

Multicenter Trial of Fluoxetine as an Adjunct to Behavioral Smoking Cessation Treatment

Raymond Niaura
Brown Medical School

Bonnie Spring
University of Illinois at Chicago

Belinda Borrelli
Brown Medical School

Donald Hedeker
University of Illinois at Chicago

Michael G. Goldstein
Brown Medical School

Nancy Keuthen
Massachusetts General Hospital

Judy DePue
Brown Medical School

Jean Kristeller
Indiana State University

Judy Ockene
University of Massachusetts Medical School, Worcester

Allan Prochazka
Denver Veterans Affairs Medical Center, Denver, Colorado

John A. Chiles
University of Texas Health Science Center at San Antonio

David B. Abrams
Brown Medical School

The authors evaluated the efficacy of fluoxetine hydrochloride (Prozac; Eli Lilly and Company, Indianapolis, IN) as an adjunct to behavioral treatment for smoking cessation. Sixteen sites randomized 989 smokers to 3 dose conditions: 10 weeks of placebo, 30 mg, or 60 mg fluoxetine per day. Smokers received 9 sessions of individualized cognitive-behavioral therapy, and biologically verified 7-day self-reported abstinence follow-ups were conducted at 1, 3, and 6 months posttreatment. Analyses assuming missing data counted as smoking observed no treatment difference in outcomes. Pattern-mixture analysis that estimates treatment effects in the presence of missing data observed enhanced quit rates associated with both the 60-mg and 30-mg doses. Results support a modest, short-term effect of fluoxetine on smoking cessation and consideration of alternative models for handling missing data.

Every year, cigarette smoking takes an estimated 430,000 U.S. lives. Nevertheless, 25.3% of men and 21.0% of women continue to smoke (Centers for Disease Control, 1999). A majority of smokers express a desire to quit but find quitting

very difficult (Centers for Disease Control, 1994; Russell, 1994).

A few drugs that were originally marketed as antidepressants have proved to be helpful quit-smoking aids. Most notably, a

Raymond Niaura, Belinda Borrelli, Michael G. Goldstein, Judy DePue, and David B. Abrams, Centers for Behavioral and Preventive Medicine, The Miriam Hospital and Brown Medical School; Bonnie Spring, Department of Psychology, University of Illinois at Chicago; Donald Hedeker, School of Public Health and Prevention Research Center, University of Illinois at Chicago; Nancy Keuthen, Department of Psychiatry, Massachusetts General Hospital, Boston; Jean Kristeller, Department of Psychology, Indiana State University; Judy Ockene, Department of Medicine, University of Massachusetts Medical School, Worcester; Allan Prochazka, Ambulatory Care, Denver Veterans Affairs Medical Center, Denver, Colorado; John A. Chiles, Department of Psychiatry, University of Texas Health Science Center at San Antonio.

This study was supported by Eli Lilly and Company. The opinions presented in this article are those of the authors and may not represent the opinions of Eli Lilly and Company. Preparation of the manuscript was also supported in part by Public Health Service Grants HL32318 and CA84719.

We thank A. Sonia Buist, Dorothy Knapp, David Gonzales, and David McCarron, Clinical Research Group of Oregon; C. R. Heim, Barbara Forbes, and Jacqueline Goffaux, Vanderbilt University; D. Jasinski, Francis Scott Key Medical Center, Baltimore; C. P. Lucas, William Beaumont Hospital, Birmingham, Michigan; B. B. Beiswanger, Indiana University School of Dentistry; R. C. Frecker, Addiction Research Foundation, Toronto, Ontario, Canada; R. A. Kaplan, Concord, California; T. W. Littlejohn, Piedmont Research Association, Winston-Salem, North Carolina; K. A. Seagraves, Metro Health Medical Center, Cleveland, Ohio; D. C. Spendlove, Utah Family Health Center, Salt Lake City, Utah; and A. Mahableshwarker and R. Pingitore, Veterans Affairs Medical Center, North Chicago.

Correspondence concerning this article should be addressed to Raymond Niaura, Centers for Behavioral and Preventive Medicine, The Miriam Hospital and Brown Medical School, Coro Building, Suite 500, One Hoppin Street, Providence, Rhode Island 02903. E-mail: raymond_niaura@brown.edu

sustained-release form of bupropion has been found to enhance cessation rates sufficiently to become the first Food and Drug Association-approved nonnicotine cessation aid. One-year validated cessation rates in a double-blind, placebo-controlled trial were 11% higher for bupropion than for placebo (23% vs. 12%; Hurt et al., 1997). Bupropion acts primarily through dopaminergic and noradrenergic mechanisms. Nortriptyline, another antidepressant that has demonstrated efficacy for smoking cessation (Hall et al., 1998; Prochazka et al., 1998), shares bupropion's catecholaminergic actions. In addition, nortriptyline has serotonergic effects similar to but less potent than those of the selective serotonin reuptake inhibitor (SSRIs) antidepressants.

SSRIs and releasing agents have been tested for efficacy in smoking cessation in several small clinical trials. In depressed alcoholic participants, the SSRI fluoxetine decreased the number of cigarettes smoked (Cornelius, Perkins, Salloum, Thase, & Moss, 1999; Cornelius et al., 1997), but other studies did not note any decreases in smoking among nondepressed alcoholics (Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990; Sellers, Naranjo, & Kadlec, 1987). However, participants in these studies were not making an effort to quit. Double-blind, placebo-controlled trials in which the serotonin precursor (L-tryptophan), SSRI (fluoxetine), or releaser (dexfenfluramine) were given to promote smoking cessation and suppress participant weight gain after quitting detected a slight enhancement of cessation rates ranging from 5% to 28% (Bowen, Spring, & Fox, 1991; Spring, Bowen, Wurtman, Pingitore, & Kessler, 1993; Spring, Pingitore, & Kessler, 1992; Spring, Wurtman, Gleason, Wurtman, & Kessler, 1991; Spring et al., 1995). In those studies, dosages of 30 and 40 mg fluoxetine yielded quit rates comparable with placebo, whereas 60 mg produced a 13% increase in cessation. The addition of a lower dose (20 mg/day) of fluoxetine did not increase cessation rates over the nicotine inhaler alone, although confidence intervals were wide (Blondal et al., 1999). A study comparing the effects of sertraline versus placebo on smoking cessation among smokers with a past history of depression found no statistically significant differences, although effects were greater for the active compared with the placebo conditions at 6-month follow-up (Covey, Glassman, Stetner, & Rivelli, 2000). Finally, adding paroxetine to the nicotine patch increased short-term (4 weeks) cessation rates, but differences were no longer observed at 10- and 26-week follow-up (Killen et al., 2000).

We report here on a multicenter, randomized, and double-blind, placebo-controlled trial of fluoxetine for smoking cessation. A sample of 989 cigarette smokers were assigned to one of two doses of fluoxetine (30 or 60 mg) or placebo, concurrent with receiving cognitive-behavioral therapy, to test for dose-dependent effects. We hypothesized that both fluoxetine doses would promote smoking cessation more effectively than placebo and that a dose-response relationship would emerge. A 30-mg dose was studied because it approximates the 20–40-mg dosage range of fluoxetine that is customarily used to treat depression. Substantial evidence has established that the presence of depressive symptoms before and during a quit attempt decreases the likelihood of successful cessation (Anda et al., 1990; Covey, Glassman, & Stetner, 1990; Glassman, Stetner, Walsh, & et al., 1988; Glassman, 1993; Hughes, 1992; Kendler et al., 1993; Rausch, Nicholson, Lamke, & Matloff, 1990; West, Hajek, & Belcher, 1989; Zelman, Brandon, Jorenby, & Baker, 1992).

A 60-mg dose was studied because dosages of 60–80 mg have been found effective in treating other forms of compulsive behavior, including alcohol abuse (Goldbloom & Olmsted, 1993; Jimeron, Lesem, Kaye, & Brewerton, 1992; Piccinelli, Pini, Bellantuono, & Wilkinson, 1995; Wood, 1993). The higher dosage required to affect compulsive behavior, as compared with depression, has been attributed to the need to correct metabolic dysfunction in the orbital prefrontal cortex (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). It has been reported that high-dose chronic fluoxetine is required to cause down regulation of autoreceptors and serotonin release in the orbitofrontal cortex, whereas low-dose fluoxetine is ineffective (Ducharme, Bouchard, & Blier, 1996).

A task force of the Society for Research on Nicotine and Tobacco recently recommended improvements in data analysis for clinical trials of smoking treatments (Hall et al., 2001). The group was critical of the most widely used analytic strategy, which involves comparing the proportion abstinent in each treatment at each timepoint and assuming that missing data counted as smoking. Although that approach has the advantage of familiarity to investigators and ease of computation, it also presents many disadvantages. One drawback is that it assumes a perfect correlation between missingness and smoking status, thus artificially reducing the variance in the smoking status variable (to the extent that the correlation is not perfect). Additionally, the amount of data included in the missing-counted-as-smoking analysis is greater than the amount actually collected, thereby also reducing the observed variance in the smoking status variable. Artificially reducing the variance in smoking status yields statistical tests that are artificially too powerful, thus leading to overrejection of the null hypothesis. Finally, if treatment groups differ in the amount of missing data, this approach can also produce biased treatment comparisons. For example, if more missing data were present in the control than the experimental group, recoding missing to smoking would yield group comparisons favoring the experimental group (again, to the extent that the correlation between missingness and smoking status is less than the assumed perfect correlation). Thus, the widely held assumption that equating missing data with smoking represents a conservative (i.e., in terms of not rejecting the null hypothesis) approach to data analysis is not necessarily true. For these reasons, the Society for Research on Nicotine and Tobacco Task Force recommended alternative approaches that do not assume that missing counted as smoking and that permit modeling of change in smoking status over time. Here we report the use of one such longitudinal approach, pattern-mixture analysis, which makes it possible to directly evaluate the degree to which treatment effects, including the Treatment \times Time interaction, are affected by missing data. We compared the effects of fluoxetine on smoking cessation by longitudinal pattern-mixture analysis with cross-sectional analysis of the proportions at each time point made assuming that missing data counted as smoking.

In sum, the goals of this research were twofold. The first aim was to explore the dose-response effect of fluoxetine on smoking cessation. The second aim was to compare the outcomes of two different approaches with modeling missing data. One approach (missing data counted as smoking) has traditionally been considered the most conservative but more recently has been criticized as biased. The other (pattern mixture) represents a newly emerging and innovative approach to handling missing data.

Method

Participants

Participants enrolled in a double-blind, placebo-controlled multicenter trial investigating the effect of fluoxetine on smoking cessation. Participants were recruited by local radio, television, and print ads. The study was presented as an investigation of the efficacy of fluoxetine for smoking cessation. Sixteen sites screened a total of 1,137 participants, of whom 989 met eligibility criteria and were randomized. Entry criteria required that participants be 18–65 years old, have smoked daily for at least 1 year, exhibit a baseline breath carbon monoxide level greater than 8 ppm, agree to declare a quit date within 2 weeks after their second study visit, and read and sign an informed consent form. Study procedures and the consent form were reviewed and approved by institutional review boards at each study site. Exclusion criteria were a Hamilton Depression Rating Scale (Endicott, Cohen, Nee, Fleiss, & Sarantakos, 1981; Hamilton, 1960) score greater than 14; pregnancy; hypertension; use of psychotropic medication or current psychiatric illness; alcohol or drug abuse in the past year; current use of nicotine replacement; unstable medical condition or major health event in the past 6 months; use of smokeless tobacco, pipes, or cigars; recent experience of a major “life event” (e.g., divorce, major job change); suicidal ideation; and history of bipolar disorder.

A majority of participants were women (60.5%), and the average age was 41.7 years ($SD = 9.3$). The ethnic composition of the sample was 94.9% Caucasian, 4.0% African American, 0.3% Hispanic, 0.4% Asian, and 0.4% other ethnicity. At study entry, the average participant had smoked for 23.7 years ($SD = 9.3$) and smoked 27.6 cigarettes per day ($SD = 11.2$). Enrollees were moderately dependent on cigarettes, as indicated by a mean score of 6.4 ($SD = 1.9$) on the Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978). The entry cotinine level averaged 284 ng/mL ($SD = 178$), and mean baseline carbon monoxide level was 24 ppm ($SD = 11$).

Procedure

After an initial screening period, participants underwent a physical examination, chest X-ray, blood tests (complete blood chemistry and differential), and medical history. Candidates fulfilling eligibility criteria were randomly assigned to the placebo ($n = 333$), 30-mg ($n = 328$), or 60-mg ($n = 328$) conditions. At Visit 1, participants began the first of nine sessions of individual cognitive-behavioral treatment aimed at achieving and maintaining smoking cessation by the development of coping skills, stimulus control techniques, and relapse prevention. Each session lasted between 60 and 90 min. There was a treatment manual that outlined therapist and participant tasks and homework assignments for each visit. The therapists were doctoral-level staff who received standardized training in the cognitive-behavioral protocol during a prestudy investigator meeting. Treatment fidelity was ensured by prestudy training and by use of the treatment manual, which contained a checklist for each session. The checklist had to be completed by the clinician after each visit. Weekly local group supervision of therapy sessions included review of therapist session checklists and notes. The 10-week double-blind medication treatment phase began at Visit 2 (approximately 2 weeks prior to quit day) and continued through visits representing treatment Sessions 3–9 (2 weeks prior to quit day, and Days 1–3 postquit and Weeks 1, 2, 4, 6, and 8 postquit day, with the final visit representing end of treatment). During the medication phase, participants received either study medication or placebo and were instructed to take one capsule every morning. At Visit 2, participants were also required to set a quit date by Visit 4 (1–3 days after at least 14 days on medication). Participants were required to pay a \$25 deposit that was refunded at their last visit noncontingent on completion of the study or smoking status.

The final phase of the study was a 6-month no-drug follow-up period, which began after end of treatment (8 weeks after quit day and 10 weeks

after starting medication) and included only those participants who were abstinent at Visit 9, as verified by saliva cotinine (see *Smoking status* section). Follow-up Visits 10–13 were 12, 16, 24, and 32 weeks following quit day (or 4, 8, 16, and 26 weeks following end of treatment).

Measures

Smoking status. Smoking status was assessed at each visit. To be considered abstinent, participants were required to meet all three of the following criteria: (a) self-report of no smoking in the past 7 days, (b) carbon monoxide less than 8 ppm, and (c) saliva cotinine concentration less than 20 ng/mL (Cummings & Richard, 1988). Saliva cotinine samples were analyzed by SciCor Laboratory (Indianapolis, IN).

Treatment-emergent adverse events. Treatment-emergent adverse events were defined as conditions that were not present at baseline but appeared during the study or as conditions present at baseline that increased in severity during the study. Treatment-emergent adverse events were assessed by participant interview at each visit.

Reason for discontinuation was assessed at the end of the enrollee's participation in the study. Medication and behavioral treatment finished at Visit 9 (8 weeks postquit day), but participants may have terminated the study early for personal reasons or because of adverse events. Alternatively, they may have progressed through the end-of-treatment protocol and, if they were smoke free at end of treatment, continued on through the off-drug follow-up phase. Participants who were not abstinent at the end of treatment were not entered into the follow-up phase because it was assumed that they continued to smoke. If discontinuation occurred prior to end of treatment, blood, urine, and saliva were collected for laboratory and cotinine analyses. At the time of discontinuation, study medication was retrieved, and the participant received an exit physical examination.

Approach to Data Analysis

Baseline smoking history and sociodemographic variables were compared across conditions with one-way analyses of variance for continuously scaled variables and chi-square tests for differences between proportions for categorical variables. Incidence of treatment-emergent side effects and rates of treatment discontinuation were compared across treatment conditions using chi-square tests.

The primary outcome variable was biochemically verified smoking status at each treatment visit following quit day. Smoking status was analyzed using two approaches. The first approach consisted of chi-square tests for cross-sectional differences in the proportion of participants abstinent between conditions at each assessment interval. Logistic regression analyses of the same data were also performed allowing for the inclusion of covariates such as treatment site, gender, and Fagerstrom score. For these analyses, participants with missing data were counted as smokers at the intervals at which data were missing. This follows what has heretofore been standard procedure for intention-to-treat analyses. It has long been supposed that the missing-counted-as-smoking assumption implements a generally true, conservative strategy. It has also been assumed that even if the assumption is untrue, it biases outcome against the experimental treatment by reducing differences between experimental and control treatments. However, it is now recognized that the missing-data-counted-as-smoking assumption can lead to unpredictable and inaccurate estimates of treatment effects to the degree that missingness and smoking are not perfectly correlated as assumed (Hall et al., 2001). Consequently, we also used an alternative statistical method, a longitudinal pattern-mixture analysis (Hedeker & Gibbons, 1997; Hedeker & Rose, 2000; Little, 1995) that

provides more accurate estimates of treatment effects in the instance of missing data.¹

In the pattern-mixture approach, the effects of missing data patterns are included as explanatory variables in the longitudinal model of the repeated dichotomous smoking cessation outcomes. For example, participants might simply be classified into two patterns: those with complete versus those with incomplete smoking data across time. This subject-level variable and interactions with this variable are then included in the analysis to assess their influence on the longitudinally observed smoking outcomes. In this way, the influence of missing data on the study results is specifically examined rather than simply ignored. Because the pattern-mixture approach divides participants into missing-data groups (e.g., complete vs. incomplete data across time), it can be applied within any longitudinal data analysis model that allows incomplete data across time. Here, we embedded the pattern-mixture approach within a mixed-effects logistic regression model for longitudinal dichotomous data. Mixed-effects models have become increasingly used for analysis of longitudinal data (Verbeke & Molenberghs, 2000), and because our outcome is dichotomous (smoking: yes–no), we utilized the logistic regression version of the mixed-effects model. Finally, because smokers at the end of treatment were not allowed into the 6-month follow-up phase of the study, the pattern-mixture analysis was performed only on data available during the treatment phase of the study; the analysis could not be extended to the follow-up phase because this design limitation resulted in sparseness of data that precluded reliable model estimation. However, we conducted a survival analysis on time to relapse according to treatment condition for those participants who were abstinent at the end of treatment and who were followed during the next 6 months.

Results

Baseline Smoking History and Demographic Characteristics

As Table 1 shows, smokers randomized to the different treatment conditions showed no significant differences on age, number of years smoking, nicotine dependence, number of cigarettes smoked, carbon monoxide level, and cotinine level.

Adverse Events and Reasons for Discontinuation

Table 2 shows the incidence of treatment-emergent adverse events reported by at least 10% of participants and for which there was a statistically significant treatment difference ($p < .05$). Treatment-emergent side effects were in the expected direction

Table 1
Baseline Demographic and Smoking Variable Means and Standard Deviations by Condition

Variable	Placebo (<i>n</i> = 333)		30 mg (<i>n</i> = 328)		60 mg (<i>n</i> = 328)	
% female	61		63		58	
<i>M</i> and <i>SD</i>						
Age	41.4	9.6	41.6	9.1	42.1	9.4
CO level (ppm)	24.0	10.8	25.2	10.2	24.0	10.4
Fagerstrom	6.5	2.0	6.5	1.8	6.3	1.8
Cigs/day	26.8	11.0	27.9	11.1	28.2	11.7
No. of years smoking	23.4	9.6	23.6	9.1	24.3	9.3
Cotinine level (ng/mL)	289	179	312	180	294	171

Note. All comparisons of variables by condition were nonsignificant. CO = carbon monoxide; Cigs = cigarettes.

Table 2
Treatment-Emergent Signs and Symptoms by Condition

Event classification	Placebo (<i>n</i> = 333)		30 mg (<i>n</i> = 328)		60 mg (<i>n</i> = 328)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Amblyopia	1	0.3	4	1.2	11	13.4
Anorexia	11	3.3	19	5.8	33	10.1
Constipation	38	11.4	27	8.2	20	6.1
Gastrointestinal disorder	8	2.4	12	3.7	21	6.4
Nausea	45	13.5	87	26.5	104	31.7
Palpitation	4	1.2	12	3.7	15	4.6
Somnolence	29	8.7	55	16.8	77	23.5
Sweating	10	3.0	41	12.5	35	10.7
Thinking abnormal	45	13.5	45	13.7	64	19.5
Tremor	13	3.9	32	9.8	62	18.9
Yawn	2	0.6	22	6.7	47	14.3

Note. Conditions used were reported by at least 10% of the participants and had statistically significant condition differences ($p < .05$ as indicated by a chi-square test).

and generally appeared to be linearly dose dependent. Participants in the high-dose condition reported more adverse events than did participants in the placebo condition, and participants in the low-dose condition reported an intermediate number of side effects (see Table 2). Compared with participants in the placebo condition, participants treated with fluoxetine reported more amblyopia (dimness of sight), anorexia, gastrointestinal disorders, nausea, palpitations, somnolence, abnormal thinking, tremor, and yawning. Fluoxetine treatment was also associated with decreased constipation.

Compared with participants in the active-dose conditions, participants who received a placebo were more likely to discontinue treatment because of perceived lack of efficacy and participant decision not otherwise specified (Table 3). There was a dose-dependent relationship for discontinuation due to adverse events, with higher dose fluoxetine associated with higher rates of discontinuation in that category. However, there was no evidence of overall differential dropout in terms of either loss to follow-up or total discontinuations, which included discontinuation because of smoking at the final treatment visit.

Cessation Outcomes

In the first set of analyses, the primary outcome variable, biochemically verified abstinence from smoking (yes or no) at each treatment visit following quit day, was analyzed cross-sectionally using chi-square tests for differences between proportions. Missing data were assumed to equal smoking in these initial analyses.

¹ In addition to the pattern-mixture approach, missing data can be handled through a variety of other methods including data imputation methods and selection models. The appropriate use of various methods depends to a large degree on the pattern of missing data (e.g., missing completely at random, missing at random, nonignorable nonresponse). Discussion of these various approaches is beyond the scope of this article, and the reader is referred to a recent article by Hall et al. (2001), which discusses these issues in greater detail in relation to analysis of longitudinal smoking cessation outcomes in clinical trials.

Table 3
Reasons for Discontinuation According to Treatment Condition

Reason	Placebo (n = 333)		30 mg (n = 328)		60 mg (n = 328)	
	n	%	n	%	n	%
Lack of efficacy ^a	29	8.7	15	4.6	16	4.9
Lost to follow-up	13	3.9	16	4.9	22	6.7
Patient decision ^a	67	20.1	48	14.6	39	11.9
Adverse event ^a	16	4.8	51	15.5	80	24.4
Satisfactory response	4	1.2	2	0.6	0	0.0
Smoking at end of treatment	136	40.8	132	40.2	112	34.1
Total discontinued	265	79.6	264	80.5	269	82.0

^a Significant difference between groups at the $p < .05$ level, as indicated by a chi-square test. However, note there is no significant overall differential discontinuation according to treatment condition.

Table 4 presents the results in the top section. In general, there is little evidence for differentiation among the treatment conditions at any assessment interval, and there appears to be a steady decline in the proportion abstinent over time, which also does not appear to be influenced by treatment. Analyses of outcomes at each time-point with logistic regression, and including covariates such as site,² gender, and Fagerstrom score, showed no differences compared with the results of the chi-square analyses.

The second approach used a longitudinal perspective on the repeated smoking outcomes assessed during the treatment phase of the study; specifically, we used a mixed-effects logistic regression model implemented in the MIXOR software program (Hedeker & Gibbons, 1996). Mixed-effects models have become increasingly used for analysis of longitudinal data (Verbeke & Mohlenberghs, 2000), and because our outcome is dichotomous (smoking: yes–no), we used the logistic regression version of the mixed-effects model. In this approach, the dependency in the data due to the repeated assessment of participants over time is accounted for by including (random) subject effects in the model that indicate the influence of each subject on the outcome data. The subject effects are random because the study participants represent a sample from a larger population of participants. A primary advantage of mixed-effects models for longitudinal data is that they allow participants with incomplete data across time to be included in the analysis. The assumption of the mixed model is that that the missing outcomes are “ignorable” after accounting for a participant’s observed data (Laird, 1988). Essentially, this means that a participant’s missing outcome data are assumed to be statistically well-represented by their observed outcome data (in addition to any model covariates like treatment group and time). Because the plausibility of this assumption is difficult to ascertain (because the data are missing), we further examined the influence of missing data using a pattern-mixture approach (Hedeker & Gibbons, 1997; Little, 1995) as applied to our mixed-effects model. For this, participants were first divided into groups according to their pattern of missing data across time. After inspection of the patterns of missing visits, participants could be most efficiently grouped into two broad categories: (a) completers (those who attended all of the treatment visits, including the end-of-treatment visit prior to the follow-up phase; $n = 570$) and (b) noncompleters (those who

dropped out of treatment prior to the end-of-treatment; $n = 289$). Thus, the pattern-mixture mixed-effects logistic regression model of the repeated dichotomous smoking-cessation outcomes includes main effects for the missing data pattern, time, and treatment condition, followed by all two- and three-way interaction effects. In this way, we are not assuming perfect correlation of missingness and smoking (as does missing data counted as smoking), nor are we assuming that the missing data are ignorable (as in the ordinary mixed-effects logistic regression model), but instead we are going further and allowing the effect of the missing data pattern to be estimated and controlled. Additionally, estimates of the primary model effects (i.e., treatment condition, time, and their interaction) can be obtained by averaging across the missing-data patterns if there are no interactions with completer status. The pattern-mixture model therefore accommodates missing data, which is inevitable in most clinical trials, and it has the advantage of modeling and controlling for the effect of missing data on the effects of interest. The influence of treatment site was controlled for by including site as a series of dummy variables in the analysis (i.e., 15 dummy variables representing differences between the 16 sites).

Of the 989 participants, 130 provided no smoking status data at any of the postquit date treatment and follow-up visits (Visits 5 to 13) and so were not able to be included in the longitudinal analysis because they had no longitudinal data. However, we needed to verify that the 130 excluded participants would not introduce bias in the subsequent analyses. First, we examined the frequency distribution of those excluded according to treatment condition. These 130 individuals represented approximately equal percentages in all three intervention groups (13%, 12%, and 14% for the placebo, 30-mg, and 60-mg groups, respectively). We also examined whether the subject characteristics of those excluded differed according to treatment condition. In terms of variables assessed at baseline (see Table 1 for list), there were (a) no differences by included/excluded Status \times Treatment condition; (b) no interaction effects between those included and those excluded and treatment condition on these variables, and (c) significant group differences on certain variables between those included and those excluded. Compared with those participants whose outcome data were included in subsequent analyses, those excluded because of insufficient longitudinal data had higher Fagerstrom scores ($p < .01$), higher CO levels ($p < .05$), smoked more cigarettes/day ($p < .01$), smoked for fewer years ($p < .01$), and were younger ($p < .01$). Therefore, we concluded that excluding data by necessity (noninformativeness) for the 130 participants was not likely to have any material influence on the treatment-related findings derived from subsequent analyses. It is also important to note that by excluding the 130 participants, the groups may no longer have remained truly randomized if they differed on some unknown, unmeasured variable.

The incomplete treatment phase data section and the complete treatment phase data section of Table 4 present the proportion quit by time according to treatment condition and missing-data group (completer vs. noncompleter). From the pattern-mixture analysis, three sets of results pertaining to treatment completers and non-

² A list of the 16 sites along with site-specific enrollment and drop-out rates by treatment condition is available on request from Raymond Niaura.

Table 4
Proportion Quit × Time (7-Day Point Prevalence)

Condition	Week postquit day								MPP ^b	
	1	2	4	6	8 ^a	12	16	24		32
Missing data = smoking (<i>n</i> = 989)										
Placebo	.39	.36	.29	.27	.26	.25	.26	.19	.18	.10
30 mg	.43	.41	.38*	.34	.32	.27	.25	.20	.16	.10
60 mg	.45	.39	.38*	.35	.33	.29	.23	.19	.15	.10
Incomplete treatment phase data ^c										
Placebo	.25	.18	.09	.04						
30 mg	.29	.24	.18	.19						
60 mg	.29	.23	.18	.11						
Complete treatment phase data ^d										
Placebo	.54	.55	.46	.45	.44					
30 mg	.59	.60	.60*	.58*	.54*					
60 mg	.67*	.62	.63*	.64*	.62*					
Averaged results ^e										
Placebo	.45	.46	.39	.40	.44					
30 mg	.49	.50	.51*	.53*	.54*					
60 mg	.53	.50	.51*	.57*	.62*					
End-of-treatment abstainers ^f										
Placebo					.92	.96	.90	.91		
30 mg					.83	.84*	.91	.83		
60 mg					.85	.80*	.81	.86		

^a End of treatment. ^b Multiple point prevalence (MPP) denoting verified abstinence at the 26-week follow-up and at all preceding intervals. ^c *ns* = 289, 222, 163, and 80, respectively. ^d *ns* = 570, 570, 568, 558, and 570, respectively. ^e *ns* = 859, 792, 731, 638, and 570, respectively. ^f *ns* = 281, 256, 210, and 180, respectively. * Different than placebo at $p \leq .05$ by chi-square test.

completers are presented in Table 5: (a) the overall pattern-mixture model estimates for all participants introducing effects for completer status, its interaction with treatment, and the interactions between completer status, treatment, and time (note: the first six estimates [Pattern-mixture columns] characterize completers, whereas the next six estimates [Noncompleters columns] indicate deviations attributable to noncompleters); (b) estimates of treatment and time main effects, as well as their interactions, for participants with incomplete data based on the pattern-mixture model (note: these are obtained by adding the completer estimates with the estimates of the deviations attributable to noncompleters); and (c) results averaging across completers and noncompleters based on the pattern-mixture model (note: these are obtained as weighted averages of the completer and noncompleter estimates, the weight simply equaling the sample proportion of completers and noncompleters, respectively). Note that treatment effects were defined a priori as two contrasts: One compares the effect of placebo versus 30 mg fluoxetine, and the second compares the effect of placebo versus 60 mg fluoxetine.

The pattern-mixture analysis shows several results worth noting. First, the pattern-mixture effects for drug, time, and their interactions are to be interpreted as are those for completers. The main effect for noncompleter status and the interaction of Noncompleter Status × Time were both significant indicating, as expected, that noncompleters are more likely to be smokers and that their rate of

return to smoking is steeper compared with participants who complied with the protocol and provided complete data. However, because there are no significant three-way interactions of Drug × Noncompleter Status × Time, the averaged results across both completers and noncompleters can be interpreted (Table 5). The results for completers, noncompleters, and the averaged results are described in the paragraphs that follow.

Among the study completers, the placebo group increased smoking over time ($z = 0.27/0.06 = 4.67, p < .01$). The low-dose drug group did not differ significantly from the placebo group in terms of either Visit 5 (1 week postquit day) smoking or the trend across time in smoking (Table 4, complete treatment phase data). At Visit 5, the high-dose drug group showed less smoking than the placebo group ($z = -0.85/0.41 = -2.06, p < .04$) and this difference increased over time ($z = -1.90/0.08 = -2.28, p < .03$).

Among the study noncompleters, the placebo group increased smoking over time ($z = 1.63/0.403 = 3.99, p < .01$; Table 4, incomplete treatment phase data). Neither the low- or high-dose groups differed from the placebo group at Visit 5; however, the low-dose group showed significantly less smoking over time than the placebo group ($z = -0.94/0.46 = 2.03, p < .05$).

When results were averaged across completers and noncompleters, the placebo group showed increased smoking over time ($z = 0.58/0.26 = 2.28, p < .03$). Both drug groups significantly

Table 5
Longitudinal Analysis for Intratreatment Sessions: Mixed-Effects Pattern-Mixture Logistic Regression Results (n = 859)

Condition	Pattern mixture			Noncompleters			Averaged results		
	Est.	SE	p <	Est.	SE	p <	Est.	SE	p <
Intercept	-0.40	.27	.14	2.53	.54	.01	0.58	.26	.03
Time	0.27	.06	.01	1.63	.40	.01	0.73	.14	.01
Drug 1 (30 mg vs. placebo)	-0.52	.40	.21	-0.45	.72	.54	-0.49	.36	.18
Drug 2 (60 mg vs. placebo)	-0.85	.41	.04	-0.31	.71	.66	-0.67	.36	.07
Drug 1 × Time	-0.14	.09	.14	-0.94	.46	.05	-0.41	.17	.02
Drug 2 × Time	-0.19	.08	.03	-0.83	.47	.08	-0.40	.17	.02
Noncompleter	2.93	.62	.01						
Noncompleter × Time	1.35	.41	.01						
Noncompleter × Drug 1	0.07	.83	.94						
Noncompleter × Drug 2	0.54	.83	.52						
Noncompleter × Drug 1 × Time	-0.81	.47	.09						
Noncompleter × Drug 2 × Time	-0.64	.48	.19						

Note. Time is coded 0–4, representing Treatment Sessions 5–9 (Weeks 1, 2, 4, 6, and 8 postquit day, with the final visit representing end of treatment). Smoking outcomes are coded as 0 = not smoking and 1 = smoking. Noncompleter is coded as 0 = present at end of treatment (n = 570) and 1 = missing at end of treatment (n = 289). Dummy-coded site variables were also included in the analysis (not shown in the table) to account and adjust for possible site differences. Random subject effects were included in the analysis (not shown in the table) to account for the repeated measurements obtained from participants. Time, drug, and Time × Drug interaction effects in the pattern mixture analysis were equivalent to those for study completers. Est. = parameter estimate.

decreased smoking relative to the placebo group over time (low dose: $z = -0.41/0.17 = -2.43, p < .02$; high dose: $z = -0.40/0.17 = -2.41, p < .02$).

The results presented in Table 5 controlled for site effects, but for ease of presentation, the parameter estimates for the site effects are not shown. Effects were similar whether or not site was included as a covariate in the analysis. We also included as covariates in separate models gender, nicotine dependence score (Fagerstrom Tolerance Questionnaire), and their interactions with treatment condition. None of the main effects or interactions was significant. Therefore, we excluded these variables from the final model.

Participants with missing data during scheduled treatment visits were not assumed to be smokers on those occasions. However, on the basis of study protocol, participants who were smokers at the last treatment visit were excluded from further participation in the follow-up phase because it was assumed they were smoking. We therefore conducted a survival analysis (Cox regression) on time to relapse (smoking in the past 7 days) for those participants who were abstinent at end of treatment. Time to relapse was calculated as the interval between the end-of-treatment visit and the follow-up visit at which smoking was reported. Data were censored at time of subsequent loss to follow-up or at the end of the follow-up interval for those who completed all follow-up assessments and remained abstinent. Site effects were also included in this analysis as covariates. Results showed that both drug groups have an increased risk of relapse relative to the placebo group (Tables 6 and 7).

Discussion

Pattern-mixture analysis offered a more informative characterization of fluoxetine’s short-term effect on smoking cessation.

Unlike the traditional approach that counts missing as smoking, pattern mixture enabled us to model the effects of missing data on cessation outcomes during treatment, test Treatment × Time interactions, and determine whether treatment effects were consistent across different patterns of missing data. If we focus on the results of the pattern-mixture analysis, this study provides evidence that, compared with placebo, fluoxetine confers a significant, short-term benefit in terms of smoking cessation. This is illustrated most clearly when examining data from participants who completed treatment and results averaged across completers and noncompleters (Table 4). The pattern of missing data (i.e., whether participants dropped out before the end of treatment) did not apparently affect the results—although, predictably, dropping out was associated with a greater likelihood of being a smoker. It should be noted, however, that the pattern-mixture analyses cannot show whether the short-term effects of fluoxetine on cessation were maintained because not all participants were followed after the end of treatment. Of note, however, is the finding that, among those abstinent at the end of treatment, there was a significantly higher relapse rate among those who had been treated with fluoxetine at either dose compared with placebo. It would be interesting to know whether relapse to smoking among those who attained abstinence while on fluoxetine is related to unwanted effects, like

Table 6
Comparison of Drugs 1 and 2 by Estimated Parameter (Est.), Standard Error, and Probability

Contrast	Est.	SE	p
Drug 1 (30 mg vs. placebo)	.580	.291	.05
Drug 2 (60 mg vs. placebo)	.698	.279	.05

Table 7
*Time-to-Relapse Analysis for Post-End-of-Treatment Follow-Up:
 Cox Regression Results (End-of-Treatment Abstainers, n = 281)*

Group	n	Relapsed	Censored	Relapse rate
Placebo	82	20	62	24%
30 mg	98	35	63	36%
60 mg	101	39	62	39%

Note. Relapse times coded as 1–4, representing Follow-Up Visits 10–13 (Weeks 12, 16, 24, and 32 following quit day or Weeks 4, 8, 16, and 26 following end of treatment). Dummy-coded site variables were also included in the analysis (not shown in the table) to account and adjust for possible site differences. Outcomes coded as 0 = censor and 1 = relapse.

weight gain, that have been observed to occur after ex-smokers discontinue use of serotonergic agents (Spring et al., 1991, 1995).

Results of analyses that assumed missing data count as smoking can be interpreted as providing little to no evidence of efficacy of fluoxetine for smoking cessation either in the short- or in the long-term. These results contrast with the somewhat more optimistic findings obtained by the pattern-mixture analysis, at least for the short-term outcome. This presents a quandary for researchers who rely on studies to present definitive conclusions regarding the efficacy of a particular treatment. For reasons outlined previously and discussed elsewhere (Hall et al., 2001), we are inclined to reject the argument that missing data counted as smoking is the most conservative approach to analysis of smoking cessation outcomes in randomized clinical trials. The results of the pattern-mixture analysis are much more informative insofar as the effects of missing data can be formally modeled and can include tests of interactions with treatment and time. However, in this instance, even though results are more encouraging, there is insufficient evidence, in our opinion, to consider fluoxetine as either a first- or even a second-line treatment for smoking cessation. The results do suggest, however, that there may be reason to pursue testing the efficacy of SSRIs for certain subgroups of smokers, given the positive short-term findings. For those who adhere to a traditional standard, however, the results may suggest abandoning this line of investigation entirely.

Interpretation of the potential for therapeutic efficacy of fluoxetine must also be tempered by data on reasons for discontinuation and adverse events. Results for side effects and reasons for discontinuation are consistent with those seen in fluoxetine trials for other indications (Goldstein et al., 1994; Levine, Enas, & Thompson, 1989). Although rates of treatment completion did not differ between groups, discontinuation due to adverse events demonstrated a dose-dependent increase, and the rates of discontinuation due to adverse events at the 60-mg dose were quite high (e.g., greater than 25%), for example, compared with those seen for bupropion (less than 5%; Hurt et al., 1997). Thus, clinicians who choose to treat smokers with fluoxetine, especially at relatively high doses, should be prepared to encounter increased incidence of side effects and adverse events and will need to weigh these risks against possible clinical benefits.

The results of this study must also be evaluated in light of recent clinical trials for smoking cessation with other antidepressant agents. Hurt et al. (1997) demonstrated a linear dose-dependent increase in quit rates at 6 weeks and 3 months when

comparing three doses of bupropion (120 mg, 150 mg, 300 mg) with placebo. At 6 months and 1 year, however, the two higher doses produced similar quit rates, both of which were significantly greater than those seen in the placebo condition (e.g., 27.5% and 26.9% vs. 15.7% for 300 mg, 150 mg, and placebo, respectively, at 6 months). Hall et al. (1998) demonstrated a significant improvement in smokers treated with nortriptyline over smokers treated with placebo in 6- and 12-month quit rates (e.g., approximately 50% vs. 30% same-day point-prevalence abstinence for nortriptyline vs. placebo, respectively, at 6 months). Prochazka et al. (1998) reported a 6-month cessation rate of 14% versus 3% for smokers treated with nortriptyline versus placebo. In the present study, 6-month point-prevalence quit rates for participants who completed the treatment phase were 18%, 16%, and 18% for the 60-mg, 30-mg, and placebo conditions, respectively, assuming missing data counted as smoking. It is difficult to evaluate the comparative efficacy of the different antidepressant compounds across trials because of, among other factors, varying definitions of abstinence, varying types and duration of behavioral treatment, different placebo cessation rates, and whether dropouts were counted as smokers or not. However, compared with the antidepressant compounds tested in other trials, fluoxetine appears to have produced a smaller relative difference versus placebo.

Evidence indicates that three pharmacologically distinct compounds originally marketed for their antidepressant properties have similar, but not identical, effects on smoking. When combined with behavioral treatment, bupropion, nortriptyline, and fluoxetine all increase the likelihood of smoking cessation, although the relative effect of the first two compounds compared with placebo appears to be substantially greater than fluoxetine's. One possible way to interpret these findings is to propose that, with respect to antismoking impact, fluoxetine is functionally a weaker version of the other two compounds because it lacks significant dopaminergic action. According to this explanation, the serotonergic action of fluoxetine supplies a modest antismoking effect that is shared by nortriptyline and possibly also by bupropion. However, the catecholaminergic and particularly the dopaminergic action of the other two compounds may convey a more powerful antismoking action that fluoxetine lacks.

Another possible explanation is that fluoxetine exerts its antismoking effect differently and at least partially by its antidepressant action. Notably, neither history of depression nor current symptoms of depression (as measured by the Beck Depression Inventory) has been found to predict differential response to bupropion (Hayford et al., 1999). Similarly, Hall et al. (1998) found that history of depression failed to moderate the effect of nortriptyline on smoking cessation, although there was some suggestion that nortriptyline-induced alleviation of negative affect was related to abstinence, but only in the subset of smokers without a history of major depression. Findings for fluoxetine have been different, however. In analyses of subsets of smokers from this and related studies, we found that the presence of low-grade, subclinical symptoms of depression defined a subgroup of smokers who responded especially favorably to fluoxetine treatment (Hitsman et al., 1999; Niaura et al., 1995). Heightened responsiveness of depression-prone smokers to fluoxetine, and the absence of such selective response to bupropion or nortriptyline, occurred even though smokers in all of these trials were excluded if they were

clinically depressed. In this study, however, fluoxetine was not differentially effective for women versus men or for high- versus low-dependence smokers.

Several strengths and limitations of this study should be mentioned. This was a large, multicenter, randomized, double-blind clinical trial that evaluated effects of two doses of fluoxetine for smoking cessation among a sample of nicotine dependent, heavy smokers. Groups were equivalent at baseline on key sociodemographic and smoking related variables. Advanced statistical techniques were used to analyze the data, permitting accommodation for missing data, and more efficient use of available information. Moreover, we were able to evaluate and control for the effects of missing-data patterns on cessation outcomes. Site effects were also controlled in the analyses and did not materially affect the results. Among the limitations are failure to include process-to-outcome measures (e.g., changes in depressive symptoms, craving, coping behavior), which may have shed light on the mechanisms responsible for fluoxetine's short-term efficacy at high doses. Also, our pattern-mixture analysis only included those participants who provided smoking data at one postquit date visit at least. Thus, the 130 participants who were randomized to treatment but provided no postquit date smoking data were not included. These participants were equally represented in the three treatment groups, so the treatment-related comparisons of our pattern-mixture analysis are unlikely to be biased; however, the absolute quit rates may be inflated. The reported abstinent rates for completers and noncompleters in Table 4 also may generalize only to the subset of smokers who stay in treatment at least until after quit day. Another limitation of our use of the pattern-mixture approach is that we combined many patterns of missing data into a single noncompleter group. However, the sample size and relatively low rates of abstinence among these noncompleters did not support finer divisions within this group. The study was also limited by the design feature in which smokers at the end of treatment were excluded from follow-up, necessitating a loss of information. Yet another limitation, common to most clinical trials of this nature, is the highly select nature of the sample in terms of high levels of motivation to quit and generally good physical and mental health. It is unknown to what degree the results of this study would generalize to other populations of smokers, especially those interested in trying to quit with no or minimal additional assistance. It should also be noted that the adjunctive behavioral treatment was quite intense in frequency and duration, and it is unknown to what degree behavioral treatment may have interacted with the pharmacologic treatment. For example, intense behavioral treatment, which is a powerful intervention in its own right (Fiore et al., 2000), may have decreased the opportunity to observe larger differences between the drug conditions had a less intensive behavioral adjunct been used.

In summary, this study provides support for a modest, short-term effect of high-dose fluoxetine on smoking cessation. Use of fluoxetine must be weighed against a high incidence of side effects. Research efforts are warranted to compare the relative efficacy of different antidepressant agents as adjuncts to standardized behavioral smoking cessation treatment. Efforts are also needed to define subgroups of smokers who may benefit more from fluoxetine's effects.

References

- Anda, R. F., Williamson, D. F., Escobedo, L. G., Mast, E. E., Giovino, G. A., & Remington, P. L. (1990). Depression and the dynamics of smoking. A national perspective. *JAMA*, *264*, 1541-1545.
- Blondal, T., Gudmundsson, L. J., Tomasson, K., Jonsdottir, D., Hilmarsdottir, H., & Kristjansson, F. (1999). The effects of fluoxetine combined with nicotine inhalers in smoking cessation—A randomized trial. *Addiction*, *94*, 1007-1015.
- Bowen, D. J., Spring, B., & Fox, E. (1991). Tryptophan and high-carbohydrate diets as adjuncts to smoking cessation therapy. *Journal of Behavioral Medicine*, *14*, 97-110.
- Centers for Disease Control. (1994). Cigarette smoking among adults: United States, 1993. *Morbidity and Mortality Weekly Report*, *43*, 925-930.
- Centers for Disease Control. (1999). State-specific prevalence of current cigarette smoking among adults: United States, 1998. *Morbidity and Mortality Weekly Report*, *48*, 1034-1039.
- Cornelius, J. R., Perkins, K. A., Salloum, I. M., Thase, M. E., & Moss, H. B. (1999). Fluoxetine versus placebo to decrease the smoking of depressed alcoholic patients [letter]. *Journal of Clinical Psychopharmacology*, *19*, 183-184.
- Cornelius, J. R., Salloum, I. M., Ehler, J. G., Jarret, P. J., Cornelius, M. D., & Black, A. (1997). Double-blind fluoxetine in depressed alcoholic smokers. *Psychopharmacology Bulletin*, *33*, 165-170.
- Covey, L. S., Glassman, A. H., & Stetner, F. (1990). Depression and depressive symptoms in smoking cessation. *Comprehensive Psychiatry*, *31*, 350-354.
- Covey, L. S., Glassman, A. H., Stetner, F., & Rivelli, S. (2000, March). A trial of sertraline for smokers with past major depression. Paper presented at the Society for Research on Nicotine and Tobacco, Arlington, VA.
- Cummings, S. R., & Richard, R. J. (1988). Optimum cutoff points for biochemical validation of smoking status. *American Journal of Public Health*, *78*, 574-575.
- Ducharme, V. G., Bouchard, C., & Blier, P. (1996). Terminal 5-HT autoreceptor desensitization in the orbitofrontal cortex is produced exclusively by drugs effective in obsessive compulsive disorder. *Society for Neuroscience Abstracts*, *22*, 525.
- Endicott, J., Cohen, J., Nee, J., Fleiss, J., & Sarantakos, S. (1981). Hamilton Depression Rating Scale: Extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. *Archives of General Psychiatry*, *38*, 98-103.
- Fagerstrom, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors*, *3*, 235-241.
- Fiore, M., Bailey, W., Cohen, S., Dorfman, S. F., Goldstein, M. G., Gritz, E. R., et al. (2000). *Treating tobacco use and dependence. Clinical practice guideline*. Rockville, MD: Department of Health and Human Services, Public Health Service.
- Glassman, A. (1993). Cigarette smoking: Implications for psychiatric illness. *American Journal of Psychiatry*, *150*, 546-553.
- Glassman, A., Stetner, F., Walsh, B., Raizman, P. S., Fleiss, J. L., Cooper, T. B., & Covey, L. S. (1988). Heavy smokers, smoking cessation, and clonidine: Results of a double-blind, randomized trial. *JAMA*, *259*, 2863-2866.
- Goldbloom, D. S., & Olmsted, M. P. (1993). Pharmacotherapy of bulimia nervosa with fluoxetine: Assessment of clinically significant attitudinal change. *American Journal of Psychiatry*, *150*, 770-774.
- Goldstein, D. J., Rampey, A. H. J., Enas, G. G., Potvin, J. H., Fludzinski, L. A., & Levine, L. R. (1994). Fluoxetine: A randomized clinical trial in the treatment of obesity. *International Journal of Obesity*, *18*, 129-135.
- Hall, S. M., Delucchi, K., Velicer, W., Kahler, C., Ranger-Moore, J., Hedeker, D., et al. (2001). Statistical analysis of randomized trials in

- tobacco treatment: Longitudinal designs with dichotomous outcomes. *Nicotine & Tobacco Research*, 3, 193–202.
- Hall, S. M., Reus, V. I., Munoz, R. F., Sees, K. L., Humfleet, G., Hartz, D. T., et al. (1998). Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Archives of General Psychiatry*, 55, 683–690.
- Hamilton, M. A. (1960). A rating scale for depression. *Journal of Neurological and Neurosurgical Psychiatry*, 23, 56–62.
- Hayford, K. E., Patten, C. A., Rummans, T. A., Schroeder, D. R., Offord, K. P., Croghan, I. T., et al. (1999). Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *British Journal of Psychiatry*, 174, 173–178.
- Hedeker, D., & Gibbons, R. D. (1996). MIXOR: A computer program for mixed-effects ordinal regression analysis. *Computer Methods and Programs in Biomedicine*, 49, 157–176.
- Hedeker, D., & Gibbons, R. D. (1997). Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods*, 2, 64–78.
- Hedeker, D., & Rose, J. S. (2000). The natural history of smoking: A pattern-mixture random-effects regression model. In J. S. Rose, L. Chassin, C. C. Presson, & S. J. Sherman (Eds.), *Multivariate applications in substance abuse research* (pp. 79–112). Mahwah, NJ: Erlbaum.
- Hitsman, B., Pingitore, R., Spring, B., Mahableshwarkar, A., Mizes, J. S., Segraves, K. A., et al. (1999). Antidepressant pharmacotherapy helps some smokers more than others. *Journal of Consulting and Clinical Psychology*, 67, 547–554.
- Hughes, J. (1992). Tobacco withdrawal in self-quitters. *Journal of Consulting and Clinical Psychology*, 60, 689–697.
- Hurt, R. D., Sachs, D. P. L., Glover, E. D., Offord, K. P., Johnston, J. A., Dale, L. C., et al. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine*, 337, 1195–1202.
- Jimerson, D. C., Lesem, M. D., Kaye, W. H., & Brewerton, T. D. (1992). Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. *Archives of General Psychiatry*, 49, 132–138.
- Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J., Kessler, R. C., et al. (1993). Smoking and major depression: A causal analysis. *Archives of General Psychiatry*, 50, 36–43.
- Killen, J. D., Fortmann, S. P., Schatzberg, A. F., Hayward, C., Sussman, L., Rothman, M., et al. (2000). Nicotine patch and paroxetine for smoking cessation. *Journal of Consulting and Clinical Psychology*, 68, 883–889.
- Laird, N. M. (1988). Missing data in longitudinal studies. *Statistics in Medicine*, 7, 305–315.
- Levine, L. R., Enas, G. G., & Thompson, W. L. (1989). Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: A dose-response study. *International Journal of Obesity*, 13, 635–645.
- Little, R. J. A. (1995). Modeling the drop-out mechanism in repeated-measures studies. *Journal of the American Statistical Association*, 90, 1112–1121.
- Naranjo, C. A., Kadlec, K. E., Sanhueza, P., Woodley-Remus, D., & Sellers, E. M. (1990). Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clinical Pharmacology and Therapeutics*, 47, 490–498.
- Niaura, R., Goldstein, M., DePue, J., Keuthen, N., Kristeller, K., & Abrams, D. (1995). Fluoxetine, symptoms of depression, and smoking cessation. *Annals of Behavioral Medicine*, 17(Suppl.), 61.
- Piccinelli, M., Pini, S., Bellantuono, C., & Wilkinson, G. (1995). Efficacy of drug treatment in obsessive-compulsive disorder: A meta-analytic review. *British Journal of Psychiatry*, 166, 424–443.
- Prochazka, A. V., Weaver, M. J., Keller, R. T., Fryer, G. E., Licari, P. A., & Lofaso, D. (1998). A randomized trial of nortriptyline for smoking cessation. *Archives of Internal Medicine*, 158, 2035–2039.
- Rausch, J. L., Nicholson, B., Lamke, C., & Matloff, J. (1990). Influences of negative affect on smoking cessation treatment outcome: A pilot study. *British Journal of Addiction*, 85, 929–933.
- Russell, M. A. H. (1994). Overview of research on smoking cessation. In K. Sima (Ed.), *Tobacco and health* (pp. 425–429). New York: Plenum Press.
- Schwartz, J. M., Stoessel, P. W., Baxter, L. R., Jr., Martin, K. M., & Phelps, M. E. (1996). Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Archives of General Psychiatry*, 53, 109–113.
- Sellers, E. M., Naranjo, C. A., & Kadlec, K. (1987). Do serotonin uptake inhibitors decrease smoking? Observations in a group of heavy drinkers. *Journal of Clinical Psychopharmacology*, 7, 417–420.
- Spring, B., Bowen, D., Wurtman, J., Pingitore, R., & Kessler, K. (1993). Weight gain related to tobacco withdrawal. In E. Ferrari, F. Brambilla, & S. B. Solerte (Eds.), *Primary and secondary eating disorders: A psychoendocrine and metabolic approach* (pp. 501–506). New York: Pergamon Press.
- Spring, B., Pingitore, R., & Kessler, K. (1992). Cigarette smoking and body weight: Strategies to minimize weight gain after smoking cessation. *International Journal of Obesity*, 16(Suppl. 3), 19–23.
- Spring, B., Wurtman, J., Gleason, R., Wurtman, R., & Kessler, K. (1991). Weight gain and withdrawal symptoms after smoking cessation: A preventive intervention using d-Fenfluramine. *Health Psychology*, 10, 216–223.
- Spring, B., Wurtman, J., Wurtman, R., El-Khoury, A., Goldberg, H., McDermott, J., & Pingitore, R. (1995). Efficacies of dexfenfluramine and fluoxetine in preventing weight gain after smoking cessation. *American Journal of Clinical Nutrition*, 62, 1181–1187.
- Verbeke, G., & Mohlenberghs, G. (2000). *Linear mixed models for longitudinal data*. New York: Springer-Verlag.
- West, R. J., Hajek, P., & Belcher, M. (1989). Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. *Psychological Medicine*, 19, 981–985.
- Wood, A. (1993). Pharmacotherapy of bulimia nervosa—Experience with fluoxetine. *International Journal of Clinical Psychopharmacology*, 8, 295–299.
- Zelman, D. C., Brandon, T. H., Jorenby, D. E., & Baker, T. B. (1992). Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. *Journal of Consulting and Clinical Psychology*, 60, 943–952.

Received July 20, 2000

Revision received August 14, 2001

Accepted October 12, 2001 ■