A Randomized, Placebo-Controlled Clinical Trial of Bupropion for the Prevention of Smoking in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

Michael C. Monuteaux, Sc.D.; Thomas J. Spencer, M.D.; Stephen V. Faraone, Ph.D.; Angela M. Wilson, M.A.; and Joseph Biederman, M.D.

Objective: Since attention-deficit/hyperactivity disorder (ADHD) is a well-documented risk factor for smoking and bupropion has been shown to be effective for smoking cessation, we tested the efficacy of bupropion as a prophylactic agent for the prevention of smoking in children and adolescents with ADHD.

Method: We conducted a longitudinal, randomized, double-blind, placebo-controlled, parallel-group study of bupropion at a large, urban, outpatient medical center. Recruitment began in April 1999, and the last subject was followed until September 2004. Patients were nonsmoking youth, of both sexes, between 9 and 18 years of age, with DSM-IV ADHD. After random assignment to either bupropion or placebo, subjects were assessed weekly for 8 weeks, biweekly for 4 weeks, and monthly thereafter for up to 6.5 years (mean 12 months). Also, patients received treatment with psychostimulants for ADHD symptoms as needed. To assess smoking, we used an assay of cotinine in urine.

Results: Fifty-seven subjects (28 receiving bupropion and 29 receiving placebo) were randomly assigned and included in the analysis. No differences were found between the bupropion and placebo groups on demographic factors. About half of each group was treated with stimulants for ADHD. Statistical separation between bupropion and placebo in the rate of smoking initiation or continued smoking was not demonstrated. However, secondary post hoc analyses revealed that concurrent stimulant treatment was significantly associated with a lower rate of smoking onset (hazard ratio [HR] = 0.2, 95% CI = 0.08 to 0.89; z = –2.2, p = .03) and a lower rate of continued smoking (HR = 0.3, 95% CI = 0.11 to 0.85; z = –2.3, p = .02).

Conclusion: While bupropion was not associated with a lower rate of smoking in youth with ADHD, post hoc analyses suggest that stimulant treatment was. Future controlled studies should investigate the role of stimulants in the prevention of smoking in children and adolescents with ADHD.

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Corresponding author and reprints: Michael C. Monuteaux, Sc.D., Pediatric Psychopharmacology Program, 55 Fruit Street, Warren 705, Boston, MA 02114 (e-mail: mmonuteaux@partners.org).

Cigarette smoking among children and adolescents has long been recognized as a serious public health problem.[1] A nationwide survey of high school students revealed that nearly 70% of students had tried cigarette smoking in their lifetime, and nearly one third of the students were smoking currently.[2] Of those students who smoked daily, 44% believed that, in 5 years, they would not be smoking; however, at follow-up 5 to 6 years later, 73% remained daily smokers.[2]

One well-documented risk factor for regular smoking and nicotine dependence is attention-deficit/hyperactivity disorder (ADHD). Studies show that as children with ADHD reach adolescence, they are significantly more likely to smoke than controls.[3–7] Our group[5,6] showed that ADHD was a significant predictor of early initiation of cigarette smoking (mean age 15 years). Downey et al.[8] showed that adult ADHD smokers began smoking at a younger age than non-ADHD smokers. Moreover, adult ADHD patients have elevated rates of smoking and find it extremely difficult to quit.[9]

In addition to the direct health effects, cigarette smoking often represents an early stage of the developmental sequence into illicit drug use.[10,11] We recently found smoking to be a significant risk factor for the subsequent use and abuse of drugs, particularly in ADHD youth.[12] Thus, efforts aimed at the prevention of smoking would have impact not only on reduction in cancer, chronic lung

disease, and coronary heart disease but possibly on the serious problem of substance abuse.

Although the reasons for the link between smoking and ADHD remain unclear, theoretical considerations suggest that the 2 conditions might share common underlying mechanisms. Notably, the putative underlying mechanisms of ADHD[13] and the pharmacologic effects of nicotine in the brain are believed to share common neurotransmitter systems.[14,15] Medications that are effective in the treatment of ADHD (e.g., stimulants and noradrenergic/dopaminergic antidepressants) modulate noradrenergic and dopaminergic activity,[16–18] which parallel the effects of nicotine in the central nervous system.[19]

Bupropion is an aminoketone compound that is thought to work primarily via noradrenergic and dopaminergic pathways in the central nervous system.[20,21] Bupropion has been shown to be effective for smoking cessation in adult smokers and has gained FDA approval for smoking cessation. Bupropion has also been shown to be effective in the treatment of ADHD in both adults[22,23] and children.[24] Because of its unique pharmacologic profile of mixed dopaminergic and noradrenergic effects, along with its known efficacy for the treatment of smoking cessation, bupropion could be an ideal candidate for an intervention seeking to prevent initiation of smoking in children and adolescents with ADHD.

The objective of the present study was to evaluate the prophylactic effects of bupropion to avert initiation of smoking in youths with ADHD. The study used a balanced, double-blind, placebo-controlled study design assessing bupropion's efficacy for the prevention of smoking in a high-risk group of children and adolescents with ADHD, some of whom are treated with psychostimulants. We hypothesized that bupropion would be associated with a reduced rate of smoking initiation compared to placebo in children and adolescents with ADHD.

METHOD

Subjects

We enrolled outpatient youth of both sexes between 9 and 18 years of age diagnosed with DSM-IV ADHD who were without a history of regular nicotine use (i.e., at least one cigarette per day for at least 30 days) from the pediatric psychiatric clinic at the Massachusetts General Hospital (MGH) and through advertisement in local and regional media. We included subjects who had experimented with smoking (i.e., 1–2 cigarettes smoked lifetime). No ethnic or racial groups were excluded. Potential subjects were excluded if they were currently using psychotropic medications (except stimulants to treat ADHD), or if they had any clinically significant chronic medical conditions (including serious hypertension), clinically significant abnormal baseline laboratory values, a history of seizures, an I.Q. less than 75, organic brain disorders, an eating disorder, psychosis, or an inadequate command of the English language. We also excluded patients currently (within the past 2 months) known to have abused or to have been dependent on any drug, including alcohol, patients with current bipolar disorder, and pregnant or nursing females. Recruitment began in April 1999, and the last subject was followed until September 2004. After a complete description of the study, the parents of all patients provided written informed consent prior to any study procedures. In addition, patients provided a written assent. The institutional review board of Massachusetts General Hospital approved this study.

Procedure

We conducted a balanced, randomized, double-blind, placebo-controlled, parallel-design study of bupropion. After an initial baseline assessment to determine study eligibility, patients were randomly assigned to bupropion or placebo by the Massachusetts General Hospital research pharmacy at a ratio of 1:1 and assessed weekly for 8 weeks, biweekly for a month (2 visits), and monthly thereafter until the patient discontinued participation or the study concluded. Raters and patients were blind to treatment assignment.

Study medication (bupropion/placebo) was taken once a day (if subjects were taking one tablet) or twice a day (if subjects were taking 2 tablets). All patients began study medication at 100 mg/day at baseline and were then titrated up to 2 mg/kg to a maximum 150 mg daily in week one, 3 mg/kg to a maximum 200 mg daily by week 2, and 4 mg/kg maximum of 300 mg daily by week 3. Doses were adjusted downward if the patient reported side effects due to the medication.

Patients, in conjunction with a study physician, determined the need to stabilize ADHD symptoms prior to random assignment with openly administered stimulant treatment. Also, subjects were permitted to begin concurrent stimulant treatment during the trial if the judgment of the study physician deemed such therapy necessary to control ADHD symptoms. Among the 99 subjects who were randomly assigned, 14 began stimulant therapy prior to randomization, and an additional 16 subjects were treated with concurrent stimulants subsequent to being randomized. We converted doses for mixed amphetamine salts to methylphenidate equivalents using a 3:4 ratio (i.e., 1 mg of methylphenidate = 0.75 mg of mixed amphetamine salts).[25,26]

Assessment

At the screening, we obtained demographic information, including social class as measured by the Hollingshead scale,[27] and racial/ethnic background. The investigator defined the answer options for racial/ethnic background, and the subjects classified themselves. At baseline, we obtained blood pressure, pulse, height, and

weight measurements; electrocardiograms; illicit drug tests (via urine); and standard clinical blood tests (complete blood count [CBC]/liver function) to determine study eligibility. All patients were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Lifetime Version (K-SADS-L),[28] a semistructured interview designed to assess current and past episodes of psychopathology in youth according to DSM-IV criteria. We conducted direct interviews with subjects and indirect interviews with their mothers (i.e., mothers completed the structured interview about their offspring). We combined data from direct and indirect interviews by considering a diagnostic criterion positive if it was endorsed in either interview.

Measures of smoking status, psychiatric symptoms, and clinical outcomes were collected at every study visit. To avoid uncertainties of self-report, assessment of smoking relied on a radioimmunoassay of cotinine in urine, which can detect cotinine concentrations in urine as low as 0.01 mcg/mL. A positive test was defined as a cotinine level of 200 ng/mL or greater. Cotinine, the major metabolite of nicotine, is widely used and accepted as a biological marker to confirm nicotine exposure.[29] Although quantitative cotinine measures have been used to detect both smoking and environmental exposure to nicotine, the amount of cotinine excreted as a result of environmental exposures is considerably less than concentrations from smoking. Since the half-life of cotinine is variable (17 ± 5 hours), and consistent nicotine administration results in the accumulation and slow release of nicotine from tissue stores, a urine test will detect nicotine use in children who are smoking regularly.

Weight, height, vital signs, use of concomitant medications, and adverse events were obtained at each visit. At the last study visit, blood pressure, pulse, height, and weight measurements, electrocardiograms, and standard clinical blood tests (CBC/liver function) were repeated.

Statistical Analysis

Although we randomly assigned patients to a treatment regimen, the groups may still have differed on factors relevant to the study hypotheses. Thus, we first compared the bupropion and placebo groups on baseline demographic and clinical features using t tests for dimensional variables (e.g., age) and Pearson χ^2 tests for binary variables (e.g., sex).

To assess our primary hypothesis, that bupropion therapy would be associated with a reduced initiation of smoking, we used Cox proportional hazard survival models.[30] Advantages of the proportional hazards model are its ability to handle censored observations (e.g., subjects who do not smoke or who are lost to follow-up) and its ability to model variables that change over time (e.g., concurrent therapy). For each patient at each assessment, the outcome was defined as a positive cotinine test and negative otherwise. We used the earliest week with a positive cotinine test as the survival time for cases and the last week of follow-up as the time of censoring for noncases. We used multiple observations per subject to accommodate time-varying covariates. Measures of effect and precision from Cox models were expressed as hazard ratios (HRs) and 95% CIs. All tests were 2-tailed, and significance was determined at $p < .05$.

RESULTS

Recruitment, Screening, and Attrition

One hundred thirty subjects were screened (Figure 1). Thirty-one subjects were either excluded by design or were unwilling to participate in the study, leaving 99 subjects to be randomly assigned (49 to bupropion and 50 to placebo). Forty-two subjects were dropped or withdrew from the study before the fourth week: 3 at baseline, 35 at week 1, 3 at week 2, and 1 at week 3. Dropouts were due to a withdrawal of consent (N = 38) and a failure to adhere to the study schedule (N = 4). The proportion of subjects dropping from the study prior to week 4 did not differ between the bupropion and placebo groups (43% vs. 42%, respectively, $\chi^2 = 0.01$, df = 1, p = .93). There were no positive cotinine tests at any week among the 42 dropped subjects. Unless otherwise noted, the following results pertain to the subjects (28 receiving bupropion and 29 receiving placebo) who were followed for at least 4 weeks.

The mean ± SD length of follow-up did not significantly differ between the placebo and bupropion groups (72.1 ± 48.2 weeks versus 54 ± 48 weeks, respectively; t = 1.42, df = 55, p = .16). The minimum length of follow-up was 4 weeks (1 bupropion patient), and the maximum was 168 weeks (1 patient from each group).

Demographic Characteristics

We compared the 2 groups on baseline demographic factors. As noted in Table 1, there were no statistically significant differences between the bupropion and placebo groups in age, sex, social class, race/ethnicity, cognitive performance, symptomatology, or stimulant treatment. The sample had a mean age of approximately 13 years, was 70% male, 80% white, and had slightly below average cognitive performance. There were also no differences at baseline in heart rate, weight, height, or diastolic blood pressure. However, the bupropion group had a significantly higher systolic blood pressure compared to the placebo group.

Bupropion Therapy

The mean dose of bupropion (or placebo) was titrated upward in the first 4 weeks of the study, per the protocol. The mean ± SD doses in weeks 1, 2, 4, 12, 24, and 52 were 1.7 ± 0.6 mg/kg, 2.3 ± 0.8 mg/kg, 3.1 ± 1.0 mg/kg, 3.3 ± 0.9 mg/kg, 3.3 ± 0.9 mg/kg, and 3.2 ± 1.0 mg/kg.

Figure 1. Recruitment and Treatment Assignment

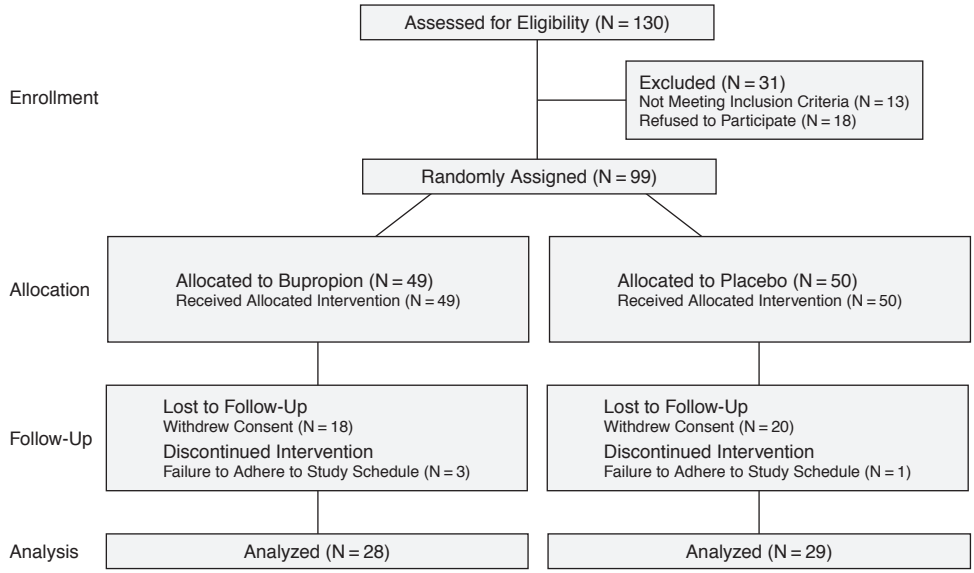


Table 1. Baseline Comparison of Demographic Features in Children and Adolescents Randomly Assigned to Bupropion or Placebo

Characteristic	Placebo, N = 29	Bupropion, N = 28	Baseline Comparisons		
			Test Statistic	df	p Value
Age, mean ± SD, y	13.2 ± 2.3	13.0 ± 2.3	t = 0.32	55	.75
Male sex, N (%)	20 (69)	20 (71)	χ^2 = 0.04	1	.84
Socioeconomic status,[a] mean ± SD	2.1 ± 0.8	2.0 ± 0.8	t = 0.82	55	.42
Race/ethnicity, N (%)			χ^2 = 3.62	4	.46
African American	2 (7)	5 (18)			
Asian	0 (0)	1 (4)			
White	25 (86)	21 (75)			
Hispanic	1 (3)	1 (4)			
Other	1 (3)	0 (0)			
Full-Scale IQ estimate, mean ± SD	99.6 ± 14.1	102.0 ± 11.7	t = –0.66	50	.51
WRAT[31] reading score, mean ± SD	102.2 ± 9.1	102.6 ± 11.7	t = –0.12	50	.91
WRAT[31] arithmetic score, mean ± SD	96.9 ± 9.4	96.3 ± 14.5	t = 0.17	50	.87
Learning disability, N (%)	8 (29)	6 (24)	χ^2 = 0.14	1	.71
DSM-IV ADHD checklist, mean ± SD	22.7 ± 13.2	20.3 ± 13.7	t = 0.69	55	.50
Conduct disorder checklist, mean ± SD	1.2 ± 2.8	0.7 ± 1.7	t = –0.73	49	.47
BDI score, mean ± SD	3.8 ± 5.0	4.8 ± 5.9	t = –0.71	49	.48
Stimulant treatment, N (%)	4 (14)	9 (32)	χ^2 = 2.72	1	.10
Heart rate, mean ± SD, bpm	82.1 ± 10.6	80.8 ± 14.0	t = 0.39	54	.70
Systolic blood pressure, mean ± SD, mm Hg	108.8 ± 17.1	118.5 ± 17.2	t = –2.10	54	.04
Diastolic blood pressure, mean ± SD, mm Hg	63.1 ± 8.7	65.7 ± 9.7	t = –1.04	54	.30
Height, mean ± SD, m	1.6 ± 0.2	1.6 ± 0.2	t = –1.24	54	.22
Weight, mean ± SD, kg	52.5 ± 16.9	63.0 ± 25.5	t = –1.82	54	.07

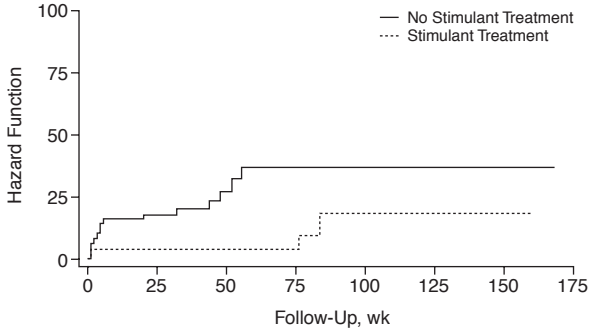
[a]Socioeconomic status measured by the Hollingshead scale[27]; score ranges from 1(most affluent) through 5 (least affluent).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BDI = Beck Depression Inventory, df = degrees of freedom, WRAT = Wide Range Achievement Test.

The mean ± SD maximum dose per subject was 3.5 ± 0.8 mg/kg. Doses ranged from 100 mg per day to 350 mg per day.

Concurrent Stimulant Therapy

As noted in Table 1, 13 subjects (4 in the placebo group and 9 in the bupropion group) began stimulant therapy prior to randomization. Among placebo patients, 3 were given osmotically controlled-release oral delivery system methylphenidate (OROS-MPH) and 1 a biphasic long-acting formulation of MPH. Bupropion patients were treated with mixed amphetamine salts (N = 4), OROS-MPH (N = 3), and spheroidal oral drug absorption system methylphenidate (SODAS-MPH) (N = 2). Subsequent to random assignment, an additional 10 subjects in the placebo group and 6 subjects in the bupropion group were

Figure 2. Concurrent Stimulant



treated with concurrent stimulants. The 10 placebo patients were treated with mixed amphetamine salts (N = 4), OROS-MPH (N = 5), and SODAS-MPH (N = 1). The 6 bupropion patients were treated with OROS-MPH (N = 5) and SODAS-MPH (N = 1). The overall rate of stimulant treatment between the placebo and bupropion groups did not significantly differ (N = 14, 48% versus N = 15, 54%, respectively; $\chi^2 = 0.16$, df = 1, p = .69). The mean ± SD maximum dose per subject (mg/kg) did not significantly differ between the placebo and bupropion groups (1.0 ± 0.4 versus 1.0 ± 0.4, respectively; t = –0.47, df = 27, p = .64; range 0.2–2.0 mg/kg).

Prevention of Smoking

Throughout the study, the rate of any positive cotinine screen was 28% in the placebo group and 46% in the bupropion group ($\chi^2 = 2.17$, df = 1, p = .14). We estimated the effect of bupropion on the onset of smoking as measured by the first positive cotinine screen, adjusted for sex with a Cox survival model. Patients treated with bupropion were 2.3 times more likely to initiate smoking over the course of the follow-up period relative to those treated with placebo, although this difference was not significant (HR = 2.3, 95% CI = 0.94 to 5.41); z = 1.8, p = .07). We repeated this model, allowing subjects who initiated smoking to reenter the analysis. Thus, we allowed for multiple failures per subject, testing the hypothesis that bupropion would be associated with a decrease in continued smoking relative to placebo. Patients treated with bupropion were 1.9 times more likely to test positive for smoking over the course of the follow-up period relative to placebo, although this difference was not significant (HR = 1.9, 95% CI = 0.93 to 4.06; z = 1.8, p = .08).

When including subjects who were lost to follow-up prior to week 4 (N = 42, total N = 99), the effect of bupropion on the onset of smoking (i.e., as measured by the first positive cotinine screen) and continued smoking (i.e., allowing subjects who initiated smoking to reenter the analysis) did not change (HR = 2.3, 95% CI = 0.95 to 5.48; z = 1.9, p = .07; and HR = 2.0, 95% CI = 0.94 to 4.13, z = 1.8, p = .07, respectively).

As a post hoc secondary analysis, we then estimated the effect of adjunct stimulant treatment on the initiation of smoking, adjusted for sex and randomization assignment (i.e., placebo or bupropion). Patients treated with stimulants experienced a statistically significant reduction of 73.6% in the risk for smoking initiation over the course of the follow-up period relative to those who did not receive stimulants (HR = 0.2, 95% CI = 0.08 to 0.89; z = –2.2, p = .03; Figure 2). As before, we also tested the hypothesis that stimulant treatment would be associated with a decrease in continued smoking. Patients treated with stimulants experienced a statistically significant reduction of 69.3% in the risk for continued smoking over the course of the follow-up period relative to those who did not receive stimulants (HR = 0.3, 95% CI = 0.11 to 0.85; z = –2.3, p = .02). When subjects who were lost to follow-up prior to week 4 were included, the protective effect of stimulants remained statistically significant.

We then examined the effect of stimulant dose on smoking initiation. We restricted this analysis to subjects who received stimulants during the trial, excluding any observation time that accrued prior to the onset of stimulant therapy, as well as observation time that occurred after the first positive cotinine screen (N = 24/57). We calculated the mean dose of the remaining observation time and dichotomized this score at the 50th percentile (mean stimulant dose of 0.82 mg/kg). Although the high-stimulant dose group was followed for 76 weeks without a positive cotinine screen and was 54% less likely to initiate smoking, this effect was not statistically significant (HR = 0.4, 95% CI = 0.06 to 3.15; z = –0.8, p = .42).

Safety Parameters and Adverse Events

We compared the bupropion and placebo groups on safety parameters measured throughout the follow-up period (i.e., heart rate, diastolic blood pressure, systolic blood pressure, and weight). We modeled each safety variable as a function of time, group, and the time-by-group interaction. A model was estimated comparing baseline values to values at each of weeks 8, 12, 24, and 52 (attrition precluded meaningful analyses beyond week 52); thus, 4 models were estimated for each safety outcome. A significant interaction term would indicate a change in the bupropion group over time, beyond any change in the placebo group. There were no significant interaction effects (all p values > .05; detailed information available upon request).

We compared the rates of adverse events between the bupropion and placebo groups. The rates of the most commonly occurring adverse events (appetite loss, dry mouth, headache, insomnia, stomachache, nausea/vomiting, and weight loss) did not significantly differ (all p values > .05). Restricting the sample to those subjects who did

not take stimulants, there again were no significant differences between the bupropion and placebo groups. Also, among the placebo group, we compared subjects with (N = 14) and without (N = 15) stimulant therapy. Again, no significant differences were detected. One subject reported suicidal ideation at week 52. This subject was assigned to the placebo group and was not given stimulants. She was followed for an additional 56 weeks and did not report any additional suicidal thoughts or gestures.

DISCUSSION

In a randomized, double-blind, placebo-controlled study of bupropion for smoking prevention in children and adolescents with DSM-IV ADHD, we found no evidence that bupropion prevents smoking in youth with ADHD. However, in a post hoc secondary analysis, patients treated with stimulants were less likely to initiate and continue cigarette smoking over the course of the follow-up period. To our knowledge, this is the first study to investigate the effects of psychopharmacologic drugs on the prevention of smoking in youth with ADHD.

This study had important methodological strengths. It was a prospective, double-blind, placebo-controlled, randomized clinical trial. Subjects treated with stimulants received treatment with second-generation, long-acting formulations deployed at aggressive daily doses of approximately 1 mg/kg. The assessment of smoking relied on objective measurements of urine cotinine and not on subjective self-reports.

Our results did not support the hypothesis that bupropion would have prophylactic effects against the initiation of smoking in youth with ADHD. This is not consistent with studies showing the cessation benefit of bupropion. It is important to note that the samples used in smoking cessation studies consisted of adult smokers and were not defined according to a psychiatric diagnosis. In contrast, we studied nonsmoking adolescents with ADHD.

Our post hoc results showing that ADHD youth treated with stimulants were at significantly decreased risk for cigarette smoking are novel. Although previous naturalistic studies have suggested that pharmacologic treatment for ADHD significantly decreased the risk for subsequent abuse or dependence on drugs or alcohol,[32,33] the present results extend these prophylactic effects to cigarette smoking. This finding is consistent with a study by Whalen et al.[34] of a naturalistically treated community sample of adolescents with ADHD (11 were receiving pharmacotherapy and 16 were not) followed for 2 years. These investigators found that adolescents with ADHD who were treated pharmacologically were significantly less likely to smoke than their nonmedicated counterparts.

Considering the well-documented morbidity and mortality associated with cigarette smoking, the prophylactic effects of stimulant therapy in youth with ADHD, if confirmed, could have major clinical and public health implications. Moreover, given recent findings documenting that smoking in ADHD youth is an especially potent predictor of subsequent substance use and abuse,[12] stimulant prophylaxis may be a strategy to interrupt the noxious developmental pathway from smoking to serious substance use problems frequently found in youths with ADHD.[35,36]

Although we do not know why stimulant therapy appears to prevent smoking in children and adolescents with ADHD, theoretical considerations suggest that the 2 conditions might share common underlying mechanisms. Research suggests that ADHD is associated with hypodopaminergic synapses.[37] Because nicotine stimulates dopaminergic circuits, nicotinic agonists should have therapeutic effects on ADHD symptoms, a prediction supported by studies of the nicotine patch and nicotine analog drugs for ADHD.[14,38] Thus, stimulant treatment may reduce smoking because treated youths no longer need to self-medicate with nicotine. It is also plausible that stimulants may work in the prevention of smoking in children and adolescents with ADHD by preventing the initial dopamine release in response to nicotine administration. However, the prophylactic effects may be mediated through the reduction of ADHD symptoms in general and not specifically linked to dopaminergic alteration. For example, decreasing impulsivity may make it less likely that children and adolescents with ADHD will try cigarettes. Finally, it is possible that the protective effect of stimulant treatment found in this study is due to other nonpharmacologic factors that were not measured. For instance, positive psychosocial and familial factors may have influenced both the initiation and maintenance of stimulant therapy, as well as the rejection of smoking. Additional studies of smoking in youths in which stimulant therapy is randomly assigned and placebo-controlled are needed to investigate this question further.

These results should be considered in the light of some methodological limitations. For example, not all subjects were completely through the period of risk. It may be that with additional follow-up, the efficacy of bupropion may become apparent. Secondly, while cotinine is considered the most valid measure of recent smoking, there is still the possibility of misclassifying subjects. For example, subjects may have smoked, but the cotinine test failed to identify them. Or subjects may have been exposed to excessive amounts of second-hand smoke, triggering a positive cotinine screen when they themselves did not smoke. However, these errors are likely to be relatively rare and could not account for the results reported here. Finally, given our modest sample size, the failure to detect any significant association between bupropion therapy and the occurrence of adverse events may have been a type II error. However, the treatment

regimen was well-tolerated, as evidenced by the lengthy duration of follow-up in both the placebo and bupropion groups.

In conclusion, we found that bupropion did not provide protection against the initiation of smoking in children and adolescents with ADHD. We also found preliminary evidence from post hoc secondary analyses that stimulant treatment may be associated with a lower rate of smoking initiation in youths with ADHD. Given the significant risk that children and adolescents with ADHD have for developing nicotine dependence, this finding is important in understanding treatment and smoking prevention in youth with ADHD. Future research should examine the prophylactic effects of certain psychopharmacological drugs on smoking prevention. Because children and adolescents with ADHD are at significantly greater risk of developing nicotine dependence, it would be of tremendous public health benefit to develop successful smoking prevention programs in this population.

Drug name: Bupropion (Zyban and others).

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). Summary of notifiable diseases, United States 1994. MMWR. Morb Mortal Wkly Rep 1994;42:1–73
2. Cummings KM, Shah D, Shopland D. Trends in smoking initiation among adolescents and young adults: United States 1980–1989. MMWR. Morb Mortal Wkly Rep 1995;44:521–524
3. Barkley RA, Fischer M, Edelbrock CS, et al. The adolescent outcome of hyperactive children diagnosed by research criteria, 1: an 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1990;29: 546–557
4. Hartsough CS, Lambert NM. Pattern and progression of drug use among hyperactives and controls: a prospective short-term longitudinal study. J Child Psychol Psychiatry 1987;28:543–553
5. Milberger S, Biederman J, Faraone SV, et al. ADHD is associated with early initiation of cigarette smoking in children and adolescents. J Am Acad Child Adolesc Psychiatry 1997;36:37–44
6. Milberger S, Biederman J, Faraone S, et al. Further evidence of an association between attention-deficit/hyperactivity disorder and cigarette smoking: Findings from a high-risk sample of siblings. Am J Addict 1997;6:205–217
7. Lynskey M, Fergusson D. Childhood conduct problems, attention deficit behaviors, and adolescent alcohol, tobacco, and illicit drug use. J Abnorm Child Psychol 1995;23:281–302
8. Downey KK, Pomerleau CS, Pomerleau OF. Personality differences related to smoking and adult attention deficit hyperactivity disorder. J Subst Abuse 1996;8:129–135
9. Pomerleau OF, Downey KK, Stelson FW, et al. Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. J Subst Abuse 1995;7:373–378
10. Kandel D, Yamaguchi K. From beer to crack: developmental patterns of drug involvement. Am J Public Health 1993;83:851–855
11. Kandel DB, Kessler RC, Margulies RZ. Antecedents of adolescent initiation into stages of drug use: a developmental analysis. J Youth Adolesc 1978;7:13–40
12. Biederman J, Monuteaux M, Mick E, et al. Is cigarette smoking a gateway to alcohol and illicit drug use disorders? A study of youths with and without attention deficit hyperactivity disorder. Biol Psychiatry 2006;59: 258–264
13. Faraone SV, Biederman J. Neurobiology of Attention Deficit Hyperactivity Disorder. In: Charney DS and Nestler EJ, eds. Neurobiology of Mental Illness. 2nd ed. New York, NY: Oxford University Press; 2004: 512–522
14. Levin ED, Conners CK, Sparrow E, et al. Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology 1996;123: 55–63
15. Conners CK, Levin ED, Sparrow E, et al. Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmocol Bull 1996;32:67–73
16. Garfinkel BD, Wender PH, Sloman L, et al. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. J Am Acad Child Psychiatry 1983;22:343–348
17. Rapport MD, Carlson GA, Kelly KL, et al. Methylphenidate and desipramine in hospitalized children, 1: separate and combined effects on cognitive function. J Am Acad Child Adolesc Psychiatry 1993;32: 333–342
18. Wilens TE, Biederman J, Baldessarini RJ, et al. Developmental changes in serum concentrations of desipramine and 2-hydroxydesipramine during treatment with desipramine. J Am Acad Child Adolesc Psychiatry 1992;31:691–698
19. Clarke PE. Dopaminergic mechanisms in the locomotor stimulant effects of nicotine. Biochem Pharmacol 1990;42:595–596
20. Ascher J, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401
21. Cooper B, Wang CM, Cox RF, et al. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. Neuropsychopharmacology 1994;11: 133–141
22. Wilens TE, Spencer TJ, Biederman J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. Am J Psychiatry 2001;158:282–288
23. Wilens T, Haight BR, Horrigan JP, et al. Bupropion XL in adults with ADHD: a randomized, placebo-controlled study. Biol Psychiatry 2005; 57:793–801
24. Conners K, Casat C, Gualtieri T, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry 1996;35:1314–1321
25. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics 1999;103:e43
26. Pliszka SR, Browne RG, Olvera RL, et al. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2000;39:619–626
27. Hollingshead AB. Four Factor Index of Social Status. New Haven, Conn: Yale University Press; 1975
28. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980–988
29. Benowitz N. Cotinine as a biomarker of environmental tobacco smoke exposure. Epidemiol Rev 1996;18:188–204
30. Cox DR. Regression models and life tables. J Royal Stat Soc 1972;34:187–220

31. Jastak J, Bijou S, Jastak S. Wide Range Achievement Test. Wilmington, Del: Jastak Associates, Inc; 1978
32. Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics 1999;104:e20
33. Wilens T, Monuteaux M, Snyder L, et al. The clinical dilemma of using medications in substance abusing adolescents and adults with ADHD: what does the literature tell us? J Child Adolesc Psychopharmacol 2005; 15:787–798
34. Whalen CK, Jamner LD, Henker B, et al. Is there a link between adolescent cigarette smoking and pharmacotherapy for ADHD? Psychol Addict Behav 2003;17:332–335
35. Levin FR, Kleber HD. Attention-deficit hyperactivity disorder and substance abuse: relationships and implications for treatment. Harv Rev Psychiatry 1995;2:246–258
36. Wilens TE, Biederman J, Mick E, et al. Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. J Nerv Ment Dis 1997;185:475–482
37. Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatry 1998;44:951–958
38. Wilens TE, Biederman J, Spencer TJ, et al. A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. Am J Psychiatry 1999;156:1931–1937

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Melissa P. DelBello, M.D., at delbelmp@email.uc.edu.