Independent Effects of Tobacco Abstinence and Bupropion on Cognitive Function in Schizophrenia

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Objective: The objective of this study was to examine the effects of tobacco abstinence and bupropion treatment on cognitive functioning in adult smokers with schizophrenia in the setting of a randomized, double-blind, placebo-controlled clinical trial of bupropion for smoking cessation.

Method: Fifty-three adults with schizophrenia (DSM-IV) took part in a trial of bupropion for smoking cessation. Subjects were enrolled in the study from August 1999 to March 2003. Forty-five subjects remained in the trial at week 4; 41 subjects, 19 taking bupropion and 22 taking placebo, completed the baseline and week 4 cognitive assessments and were included in the analysis of adjusted effects of abstinence and bupropion treatment on cognitive function.

Results: Controlling for bupropion treatment and baseline performance, 7 days of tobacco abstinence was associated with slowed motor speed (finger tapping) but was not associated with worsening of performance on tests of attention (AX Continuous Performance Test [AX-CPT]), verbal learning and memory (California Verbal Learning Test [CVLT]), working memory (digit span), or executive function/inhibition (Stroop) and was not associated with worsening of any clinical measures. Controlling for abstinence status, bupropion was associated with reduction (improvement) in reaction time variability on the AX-CPT and with reduction in perseverative errors on the CVLT.

Conclusion: We conclude that 1 week of tobacco abstinence is associated with slowed motor speed but is not associated with detectable worsening in performance on a range of neuropsychological tests or clinical symptoms in the subset of patients who were able to quit smoking. We also conclude that bupropion treatment may be associated with improvement in variability of attention.

(J Clin Psychiatry 2005;66:1184–1190)

Received Aug. 10, 2004; accepted March 7, 2005. From the Schizophrenia Program (Drs. Evins, Deckersbach, Cather, Freudenreich, Henderson, and Goff and Ms. Culhane), the Addictions Research Program (Dr. Evins and Ms. Culhane), the Tobacco Treatment and Research Center (Drs. Evins and Rigotti), and the Biostatistics Center (Dr. Schoenfeld), Massachusetts General Hospital, Boston; Harvard Medical School, Boston, Mass. (Drs. Evins, Deckersbach, Cather, Freudenreich, Henderson, Schoenfeld, Rigotti, and Goff); and the Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles (Dr. Green).

This work was supported by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Affective Disorders, Great Neck, N.Y., by Department of Health and Human Services Substance Abuse and Mental Health Services Administration grant 05B1MACMHS-04, and by National Institute on Drug Abuse grants RO3 DA12542 and K23 DA00510 (Dr. Evins); National Institute of Mental Health grant K24 MH02025 (Dr. Goff); and National Heart, Lung, and Blood Institute grant K24 HL04440 (Dr. Rigotti). GlaxoSmithKline (Research Triangle Park, N.C.) provided sustained-release bupropion and placebo tablets.

This work has been presented in part at the 9th annual meeting of the Society for Research on Nicotine and Tobacco, New Orleans, La., Feb. 19–22, 2003, and the 156th annual meeting of the American Psychiatric Association, San Francisco, Calif., May 17–22, 2003.

Financial disclosure appears at the end of this article.

The authors acknowledge Dr. Kenneth Duckworth, M.D., and Dr. Joan Kerzner, Ph.D., from the Massachusetts Department of Mental Health, Boston, for their support of the project.

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Cigarette smoking is the leading preventable cause of death in the United States, and 75% to 85% of people with schizophrenia in the United States smoke, compared with 23% of the general population.[1–3] Despite a 1996 American Psychiatric Association guideline recommending routine treatment of smoking for patients with psychiatric illness and preliminary reports of the safety and efficacy of pharmacologic approaches to smoking cessation in schizophrenia,[4–10] physicians rarely advise patients with schizophrenia to quit smoking.[11,12]

In individuals without psychiatric illness, nicotine improves attention,[13–18] learning, and memory[19–23] and has produced inconsistent effects on executive function and inhibition as measured by the Stroop task.[18,24,25] Smoking abstinence for 24 hours[26,27] and up to 5 days[28] has been found to worsen performance on attention tasks. Hatsukami and colleagues[26] reported increased mean reaction time, increased variability in reaction time, and in-

creased errors of commission on an attention task in adolescent smokers deprived of cigarettes for 24 hours and increased reaction time in smokeless tobacco users deprived of tobacco for 24 hours. In another study, 24 hours of tobacco abstinence impaired recognition memory, attentional vigilance, and speed of target detection but not digit span recall, consistent with the hypothesis that tobacco abstinence impairs episodic memory and sustained attention, suggesting that some, but not necessarily all, short-term memory processes may not be influenced by tobacco abstinence.[29]

There has been a concerted effort in recent years to understand why people with schizophrenia use nicotine, with the hypothesis that this information may lead to new treatments for both schizophrenia and nicotine dependence.[30] Consistent with results in the general population, nicotine has been shown to affect attention,[31–33] reaction time,[34] delayed recognition,[35] spatial organization,[31,34] and verbal memory[34] in patients with schizophrenia. Nicotine transiently corrects some psychophysiologic deficits particular to schizophrenia in smokers with schizophrenia who are deprived of cigarettes overnight and in nonsmoking first-degree relatives of patients with schizophrenia.[36–38] Nicotine also counteracts some adverse cognitive effects of conventional antipsychotic medications.[31] Based on these findings, nicotine and nicotinic agonists have been proposed as a potential therapy for cognitive dysfunction in schizophrenia.[39]

In the absence of data on the effect of tobacco abstinence on stability of cognitive and psychiatric symptoms, treaters may be reluctant to advise their patients with schizophrenia to attempt to quit smoking, due to concern that tobacco abstinence may worsen cognitive functioning or cause clinical destabilization. Several small studies have examined the effect of tobacco abstinence on neuropsychological function and clinical symptoms in patients with schizophrenia, and the results have been inconsistent. Smoking cessation was associated with worsening of performance on a visuospatial working memory task in patients with schizophrenia, independent of bupropion treatment.[40] Smoking reduction in the context of bupropion treatment was not associated with decreased performance on a cognitive battery in a small open study.[41] Smoking reduction or cessation has been associated with mild exacerbation of psychotic symptoms after smoking reduction or cessation in the absence of nicotine replacement or bupropion in 2 studies.[4,42] Acute abstinence from nicotine and longer-term smoking cessation were not associated with symptom exacerbation in other studies.[7,43,44]

The primary purpose of this study was to examine the effect of nicotine abstinence on neuropsychological test performance in patients with schizophrenia in the setting of a randomized, double-blind, placebo-controlled study of the effect of bupropion on tobacco abstinence. Our hypothesis was that abstinence would be associated with a general worsening in neuropsychological test performance, particularly in the domains of attention, learning, memory, and executive functioning. Given that nicotine administration improves bradykinesia in smokers with schizophrenia,[45,46] we also hypothesized that tobacco abstinence would be associated with reduction in motor speed on the finger tapping task. A secondary aim was to assess the effect of tobacco abstinence on clinical symptomatology. Based on our previous finding that the changes in psychiatric symptoms in patients with schizophrenia during a quit attempt were mild and not clinically significant,[4,47] our hypothesis was that tobacco abstinence would not be associated with significant exacerbation in psychiatric symptoms. Another secondary aim was to assess the effect of bupropion on cognitive function. Based on reports that bupropion is associated with improved attentiveness in healthy males[48] and patients with attention-deficit/hyperactivity disorder (ADHD)[49–52] and depression,[53] and is associated with improvement in negative symptoms in the setting of a smoking cessation attempt,[4,9] our hypothesis was that bupropion treatment may be associated with improvement in attention in patients with schizophrenia.

METHOD

The protocol was approved by the appropriate institutional review boards. Subjects were recruited from urban community mental health centers in Massachusetts and were enrolled from August 1999 to March 2003. Capacity to consent was determined and documented for all participants by a doctoral-level clinician using a formal process established in the Massachusetts General Hospital (MGH) Schizophrenia Program. Eligible participants were adults who met DSM-IV criteria for schizophrenia or schizoaffective disorder, depressive type, who smoked 10 or more cigarettes per day, wanted to try to quit smoking, had stable psychiatric symptoms in the judgment of their treating physician and had been receiving a stable dose of antipsychotic medication for 30 days, did not meet DSM-IV criteria for current major depressive disorder, and had a baseline Hamilton Rating Scale for Depression (HAM-D) score < 20. Subjects with seizure disorder, history of bulimia, history of mania, or substance abuse disorder other than nicotine or caffeine within 6 months of enrollment were not eligible. The smoking cessation study and outcomes are previously published.[47]

Interventions

Participants were randomly assigned to receive bupropion sustained release (SR) 150 mg or identical placebo tablets. Subjects took 1 tablet daily for 7 days, then 1 tablet twice daily for the remainder of the trial. A 1-week supply of study medications was distributed weekly; medication bottles and self-report of missed doses were

collected at the weekly cognitive-behavioral therapy (CBT) group sessions. All participants received a 12-week, 12-session group CBT program that has been previously described.[4] All participants set a quit date 1 week prior to the neuropsychological and clinical assessment.

Neuropsychological Measures

Cognitive measures included an AX version of Conners' Continuous Performance Test (AX-CPT)[54] to assess sustained attention. In this paradigm, participants are to press the space bar key as quickly as possible whenever an "X" that was preceded by an "A" appears on the computer screen. Dependent variables are the ability to discriminate between targets ("X" and "distractor" letters), commission errors (not pressing "X" when it was preceded by "A"), as well as the variability in reaction times over time. The California Verbal Learning Test (CVLT),[55] a well-established measure of verbal learning and memory, was administered to assess memory for a list of 16 shopping items presented orally in 5 trials, with free recall after each trial. An interference list is presented following the fifth study-recall trial. Short- and long-delayed (20 minutes) free recall of the first list was assessed next, followed by a delayed recognition test. The CVLT provides measures of learning over 5 successive trials (sum of the words recalled in trials 1–5), short- and long-delayed recall, and retention between short- and long-delayed recall and recognition to assess verbal learning. Dependent variables in the present study were learning over the 5 learning trials, recognition, and perseverative errors (i.e., words that are recalled repeatedly). The finger-tapping subtest of the Halstead-Reitan Neuropsychological Battery[56] was used to assess motor speed (dependent variables: total scores for dominant and nondominant hands). Subjects also completed a single trial version of the Stroop[57] as a measure of selective attention and inhibition. In this version of the Stroop, subjects are provided with neutral words (e.g., dog) and color words (e.g., blue) on a computer screen. Neutral words are presented in a purple, red, blue, or green color. Color words (purple, blue, red, green) are presented either in the same color as the meaning of the word (blue presented in blue = congruent condition) or in incongruent colors (blue presented in red). Dependent measures were the reaction times for congruent, incongruent, and neutral conditions and facilitation and interference effects. We also administered the digit span subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III)[58] to assess attention span and working memory (dependent variables: digits forward and backward). Tests of cognition were administered at baseline and week 4.

Clinical Measures

Clinical outcomes were assessed at baseline and week 4 by the following: the Scale for Assessment of Negative Symptoms (SANS)[59] total score and 5 subscale scores, the Hamilton Rating Scale for Anxiety,[60] the HAM-D,[61] the Positive and Negative Syndrome Scale (PANSS)[62] total score and 5 subscale scores (positive, negative, excitement, cognitive, depression/anxiety),[63] the Simpson-Angus Scale,[64] and the Barnes Akathisia Scale.[65] Adverse events were recorded weekly using the Systematic Assessment for Treatment-Emergent Events (SAFTEE).[66] Four raters were trained on all measures, and adequate reliability was maintained.

Analysis

Seven-day point prevalence abstinence at the time of the assessments was defined as a self-report of smoking zero cigarettes in the past 7 days confirmed by an expired air carbon monoxide (CO) measurement < 9 ppm.[67]

We used a series of linear regression models that included abstinence status, study medication status, and baseline performance on cognitive and clinical outcome measures in order to evaluate the independent effects of tobacco abstinence and bupropion on cognitive and clinical outcomes as follows: outcome measure score = α + β1 (7-day point prevalence abstinence status) + β2 (drug group) + β3 (baseline score). An abstinence by medication status interaction term was tested for significance and removed if it did not have a significant effect. Effects were considered significant at a 2-sided p value of < .05.

RESULTS

After complete description of the study and provision of informed consent, 62 subjects were enrolled; 53 received study medication and took part in a smoking cessation program. Of the 53 subjects, 45 were still participating at week 4, and 41 of these subjects completed the baseline and follow-up cognitive assessments and were included in this analysis. Nineteen of the 41 subjects were taking bupropion, and 22 were taking placebo. Nine (22%) of the 41 subjects achieved 7 days of abstinence prior to the second assessment and 32 did not. Of the 9 subjects who were abstinent at week 4, 7 were in the bupropion group and 2 were in the placebo group. Those who did not achieve abstinence prior to the assessment had a mean 15.2% reduction in expired air CO with standard deviation of 42.2 prior to the assessment. Those who were abstinent had an expired air CO measurement of < 9 ppm and a self-report of smoking no cigarettes in the 7 days prior to the assessment.

Subjects ranged in age from 24 to 63 years, reported smoking a mean of 29.3 (SD = 18.0; range, 10–100) cigarettes per day, and had a mean baseline CO measurement of 28.1 (SD = 15.7; range, 11–80) ppm. Mean PANSS score was 59.9 (SD = 13.3). Mean (SD) education was 11.7 (3.0) years, but subjects ranged from 4 to 17 years of education. There were no differences between abstinent

Table 1. Baseline Characteristics of Adult Smokers With Schizophrenia[a]

Variable	Abstinent (N = 9)[b]	Not Abstinent (N = 32)
Age, y	44.6 (5.6)	46.2 (9.6)
Sex, N		
Male	6	24
Female	3	8
Education, y	11.4 (3.5)	11.8 (2.9)
Expired air CO, ppm	38.2 (21.0)	25.0 (12.5)
No. of cigarettes/d	34.4 (11.2)	27.9 (19.5)
CPT score		
d'	4.4 (1.2)	4.1 (1.4)
Reaction time variability	11.7 (6.4)	12.9 (11.3)
Errors of commission	2.3 (1.3)	4.0 (7.4)
CVLT score		
Recall list A total	35.7 (11.9)	31.4 (9.9)
Recognition hits	13.1 (2.6)	12.9 (2.4)
Perseverative errors	3.5 (5.0)	4.6 (4.2)
Finger tapping total score	40.5 (3.5)	40.6 (9.2)
Digit span score		
Forward	9.0 (1.7)	8.6 (2.6)
Backward	4.8 (1.4)	4.9 (1.9)
Stroop task score		
Congruent	842.2 (217.9)	926.4 (184.7)
Incongruent	1158.8 (150.7)	1214.8 (179.0)
Neutral	966.6 (119.6)	1041.7 (190.9)
Facilitation	–122.6 (79.4)	–115.4 (76.7)
Interference	194.0 (41.1)	173.0 (101.8)
SANS total score	38.1 (19.6)	43.3 (19.0)
PANSS total score	56.4 (13.5)	60.8 (13.2)
HAM-D score	8.7 (3.7)	8.9 (6.5)
HAM-A score	6.7 (5.0)	5.5 (4.3)
Antipsychotic dose[c]	304.7 (164.7)	330.6 (260.1)
Antipsychotic type, N[d]		
Conventional	1	3
Second generation	6	24
Combination	2	5
Clozapine	1	10

[a]Data are presented as mean (SD) unless otherwise indicated. Baseline characteristics are not significantly different (p > .05).
[b]Patients who achieved tobacco abstinence for 7 days prior to the second assessment.
[c]Daily antipsychotic dose in chlorpromazine equivalents was calculated using the method of Woods.[69]
[d]All patients were taking a stable dose of an antipsychotic medication for 30 days prior to and during the study.
Abbreviations: CO = carbon monoxide, CPT = Conners' Continuous Performance Test, CVLT = California Verbal Learning Test, d' = signal-to-noise ratio, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for Assessment of Negative Symptoms.

Table 2. Adjusted Effects of Tobacco Abstinence and Bupropion Treatment on the Performance of Neurocognitive Tests in Patients with Schizophrenia (N = 41)

Variable	Effect Estimate[a]	SE	95% CI	p
CPT				
d'				
Abstinence	–0.13	0.47	–1.09 to 0.83	.78
Bupropion	0.39	0.4	–0.44 to 1.22	.34
SE reaction time variability				
Abstinence	3.35	2.01	–0.77 to 7.47	.11
Bupropion	–4.73	1.75	–8.32 to –1.14	.012
Errors of commission, %				
Abstinence	–0.08	2.06	–4.30 to 4.14	.97
Bupropion	–2.88	1.88	–6.73 to 0.96	.136
CVLT				
Recall list A trials 1–5 total				
Abstinence	8.23	3.78	0.50 to 15.97	.038
Bupropion	–5.63	3.26	–12.30 to 1.04	.095
Recognition hits				
Abstinence	1.05	1.25	–1.50 to 3.60	.41
Bupropion	0.77	1.08	–1.44 to 2.97	.48
Perseverative errors				
Abstinence	2.12	2.09	–2.17 to 6.41	.32
Bupropion	–4.05	1.88	–7.90 to –0.20	.04
Finger tapping				
Total dominant				
Abstinence	–44.45	12.8	–71.38 to –17.51	.003
Bupropion	0.17	13.2	–27.56 to 27.90	.99
Total nondominant				
Abstinence	–22.97	10.4	–44.86 to –1.07	.041
Bupropion	–5.8	10.1	–26.97 to 15.37	.57
Digit span				
Digits forward				
Abstinence	0.71	0.86	–1.08 to 2.49	.42
Bupropion	–0.05	0.79	–1.67 to 1.58	.95
Digits backward				
Abstinence	–0.54	0.65	–1.88 to 0.80	.42
Bupropion	0.36	0.59	–0.86 to 1.58	.54
Stroop				
Reaction time congruent				
Abstinence	–164.15	96.8	–370.56 to 42.27	.11
Bupropion	–21.37	76	–183.43 to 140.69	.78
Reaction time incongruent				
Abstinence	–47.4	91.5	–242.38 to 147.57	.61
Bupropion	–145.08	72.6	–299.86 to 9.71	.06
Reaction time neutral				
Abstinence	–109.04	78.8	–276.97 to 58.89	.19
Bupropion	–44.56	62.4	–177.58 to 88.46	.49

[a]Effect estimates are controlled for abstinence status, bupropion treatment, and baseline performance.
Abbreviations: CPT = Conners' Continuous Performance Test, CVLT = California Verbal Learning Test, d' = signal-to-noise ratio, SE = standard error.

and not-abstinent groups in demographic characteristics or cognitive or clinical symptoms at baseline (Table 1). Subjects in the bupropion group missed a mean (SD) of 0.9 (.58) doses per week and subjects in the placebo group missed a mean (SD) of 0.9 (.60) doses per week by self-report, confirmed by pill count. Bupropion-treated subjects were more likely to have achieved 1 week of continuous abstinence prior to the assessment.

Effect of Abstinence on Cognitive Functioning

Seven days of tobacco abstinence was associated with significantly slowed motor speed for dominant and non-dominant hands on the finger tapping task, controlling for baseline finger tapping and bupropion treatment (Table 2). Neither type nor dose of antipsychotic medication affected motor speed.

Seven days of tobacco abstinence was also associated with improvement in immediate recall of list A trials 1 through 5 on the CVLT. Controlling for baseline performance and study medication assignment, we found that subjects could remember 8.23 (95% CI = 0.5 to 15.97) more words after 7 days of abstinence compared with those who continued to smoke (p = .038) (Table 2). One

week of abstinence was not associated with change in performance on the digit span or Stroop, but was associated with a trend toward increased distractibility as measured by variability of reaction times on the CPT, controlling for bupropion treatment and baseline performance (Table 2).

Bupropion treatment was associated with significant improvement in variability of reaction times on the CPT and reduction in perseverative errors on the CVLT, controlling for abstinence status and baseline performance.

Effect of Abstinence on Clinical Symptoms of Schizophrenia

There was no significant effect of 7-day point prevalence abstinence on clinical measures after controlling for smoking status and baseline symptoms. Likewise, there was no significant effect of bupropion on clinical measures after controlling for smoking status and baseline values. All interactions between study medication and abstinence status were not significant and were removed from the models.

Association Between Change in Smoking and Change in Cognitive Function

In the sample as a whole, there was a correlation between percent change in expired air CO and change in total recall (trials 1–5) on the CVLT ($R = –0.405$, $p = .020$) and with change in finger tapping in the dominant hand ($R = 0.42$, $p = .05$). There were also correlations at a trend level between percent change in CO and change in CPT hit reaction time standard error ($R = –0.248$, $p = .178$) and change in Stroop reaction time on incongruent stimuli ($R = –0.336$, $p = .159$).

Controlling for baseline performance and bupropion treatment, associations remained between percent change in CO and total recall (trials 1–5) on the CVLT ($t = –2.52$, $p = .017$), change in tapping in the dominant hand ($t = 1.80$, $p = .089$), and change in CPT hit reaction time standard error ($t = –2.15$, $p = .041$). The effect of change in CO on change in Stroop reaction time was not significant after controlling for bupropion treatment.

DISCUSSION

In patients who were able to achieve abstinence in a smoking cessation trial, 7 days of tobacco abstinence was associated with significantly slowed motor speed as measured by the finger tapping task but was not associated with detectable worsening of performance on neuropsychological tests of attention (AX-CPT), verbal learning and memory (CVLT), attention span and working memory (digits forward and backward), or executive function/inhibition (Stroop). Unexpectedly, abstinence was independently associated with improved recall on the main outcome of the CVLT. The findings in abstinent subjects were supported with significant correlations between reduction in expired air CO and improvement in CVLT performance and worsening in finger tapping in the sample as a whole. Tobacco abstinence was not independently associated with change in clinical symptoms as measured by standard clinical rating scales.

This study also extends previous work by suggesting that bupropion is associated with improvement in attention and memory in patients with schizophrenia. Nicotine reduces (improves) reaction time variability associated with attention deficit in schizophrenia.[31] We found that bupropion significantly improved this same measure of distractibility. This is consistent with reports that bupropion is associated with improved attentiveness in healthy males[48] and patients with ADHD[49–52] and depression.[53] This finding must be interpreted cautiously, as the effect was seen on a single measure of attention, and there was no apparent effect of bupropion on the d' measure of signal to noise discrimination. Interestingly, abstinent subjects had a trend in the opposite direction, toward increased reaction time variability.

The findings are consistent with a report that substantial smoking reduction in patients with schizophrenia was not associated with worsening of verbal memory or attention.[41] The findings are also not inconsistent with the report that improved working memory with chronic high dose nicotine in rats persists for at least 2 weeks following nicotine discontinuation,[68] because we cannot rule out that nicotine may have beneficial effects on learning, memory, and attention that persist for longer than 7 days after withdrawal of nicotine in patients with schizophrenia. These results should be confirmed in subjects who achieve sustained abstinence of several weeks or more. It would also be useful to confirm these results in subjects randomly assigned to abstinence or, more practically, to a nicotinic receptor antagonist. Although there were no differences in cognitive scores or clinical ratings at baseline between those who achieved abstinence and those who did not, it is possible that subjects who are able to maintain abstinence for 7 days may be inherently less vulnerable to adverse cognitive effects of nicotine abstinence or may have benefited less from nicotine.

Several issues limit our ability to generalize the associations detected between tobacco abstinence and cognitive function in this study. The findings are limited by the small number and nonrandom nature of patients achieving abstinence and the short duration of abstinence. The small number of patients that achieved abstinence for 7 days prior to the second assessment ($N = 9$) limits our power to detect differences that may be clinically important. As abstinence was associated with a trend toward increased reaction time variability on the CPT, the effect of abstinence on attention in particular should be further studied in a larger sample. With so few abstinent, the results may not be generalizable to the larger population of patients with schizophrenia. It is also possible that nicotine is im-

portant for visuospatial working memory[40] and auditory sensory gating[37] in patients with schizophrenia, and that the CVLT, CPT, digit span, Stroop task, and clinical rating scales are less sensitive to these clinically important effects of nicotine abstinence.[33] Alternatively, these findings may challenge the widely held belief that smoking cessation will be harmful to the clinical stability of patients with schizophrenia.

In conclusion, 7 days of tobacco abstinence was associated with reduction in motor speed but was not associated with worsening in performance on a range of other neuropsychological tests or clinical symptoms in patients with schizophrenia who quit smoking, and there was some indication that bupropion treatment was associated with improvement in variability of attention. If confirmed, these results may be a call to action to intensify the search for smoking cessation treatments that are effective in this population.

Drug names: bupropion (Zyban and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others).

Financial disclosure: Drs. Evins, Deckersbach, Henderson, Green, Schoenfeld, and Goff and Ms. Culhane report no other financial affiliation or other relationship relevant to the subject matter of this article. Dr. Cather has participated in speakers/advisory boards for Eli Lilly. Dr. Freudenreich has received grant/research support from Pfizer. Dr. Rigotti is a consultant for Pfizer and Sanofi-Aventis and has received grant/research support from GlaxoSmithKline, Pfizer, and Sanofi-Aventis.

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