

Brief Report

Selegiline Transdermal System (STS) as an Aid for Smoking Cessation

Roberta Kahn, M.D.,¹ Liza Gorgon, M.A.,¹ Karen Jones, M.S.,² Frances McSherry, M.A.,² Elbert D. Glover, Ph.D., F.A.S.H.A., F.A.A.H.B., F.R.I.P.H.,³ Robert M. Anthenelli, M.D.,⁴ Thomas Jackson, M.D.,⁵ Jill Williams, M.D.,⁶ Cristin Murtaugh, B.A.,² Ivan Montoya, M.D.,¹ Elmer Yu, M.D., F.A.S.A.M.,⁷ & Ahmed Elkashef, M.D.¹

¹ Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, Bethesda, MD

² Cooperative Studies Program Coordinating Center, Department of Veterans Affairs, Perry Point, MD

³ Center for Health Behavior Research, Department of Public and Community Health, University of Maryland, College Park, MD

⁴ Tri-State Tobacco and Alcohol Research Center, University of Cincinnati, Reading Campus and Cincinnati VA Medical Center, Cincinnati, OH

⁵ UW-Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, Madison, WI

⁶ Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ

⁷ Philadelphia VA Medical Center, Philadelphia, PA

Corresponding Author: Roberta Kahn, M.D., Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, 6001 Executive Boulevard, Room 4123, MSC 9551, Bethesda, MD 20892, USA. Telephone: 301-443-1138; Fax: 301-443-2281; E-mail: rkan@nida.nih.gov

Received February 17, 2011; accepted June 7, 2011

Abstract

Introduction: This study examined the efficacy and safety of selegiline transdermal system (STS) and brief repeated behavioral intervention (BRBI) for smoking cessation in heavy smokers. We hypothesized that the quit rate of subjects who received STS and BRBI would be significantly greater than that of those who received placebo patch and BRBI.

Methods: This was a double-blind, placebo-controlled parallel-group study in which 246 men and women were randomized to receive either STS ($n = 121$) or placebo patch ($n = 125$) for 9 weeks. Recruitment targeted heavy smokers, defined as individuals with self-reported use of ≥ 15 cigarettes/day in the 30 days prior to enrollment, who had smoked cigarettes for the past 5 years, and had an expired CO level ≥ 9 ppm during screening.

Results: Although STS was well tolerated, the overall results indicated that STS with BRBI was not more effective than placebo plus BRBI for smoking cessation ($p = .58$).

Conclusions: The results are discussed in relation to interventions for heavy smokers. Although 2 trials using oral selegiline both showed trends toward improved abstinence, these results indicate that STS with BRBI was not an effective aid for smoking cessation at the end of treatment (10 weeks), 14, or 26 weeks.

Introduction

There is a close association between depression history and inability to quit smoking or remain abstinent (Covey, Glassman, &

Stetner, 1990). Fowler, Volkow, Wang, Pappas, Logan, MacGregor, et al. (1996) and Fowler, Volkow, Wang, Pappas, Logan, Shea, et al. (1996) showed that the brains of smokers have 40% lower levels of MAO-B and 23% lower levels of MAO-A than those of nonsmokers or former smokers and proposed that reduction of MAO-B activity might synergize with nicotine to produce effects on mood or depression. Monoamine oxidase (MAO) inhibitors do not interact directly with nicotinic receptors allowing the potential for combination therapy with nicotine replacement.

There have been positive preliminary results in smoking cessation clinical trials for two MAO inhibitors, moclobemide, an MAO-A selective inhibitor, and selegiline. Berlin et al. (1995) conducted a randomized, double-blind, placebo-controlled parallel-group study of moclobemide, 400 mg/day for 2 months and 200 mg/day during the third month in 88 smokers (moclobemide [$n = 44$] or placebo [$n = 44$]). The self-reported continuous abstinence rate was higher with moclobemide than with placebo (6 months: $p < .05$; until the end of follow-up, 1 year: $p = .09$). Interestingly, no difference occurred for withdrawal symptoms.

To date, the efficacy of selegiline as a smoking cessation agent is inconsistent. In a crossover study examining treatment with selegiline and placebo, Houtsmuller, Thorton, and Stitzer (2002) found short exposure to oral selegiline to assist smoking cessation by reducing the number of cigarettes smoked and the number of puffs per cigarette. In a randomized study of oral selegiline versus placebo conducted by George et al. (2003), the selegiline group had a significantly higher 7-day point prevalence abstinence rate (45.0%) at Week 8 compared with 15.0% for the placebo controls ($p < .05$). Smoking cessation rates during

doi: 10.1093/ntr/ntr143

Advance Access published on August 16, 2011

Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco 2011.

the last four weeks of the trial were 30.0% (6/20) for the selegiline group and 5.0% (1/20) for the placebo group ($p = .07$). Biberman, Neumann, Katzir, and Gerber (2003) also conducted a trial in which oral selegiline combined with nicotine replacement therapy (NRT) was compared with NRT alone. Abstinence after 8 weeks of treatment and long-term abstinence at 1 year showed an increasing trend in favor of the group that received treatment with selegiline and NRT versus NRT alone. Moreover, craving for cigarettes at Week 4 was significantly reduced in the selegiline plus NRT group ($p = .02$). These preliminary small trials suggested that oral selegiline in a range of clinical doses from 2.5 to 10 mg/day might be efficacious as an aid for smoking cessation either alone or in combination with NRT.

Two more recent trials have had equivocal results. Weinberger et al. (2010) conducted an 8-week randomized placebo-controlled trial of oral selegiline 5 mg twice/day. Fifty-one subjects were randomized to receive selegiline versus 50 on placebo. Selegiline failed to demonstrate a significant treatment effect. In another study, conducted approximately concurrently with ours, Killen et al. (2010) conducted an 8-week placebo-controlled trial of selegiline transdermal system (STS) with cognitive behavioral therapy ($n = 243$). No significant benefits of STS over placebo were demonstrated in the intent-to-treat population. There was a gender difference observed in that more females than males in the STS-treated group remained abstinent at Week 52 of follow-up (28% vs. 16%, $p = .05$). In addition, a subgroup of subjects with high “behavioral activation” scores on STS showed greater retention in the study. The effect on the survival curve was observable as early as 8 weeks, the end of the medication period, and remained consistent to the end of follow-up at Week 52. Compliance with medication in both groups was also correlated with successful outcome.

Transdermal delivery offers a benefit over oral selegiline by delivering a sustained dose of selegiline into the bloodstream without first-pass removal through the gastrointestinal system, resulting in greatly reduced levels of metabolites N-desmethylselegiline, l-amphetamine, and l-methamphetamine. The C_{max} values for desmethylselegiline and l-methamphetamine are greater by a factor of 20 after oral compared with transdermal dosing, and l-amphetamine C_{max} is greater by approximately sixfold (Rohatagi, Barrett, DeWitt, & Morales, 1997). STS has been demonstrated to increase the blood level of selegiline by 5-fold and duration of exposure by 60-fold compared with oral selegiline as a result of bypassing first-pass metabolism in the liver (Rohatagi et al., 1997). The dose delivered by patch is sufficient for close to 100% inhibition of MAO-B and approximately 10% of MAO-A.

The present investigation was designed to examine the effects of STS and brief repeated behavioral intervention (BRBI) on smoking cessation as compared with BRBI and a placebo patch. BRBI was chosen in order to reduce the chance of a significant nonmedication effect and also to more closely replicate the type of management routinely offered to a patient in a family doctor’s clinical practice.

Methods

In the successful study of oral selegiline (George et al., 2003), the quit rate was 30% for selegiline compared with 5% for placebo.

We assumed a placebo quit rate of 23.1% and an effect size of 20% in order to approximate the outcomes seen in studies of bupropion sustained-release (SR) with NRT (GlaxoSmithKline, 2009). Assuming a normal approximation to the binomial distribution with a two-sided alpha of .05 and 80% power to detect a significant difference, 98 subjects per group were required. The number of subjects required per group was increased to 123 to allow for a 20% dropout rate.

A total of 246 subjects ($n = 121$ in the selegiline group; $n = 125$ in the placebo group) were enrolled in the study at 1 of 4 clinics: College Park, MD ($n = 52$), Cincinnati, OH ($n = 68$), Milwaukee, WI ($n = 73$), and New Brunswick, NJ ($n = 53$). Subjects were included if they met the *DSM-IV* diagnostic criteria for nicotine dependence; were at least 18 years of age; motivated to quit smoking; were currently smoking at least 15 cigarettes/day; smoked cigarettes for at least the past five years; had an expired carbon monoxide (CO) level of at least 9 ppm at screening; agreed not to use any other smoking behavioral intervention, acupuncture, or other smoking cessation pharmacotherapy during the study; were available for 28 weeks, and provided informed consent. Females were required to use contraception, and pregnant or lactating women were excluded. Other criteria for exclusion included any serious medical illnesses that may have compromised subject safety or study conduct, current diagnosis of major depressive disorder or other neuropsychiatric disorders that required current contraindicated pharmacological treatment, a known or suspected hypersensitivity to selegiline or any MAO inhibitor, a history of allergy to latex, or use of any other form of tobacco products.

This was a double-blind, placebo-controlled two-arm study with a parallel-group design. After satisfying study entry criteria and consenting to participate, subjects were randomly assigned to either STS (6 mg/24 hr) or placebo patches for 9 weeks. Adaptive randomization balanced the treatment groups with respect to the following: clinical site, gender, time to first cigarette after awakening (≤ 30 min or > 30 min), average number of cigarettes smoked per day in the 30 days prior to enrollment (< 25 or ≥ 25), and baseline Hamilton Depression Rating Scale (HAM-D; Guy, 1976; Riskind, Beck, Brown, & Steer, 1987) score (≤ 11 or > 11). Initiation of STS or matched placebo was scheduled 7 days prior to each subject’s target quit date, allowing for steady-state levels of selegiline and MAO inhibition to be reached. Following randomization, subjects were instructed to apply the STS (6 mg/24 hr) or matched placebo patch at approximately the same time daily and to leave it in place for 24 hr each day of the 9-week treatment period. Subjects were assessed for smoking status and safety measures weekly during treatment, at end of treatment (Week 10), and at follow-up visits during Weeks 14 and 26. Smoking status was assessed by measurements of expired CO and by subject self-report. Safety measures included adverse events, clinical laboratory assessments, vital signs, weight gain/loss, and ECG readings.

During the 9-week treatment period, subjects received BRBI consisting of weekly individual counseling sessions, each lasting approximately 10 min. Content of these sessions was based on the Public Health Service *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (Fiore et al., 2000), including a review of skills discussed in the National Cancer Institute’s booklet, “Clearing the Air” (provided at first session), a review

of progress, and identification and resolution of barriers to quitting. A standardized manual (Heffner et al., 2007) was provided as a guide for clinical staff to conduct the BRBI sessions, and if necessary, BRBI was provided over the telephone for any subject who was unable to attend his/her weekly in-clinic session.

The primary outcome measure was the continuous quit rate defined by the FDA for registration trials of smoking cessation pharmacotherapies (FDA, 1995) and as recommended by Hughes et al. (2003). This quit rate was 4-week prolonged abstinence in Weeks 6–9, assessed through self-report and confirmed by two exhaled CO measurements <9 ppm, with at least one of these two CO measurements taken during Weeks 8 or 9. A subject who did not provide the required CO measurements or self-reports of use during study Weeks 6–9 was considered a treatment failure. Prolonged abstinence rates were compared between treatment groups using Fisher's exact test. All statistical tests were two sided at an alpha level of .05. As a secondary analysis of the primary outcome measure, bivariate logistic regression was used to determine if any of several baseline characteristics were predictive of treatment success or failure.

Results

Overall, subjects in the STS and placebo groups were very similar in demographic and baseline smoking history characteristics (Table 1). On average, subjects smoked 22–23 cigarettes/day in the 30 days prior to enrollment, a rate that was stable over the past five years. STS-treated subjects had slightly more years of

formal education than the placebo-treated subjects ($p = .03$ by t test).

Two hundred forty-six subjects (246) were randomized (STS, $n = 121$; placebo, $n = 125$). Of the 246 randomized, 178 subjects (72%) completed study participation. Completion rates varied across sites, ranging from a low of 60% to a high of 79%. The completion rate was 70% for subjects on placebo and 74% for subjects receiving STS, but the difference was not statistically significant.

Data from all 246 subjects were used in an intent-to-treat analysis of the primary outcome measure, the 4-week prolonged abstinence rate at end of treatment. Table 2 depicts the number and percentage of subjects who were successful at quitting smoking according to the primary outcome measure. While more subjects in the STS group were successful at quitting smoking than those in the placebo group, the difference was not statistically significant (Fisher's exact test, $p = 0.58$). There was a modestly higher rate of smoking cessation sustained in STS-treated subjects at 14 and 26 weeks of follow-up. At 14 weeks, 16 (13.2%) subjects were abstinent in the STS group compared with 10 (8.0%) in the placebo group, and at 26 weeks, 11 (9.1%) subjects in the STS group compared with 7 (5.6%) in the placebo group were abstinent. As a secondary analysis of the primary outcome measure, bivariate logistic regression was performed to determine if certain baseline characteristics, including gender, current depression symptomatology, number of previous smoking quit attempts, and time to first cigarette after awakening, were predictive of treatment success or failure. Of these characteristics, only time to first cigarette smoked after awakening proved to be potentially predictive of treatment success.

Table 1. Subject Characteristics, Expressed as Percents or Means (SD)

Variable	Placebo ($N = 125$)	Selegiline ($N = 121$)
Age	47.3 (11.1)	45.6 (10.9)
Male (%)	52.8	48.8
Race (%)		
American Indian or Alaskan Native	2.4	0.0
American Indian or Alaskan Native & Black	0.8	0.0
American Indian or Alaskan Native & White	0.8	0.0
Asian	2.4	5.0
Black or African American	24.0	24.0
White	69.6	71.1
Ethnicity		
Hispanic or Latino (%)	4.0	1.7
Not Hispanic or Latino (%)	96.0	98.4
Years of formal education ^a	13.6 (2.3)	14.2 (2.2)
Hamilton Depression Rating Scale	2.0 (2.5)	1.8 (2.3)
Smoking history		
Cigarettes smoked/day in the 30 days prior to consent	22.4 (7.5)	22.4 (9.5)
Cigarettes smoked/day in the past year	22.8 (8.9)	22.6 (9.7)
Cigarettes smoked/day in the past five years	23.0 (10.8)	22.4 (10.0)

Note. ^a p Value = .03

Although all subjects can be considered heavy smokers, we differentiated severity of nicotine addiction by time to first cigarette, irrespective of treatment group, as ≤ 30 min versus > 30 min after awakening. One hundred and ninety-two (192) subjects were termed "early smokers," having smoked their first cigarette of the day ≤ 30 min after awakening, and 54 subjects were termed "later smokers," having smoked their first cigarette > 30 min after awakening. Of the "early smokers," only 20 of 192 subjects (10%) were abstinent based on the definition of a quitter, while 13 of 54 (24%) "later smokers" went on to quit (Fisher's exact test, $p = .01$). In the group of "early smokers," 11 subjects (11.5%) were abstinent on STS compared with 9 (9.4%) who were abstinent on placebo. In the group of "later smokers," seven subjects (28%) on STS were abstinent compared with six subjects (20.7%) on placebo. There was no significant difference in abstinence between the early and later smokers in the placebo arm (Fisher's exact test $p = .112$). In the STS arm, the difference in abstinence between the two groups approached significance (Fisher's exact test $p = .056$).

The most common adverse events experienced in the subjects who received STS were insomnia (16%), headache (15%), application site erythema (11%), dry mouth (7%), and nausea (7%). One adverse event, application site erythema, occurred at a significantly higher incidence for STS subjects than for placebo subjects (11% vs. 3%, $p = .02$ for odds ratio). The STS group experienced a significantly higher event incidence in the psychiatric disorder category (body system) than the placebo group (27% vs. 14%, $p = .02$ for odds ratio); the majority of complaints in

Table 2. Outcome Measures Relating to Abstinence, Expressed as Percents

Variable	Placebo (N = 125)	Selegiline (N = 121)	Fisher's exact <i>p</i> value
Primary outcome measure—quit rate (% successful at quitting)	12.0	14.9	.58
Secondary outcome measures—longer term abstinence (%)			
By self-report confirmed by exhaled CO			
Percent remaining abstinent at Week 14	8.0	13.2	.22
Percent remaining abstinent at Week 26	5.6	9.1	.33
By self-report alone			
Percent remaining abstinent at Week 14	9.6	14.1	.33
Percent remaining abstinent at Week 26	7.2	9.1	.65

this category were for insomnia, which was reported in 10 placebo subjects and 19 STS subjects ($p = .08$). Insomnia, possibly representative of nicotine withdrawal, is also commonly reported with selegiline treatment, so we are unable to conclude which was the more likely cause. There were no treatment group differences in any other individual events within this body system. Three serious adverse events were reported during the study, each due to hospitalization (fractured femur, myocardial infarction, and pneumonia) occurring when the subjects were no longer taking study medication and none related to the study medication. Increases in weight and waist circumference from baseline to Weeks 10 and 26 were observed in both treatment groups, but the differences were not statistically significant. At Week 10, mean increases from baseline were 4.06 and 5.07 pounds, and at week 26, mean weight gains were 9.20 and 9.27 pounds for STS and placebo, respectively.

Compliance (%) with medication over nine weeks was calculated on a per-subject basis by dividing the number of days on which a patch was worn by the total number of days the subject was in the study and multiplying by 100. The mean compliance rates were 91.6% and 91.3% for the STS and placebo groups, respectively, showing no significant difference (t test p value = .91). Subject retention was similar: 90/121 in the STS group and 88/125 in the placebo group completed the study ($p = .20$). Depression was not prominent in the subjects in either group. At screening, the mean (SD) HAM-D score in the STS treatment group ($n = 121$) was 1.75 (2.25) and 1.98 (2.54) in the placebo group ($n = 125$). At Week 8, during the period when subjects were supposed to maintain abstinence, mean HAM-D scores had elevated slightly: 2.53 (3.92) in STS-treated subjects ($n = 90$) and 2.02 (2.88) in placebo subjects ($n = 84$). At the final HAM-D assessment, the STS group ($n = 90$) reported a mean increase of 0.41 points and the placebo group ($n = 85$) reported a mean increase of 0.21 points. The difference between treatment groups was not statistically significant (t test, $p = .65$).

Discussion

Though two trials using oral selegiline showed trends toward improved abstinence, the recent trial by Weinberger did not. Since smokers smoke throughout the day, we postulated that transdermal delivery of selegiline would be advantageous over oral delivery because it provides a higher more consistent blood level of selegiline over 24 hr. However, the present study did not demonstrate that STS with BRBI improved quit rate during

9 weeks of treatment. Our study most closely resembles the clinical trial conducted by Killen et al. (2010) of 243 smokers randomized between STS and placebo for 8 weeks, which failed to demonstrate a difference between the treatment groups followed out to 52 weeks.

Overall, STS was well tolerated with comparable rates of compliance between treatment groups. Subjects in both groups were retained in the study at a similar rate. No effect on HAM-D scores was observed; however, only smokers with mild-to-moderate baseline HAM-D scores were included. Although we found no differences between groups in mean ratings of withdrawal symptoms in the intent-to-treat population, in the subgroup of successful quitters, some symptoms of withdrawal appeared to be alleviated more successfully by STS.

Although the metabolism of selegiline is a disadvantage in the treatment of Parkinson's disease, this may not be the case for addictions. The levo-isomers of amphetamine and methamphetamine have both cardiovascular and psychological effects, though somewhat attenuated in comparison with the dextro-isomers. Mendelson et al. (2006) demonstrated that l-methamphetamine had cardiovascular and psychoactive effects at higher doses than d-methamphetamine and dissipated sooner than the equipotent dose of d-methamphetamine. Possibly, the stimulative effects of the active metabolites are needed for the success of selegiline for drug abuse indications in general as has been suggested previously (Elkashef et al., 2006).

Molecular imaging studies have demonstrated that smokers during early abstinence have a larger than a normal population of unoccupied beta-2 acetylcholine receptors in the cortex and cerebellum, which does not begin to normalize until six or more weeks after smoking cessation (Staley et al., 2006). Availability of unoccupied cerebellar beta-2 acetylcholine receptors at 4 weeks has been correlated with craving (Cosgrove et al., 2009). Neither selegiline nor its metabolites interact with acetylcholine receptors, providing a reason why NRT combined with oral selegiline treatment was more successful than NRT alone in the one study that addressed this comparison (Biberman et al., 2003). However, STS alone at the standard therapeutic dose is unlikely to represent an effective treatment for smoking cessation for most smokers.

In conclusion, the results of the present study demonstrated that there was no significant difference between the STS and placebo treatment groups. There are now multiple clinical trials examining selegiline as a therapy for smoking cessation. Despite

earlier studies that suggest an effect of selegiline on craving that translated to reduced smoking frequency, the ostensible benefit of continuous medication delivery by transdermal application did not translate to more treatment success.

Funding

This study was supported by the National Institutes of Health, National Institute on Drug Abuse through the Department of Veterans Affairs Cooperative Studies Program (Interagency Agreement No. Y1-DA4006).

Declaration of Interests

None declared.

Acknowledgments

The authors would like to thank Somerset Pharmaceuticals for providing the selegiline (EMSAM) and placebo patches through a Cooperative Research and Development Agreement with National Institute on Drug Abuse.

References

Berlin, I., Said, S., Spreux-Varoquaux, O., Launay, J. M., Olivares, R., Millet, V., et al. (1995). A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clinical Pharmacology and Therapeutics*, 58, 444–452. doi:10.1016/0009-9236(95)90058-6

Biberman, R., Neumann, R., Katzir, I., & Gerber, Y. (2003). A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. *Addiction*, 98, 1403–1407. doi:10.1046/j.1360-0443.2003.00524.x

Cosgrove, K. P., Batis, J., Bois, F., Maciejewski, P. K., Esterlis, I., Kloczynski, M. A., et al. (2009). β_2 -Nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. *Archives of General Psychiatry*, 66, 666–676. Retrieved from <http://archpsyc.ama-assn.org/cgi/content/full/66/6/666> (last accessed on 6/22/11).

Covey, L. S., Glassman, A. H., & Stetner, F. (1990). Depression and depressive symptoms in smoking cessation. *Comprehensive Psychiatry*, 31, 350–354. doi:10.1016/0010-440X(90)90042-Q

Elkashaf, A., Fudala, P. J., Gorgon, L., Li, S. H., Kahn, R., Chiang, N., et al. (2006). Double-blind placebo-controlled trial of selegiline transdermal system (STS) for the treatment of cocaine dependence. *Drug and Alcohol Dependence*, 85, 191–197. doi:10.1016/j.drugalcdep.2006.04.010

FDA. (1995). *Transcript of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Drug Abuse Advisory Committee of the Food and Drug Administration*. Rockville, MD. Retrieved from <http://www.federalregister.gov/articles/1995/07/27/>

95-18448/cold-cough-allergy-bronchodilator-and-antiasthmatic-drug-products-for-over-the-counter-human-use

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M. G., Gritz, E. R., et al. (2000). *Treating tobacco use and dependence: Clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. Retrieved from http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf (last referenced on 6/22/11).

Fowler, J. S., Volkow, N. D., Wang, G. J., Pappas, N., Logan, J., MacGregor, R., et al. (1996). Inhibition of monoamine oxidase B in the brains of smokers. *Nature*, 379, 733–736. doi:10.1038/379733a0

Fowler, J. S., Volkow, N. D., Wang, G. J., Pappas, N., Logan, J., Shea, C., et al. (1996). Brain monoamine oxidase A inhibition in cigarette smokers. *Proceedings of the National Academy of Sciences of the United States of America*, 93, 14065–14069. doi:10.1073/pnas.93.24.14065

George, T. P., Vessicchio, J. C., Termine, A., Jatlow, P. I., Kosten, T. R., & O'Malley, S. S. (2003). A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. *Biological Psychiatry*, 53, 136–143. doi:10.1016/S0006-3223(02)01454-3

GlaxoSmithKline. (2009). *Zyban (bupropion hydrochloride) sustained-release tablets*. NDA 20-711/S-032/33 [Product Label]. Author.

Guy, W. (1976). *ECDEU. Assessment manual for psychopharmacology: Publication no. ADM 76-336*. Rockville, MD: U.S. Department of Health, Education and Welfare.

Heffner, J. L., Dawson, K., Jansern, J., Nolting, S. L., Winders-Barrett, S., & Anthenelli, R. M. (2007). *Guide to clearing the air (modified)*. Unpublished treatment manual. University of Cincinnati.

Houtsmuller, E. J., Thornton, J. A., & Stitzer, M. L. (2002). Effects of selegiline (l-deprenyl) during smoking and short-term abstinence. *Psychopharmacology*, 163, 213–220. doi:10.1007/s00213-002-1152-9

Hughes, J. R., Keely, J. P., Niaura, R. S., Ossip-Klein, D. J., Richmond, R. L., & Swan, G. E. (2003). Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine & Tobacco Research*, 5, 13–25. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12745503> (last accessed on 6/22/11).

Killen, J. D., Fortmann, S. P., Murphy, G. M., Jr., Hayward, C., Fong, D., Lowenthal, K., et al. (2010). Failure to improve cigarette smoking abstinence with transdermal selegiline + cognitive behavior therapy. *Addiction*, 105, 1660–1668. doi:10.1111/j.1360-0443.2010.03020.x

Mendelson, J., Uemura, N., Harris, D., Nath, R. P., Fernandez, E., Jacob, P., III, et al. (2006). Human pharmacology of the methamphetamine stereoisomers. *Clinical Pharmacology and Therapeutics*, 80, 403–420. doi:10.1016/j.clpt.2006.06.013

Riskind, J. H., Beck, A. T., Brown, G., & Steer, R. A. (1987). Taking the measure of anxiety and depression: Validity of the

reconstructed Hamilton scales. *Journal of Nervous and Mental Disease*, 175, 474–479. doi:10.1097/00005053-198708000-00005

Rohatagi, S., Barrett, J. S., DeWitt, K. E., & Morales, R. J. (1997). Integrated pharmacokinetic and metabolic modeling of selegiline and metabolites after transdermal administration. *Biopharmaceutics and Drug Disposition*, 18, 567–584. doi:10.1002/(SICI)1099-081X(199710)18:7<567::AID-BDD49>3.0.CO;2-7

Staley, J. K., Krishnan-Sarin, S., Cosgrove, K. P., Krantzler, E., Brohlich, E., Perry, E., et al. (2006). Human tobacco smokers in

early abstinence have higher levels of β_2^* nicotinic acetylcholine receptors than non smokers. *Journal of Neuroscience*, 26, 8707–8714. doi:10.1523/JNEUROSCI.0546-06.2006

Weinberger, A. H., Reutenauer, E. L., Jatlow, P. I., O'Malley, S. S., Potenza, M. N., & George, T. P. (2010). A double-blind, placebo-controlled, randomized clinical trial of oral selegiline hydrochloride for smoking cessation in nicotine-dependent cigarette smokers. *Drug and Alcohol Dependence*, 107, 188–195. doi:10.1016/j.drugalcdep.2009.10.009