 ± 0.84 ; medication \times time interaction: $F = 1.97$, $df = 2,52$, $p = .15$) as assessed by the Tiffany QSU.

Adverse Events and Weight Changes in Selegiline Hydrochloride and Placebo Groups

The main side effects of SEL were anorexia, gastrointestinal symptoms, and insomnia (Table 2). None of the differences in adverse event ratings were significant in the SEL compared with the PLA group, and the drug was well tolerated compared with the placebo group. Reports of anxiety/agitation in both the SEL and PLA groups during the trial were high. Interestingly, one subject in the PLA group, with no history of depression or psychosis, reported a brief episode of visual and tactile hallucinosis after abruptly discontinuing and then restarting the study medication during the fourth study week. In our analysis of adverse events data from this trial, we coded a subject's report of an adverse event as absent if the subject reported the event at baseline one week before initiation of study medication, and it did not increase in severity during the course of treatment with the study medication. We observed no occurrences of dyskinesias or hallucinosis during the tapering of SEL in the ninth week of the study (Table 2; Mahmood 1997). Weight gain in both the SEL and PLA groups during the trial was minimal (data not shown).

Compliance With Study Medication in the Selegiline Hydrochloride Group

In a subset (16/20) of subjects who were randomized to SEL and from which urines were obtained, urinary immu-

noassay for selegiline metabolites revealed that 14/16 of these SEL-treated subjects had detectable SEL metabolites in their urine samples during the trial. In a subset of PLA-treated subjects in the trial from which urine samples were available (5/20), no urinary metabolites of SEL were detected. Out of the 16 SEL-treated subjects from which urines were obtained, 11 completed the trial and provided urines for selegiline metabolite determination at week 8. The presence of a positive metabolite urine at week 8 was correlated with treatment response, as 7/11 and 5/11 of the SEL-treated subjects were smoking abstinent at trial end point and during the last 4 weeks of the trial, respectively. Neither of the two subjects (2/16) treated with SEL who had metabolite-negative urines quit smoking during the trial.

Adequacy of Study Medication Blinding

Research staff who conducted the weekly individual therapy sessions and did the majority of research assessments on the study subjects rated, for each subject, which study medication (SEL or PLA) they believed subjects had been assigned (JCV, AT). The percentage correct ratings were 17/29 (58.6%) and 15/34 (44.1%), respectively, for JCV and AT, which was not significantly different ($\chi^2 = 2.86$, $df = 1$, $p = .09$), and nonsignificant for both raters versus chance (50%); (JCV, $\chi^2 = 3.65$, $df = 1$, $p = .06$; AT, $\chi^2 = 1.72$, $df = 1$, $p = .25$).

Discussion

The results of this preliminary study suggest that the irreversible MAO-B inhibitor SEL, in comparison with PLA, is a safe and efficacious adjunctive treatment to behavioral counseling for smoking cessation in nicotine-dependent cigarette smokers. Such treatment interactions between pharmacological agents and behavioral counseling have been observed in most placebo-controlled smoking cessation pharmacotherapy studies (Hurt et al 1997; Hughes et al 1999; Jorenby et al 1999), suggesting that the combination of pharmacological and behavioral treatments leads to enhanced smoking cessation outcomes. During the trial, we also observed a reduction in expired breath CO levels in the selegiline versus placebo group during the 8-week trial, but this effect was not significant; our inability to detect a significant effect of selegiline on CO levels was likely due to a lack of power as a function of our limited sample size ($n = 40$). Furthermore, there was a higher proportion of subjects who achieved smoking cessation with selegiline as compared with placebo during the last 4 weeks of the trial. It should be noted that the rates of smoking cessation at trial end point in this study are lower (45%) than those observed with sustained-release bupropion at 300 mg/day (60%–70%) (Hurt et al 1997; Jorenby et al 1999), but are comparable to those achieved with nicotine replacement

therapies (Balfour and Fagerstrom 1996; Hughes et al 1999). We believe that since selegiline is an irreversible MAO-B inhibitor, and the neurochemical effect of complete MAO-B inhibition with this agent occurs rapidly (within 48 hours) (Mahmood 1997) at the 10 mg/day dose, the 8-week trial was of sufficient length to demonstrate the potential efficacy of this agent for smoking cessation. Durability of the antismoking effects of selegiline was not observed, as evidenced by the substantial degree of smoking relapse at the 6-month follow-up assessment, similar to that observed in previous studies with nicotine replacement therapies and bupropion (Hurt et al 1997; Hughes et al 1999; Jorenby et al 1999). This may relate in part to the fact that upon discontinuation of selegiline (10 mg/day), MAO-B activity returns to baseline levels within 30 days (Fowler et al 1994); however, the drug/placebo difference (calculated by the OR) at 6-month follow-up assessment compared with trial end point was similar, consistent with previous smoking cessation pharmacotherapy trials (Hughes 1996; Hughes et al 1999). Given that selegiline inhibits MAO-B, thereby augmenting synaptic levels of DA, our findings give further support to the notion that dopaminergic mechanisms are important in the maintenance of the nicotine dependence state and can be exploited for the pharmacological treatment of nicotine dependence. This is of interest since it has been recently demonstrated that the FDA-approved smoking cessation medication sustained-release bupropion (Zyban), which is thought to exert its antismoking effects through DA (and norepinephrine) reuptake blockade (Ascher et al 1995), is a potent noncompetitive inhibitor of high-affinity nicotinic acetylcholine receptors (Slemmer et al 2000). Thus, it is unlikely that the antismoking actions of bupropion are solely mediated by DA systems. To our knowledge, there are no published reports suggesting that selegiline interacts with central nicotinic receptors.

A substantial number of subjects (12/40) in the study population had clinically significant (mild to moderate) depressive symptoms at study baseline (e.g., BDI scores of 10–30); (Beck and Steer 1987), and a subset (10/40) had a history of major depressive disorder, consistent with previous findings suggesting high co-morbid rates of depression and cigarette smoking (Glassman et al 1990; Glassman 1993; George and Vessicchio 2001). In fact, rates of smoking in patients with a history of major depression are higher (40%–60%) than in the general population (~25%), as has been observed with other psychiatric disorders such as schizophrenia (58%–88%), bipolar disorder (50%–70%), and posttraumatic stress disorder (45%–55%), and the presence of such mental illnesses predict smoking cessation treatment failure (Glassman 1993; Lasser et al 2000). In this preliminary study, we observed that the presence of depressive symp-

toms at study baseline predicted lower smoking cessation rates on the last 4 weeks of trial continuous smoking abstinence measure. There is clinical evidence that cigarette smokers with depressive symptoms have more unsuccessful quit attempts, are frequently women and may be at risk for exacerbation of depressive symptoms during smoking cessation (Glassman et al 1988; Glassman et al 1990; Balfour and Fagerstrom 1996; Covey et al 1997; Hughes et al 1999). Selegiline is known to have antidepressant properties at doses of 15 mg/day and higher (Bodkin and Kwon 2001), and it is of interest to note that in our study that selegiline did not reduce depressive symptoms at this dose. In fact, there was a trend for an increase in depressive symptoms during weeks 2–4, as assessed by the BDI in the selegiline group, which merits further study in a larger sample; however, as in previous assessments of depressive symptoms in placebo-controlled smoking cessation pharmacotherapy trials with sustained-release bupropion (Hurt et al 1997; Jorenby et al 1999), the overall level of depressive symptoms at trial baseline in the sample was within the nondepressed range for BDI scores (Table 1). There was no evidence that selegiline worsened depressive symptoms in those subjects ($n = 3$) who were clinically depressed (e.g., BDI score ≥ 10) at trial baseline (data not shown). As these observations are preliminary, further studies of selegiline and other agents that augment dopaminergic function in smokers with and without significant clinical depression are warranted.

Side effects of selegiline were generally mild, and included anorexia, gastrointestinal symptoms, and insomnia, which have been reported in previous clinical trials (Larsen et al 1999). The high rates of anxiety/agitation in both groups (Table 2) may relate to a high degree of nicotine withdrawal symptoms during the trial, and is consistent with the high degree of cigarette cravings and urges observed in both groups; however, selegiline did not significantly alter the positive or negative effects of cigarette smoking (Factor 1 and Factor 2 of the Tiffany QSU, respectively) during the trial. In general, the drug was well tolerated and treatment retention was similar in the drug compared with the placebo group (Figure 1). While we obtained urines from only a subset (16/20) of selegiline treated smokers, compliance with the study medication appeared to be high in the selegiline group as assessed by detection of urinary selegiline metabolites, and the presence of urinary selegiline metabolites at trial end point was correlated with treatment response. The integrity of the blinding procedure was maintained as assessed by the finding that the two main research staff (JCV and AT) were not able to correctly identify which study medication the subjects were prescribed at a probability greater than chance (50%). Furthermore, no drug discontinuation effects of the active medication such as

dyskinesias and hallucinosis were observed in our sample during the dose tapering in the ninth week of the study, as have been observed in previous studies of patients with Parkinson's disease (Mahmood 1997).

Accordingly, the results from this preliminary study suggest that MAO-B inhibition may be a novel strategy for the development of effective smoking cessation pharmacotherapies and give further evidence of a role for dopaminergic mechanisms in nicotine dependence. Since doses of selegiline over 10 mg/day are associated with inhibition of MAO-A and the increased risk of hypertensive crises, the use of this agent for smoking cessation in high-risk groups such as patients with chronic mental illness (e.g., schizophrenia, bipolar disorder, borderline personality disorder) or adolescents (e.g., those who are at high risk for intentional overdoses) may be limited. Furthermore, given the limited sample size in this study, larger placebo-controlled studies of selegiline hydrochloride and other MAO-B inhibitors for the treatment of nicotine dependence are warranted.

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