A 12-Week Double-Blind, Placebo-Controlled Study of Bupropion SR Added to High-Dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia

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Abstract: The objective of this study was to examine whether there is a benefit of adding bupropion SR to high-dose combination nicotine replacement therapy (NRT) and weekly group cognitive behavioral therapy (CBT) for smoking reduction or cessation in schizophrenia. Fifty-one adult smokers with schizophrenia were randomly assigned to a 12-week trial of bupropion SR 300 mg/d or placebo added to transdermal nicotine patch, nicotine polacrilex gum, and CBT. The treatment goal was smoking cessation. The primary outcome measure was biochemically confirmed 7-day point-prevalence of 50% to 100% smoking reduction at week 12. Secondary outcomes were biochemically confirmed tobacco abstinence and change from baseline in expired air carbon monoxide (CO) and psychiatric symptoms. Subjects on bupropion + NRT had a greater rate of 50% to 100% smoking reduction at weeks 12 (60% vs. 31%; $P = 0.036$) and 24, a lower expired air CO in the treatment and follow-up periods, ($F = 13.8$; $P < 0.001$) and a greater continuous abstinence rate at week 8, before NRT taper, (52% vs. 19%; $P = 0.014$). However, relapse rates in subjects on bupropion + dual NRT were 31% during NRT taper (weeks 8–12) and 77% at the 12-month follow-up. Abstinence rates did not differ by treatment group at weeks 12 (36% vs. 19%), 24 (20% vs. 8%), or 52 (12% vs. 8%). Because abstinence rates were high during treatment with combination pharmacotherapy and relapse rates were very high during taper and after discontinuation of treatment, study of longer term treatment with combination pharmacotherapy and CBT for sustained abstinence is warranted in those who attain initial abstinence with this intervention.

(*J Clin Psychopharmacol* 2007;27:380–386)

Between 72% and 90% of patients with schizophrenia smoke cigarettes, compared with 23% in the general population,[1,2] and those with schizophrenia are more likely to smoke, smoke heavily, extract more nicotine from each cigarette, and have low smoking cessation rates, although they can be both highly motivated and persistent in attempts to quit smoking.[3–7] Age-adjusted mortality from smoking-related pulmonary and cardiovascular disease is 2 to 6 times higher among schizophrenic patients compared with age-matched samples.[8,9]

Bupropion or single preparation NRT added to CBT are well tolerated by schizophrenia patients but only modestly effective.[10–17] In controlled trials in smokers with schizophrenia, abstinence rates have been 4% to 19% at 3- to 6-month follow-up with bupropion or single preparation NRT and 0% to 6% with placebo,[14–17] rates that are less than half of those reported for smokers in the general population.[18] Combination treatments have shown promise. Nicotine nasal spray and nicotine patch were nearly twice as effective as placebo spray and nicotine patch for smoking cessation over 6 years of follow-up in smokers without psychiatric illness.[19] Nicotine patch plus bupropion was superior to nicotine patch alone and to placebo but not to bupropion alone for smoking cessation in a nonpsychiatric population.[20] Combination of bupropion SR, nicotine patch, and cognitive behavioral therapy (CBT) was associated with significantly greater smoking reduction than bupropion and CBT, nicotine patch and CBT, or CBT alone in smokers with comorbid psychiatric and substance use disorders.[21] It is not known whether the effects of bupropion and NRT are addictive in people with schizophrenia.

To evaluate whether there is a clinical benefit of adding bupropion SR to high-dose dual NRT and CBT, we conducted a 12-week, double-blind, placebo-controlled trial with the hypothesis that high-dose dual formulation NRT would be well tolerated and that subjects assigned to bupropion SR plus high-dose dual NRT and CBT would achieve greater rates of significant smoking reduction and abstinence (50%–100% reduction in smoking, as measured by self-report and expired air carbon monoxide [CO]) than those assigned to placebo, dual NRT, and CBT.

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Received July 6, 2006; accepted after revision April 9, 2007.

This work was supported by K23 DA00510 (Dr Evins) and DHHS SAMHSA 05B1MACMHS-04 Massachusetts Department of Mental Health Federal Block Grant (Dr Evins). GlaxoSmithKline provided sustained release bupropion and identical placebo.

These data have been presented in part at the 2006 Annual Meeting of the Society for Research on Nicotine and Tobacco and have not been previously published.

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ISSN: 0271-0749/07/2704-0380

DOI: 10.1097/01.jcp.0b013e3180ca86fa

MATERIALS AND METHODS

Participants were enrolled from June 2002 to February 2004 from 4 urban mental health centers. Appropriate research review boards approved the study. Eligible participants were adults with schizophrenia by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria—capacity to consent, stable psychiatric symptoms and antipsychotic dose for 30 days or more, smoked 10 cigarettes or more per day for the past year, and were willing to set a smoking-quit date within 4 weeks of enrollment. Those with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for current major depressive disorder, Hamilton Rating Scale for Depression (HAM-D) score of greater than 19, or substance use disorder other than nicotine or caffeine within 6 months of screening were not eligible, nor were those taking bupropion or NRT in the prior month, those with seizure disorder and bulimia, or those on clozapine of more than 500 mg/d without a therapeutic dose of an anticonvulsant.

Interventions

Participants were randomly assigned to receive bupropion SR 150 mg or placebo, once daily for 7 days, then twice daily for 11 weeks. Medications were dispensed, and unused medication and self-report of missed doses were collected weekly. Assessment of the blind by participants and group leaders was collected at Week 12. Participants attended a 12-session, 1-hour, weekly smoking cessation group program[15,17] with 3 to 7 participants led by a psychologist with tobacco treatment specialist training (C.C. and A.B.).[22] Subjects set a quit date, and nicotine patches (Habitrol) and nicotine polacrilex gum (Nicorette) were initiated in the fourth week. Nicotine patch was dosed at 21 mg/d for 4 weeks, 14 mg/d for 2 weeks, and 7 mg/d for 2 weeks, then discontinued. Nicotine gum (2 mg) was distributed for use as needed for craving up to 18 mg/d. Participants were asked to refrain from other nicotine-dependence treatments. The medication trial ended after 12 weeks, at which point, bupropion or placebo, NRT, and psychological treatments were discontinued. Participants and investigators remained blind to the treatment condition (bupropion or placebo) throughout the follow-up period.

Measures

Smoking behavior was assessed with self-report of cigarettes smoked in the past 7 days and expired air CO measurement (MicroSmokerlyzer; Bedfont Scientific Ltd, Kent, UK) at each meeting. Subjects who were abstinent at

TABLE 1. Baseline Characteristics

	Bupropion + NRT	Placebo + NRT
	n = 25	n = 26
Age, yrs	44.8 (9.2)	43.6 (10.9)
Education	10.8 (2.7)	12.4 (1.8)
Cigarettes per day	28.1 (14.3)	24.7 (10.1)
Expired air CO	28.3 (15.2)	22.6 (9.3)
FTND	7.2 (1.9)	7.08 (1.7)
WSWS	13.9 (7.4)	13.1 (6.1)
Medication		
Clozapine	7 (28%)	9 (35%)
Atypical antipsychotic	20 (80%)	22 (85%)
SSRI	9 (36%)	7 (27%)
Anxiolytic	11 (44%)	8 (31%)
Self-report measures		
Past substance use disorder other than alcohol	6 (24%)	6 (23%)
Past alcohol abuse or dependence	10 (40%)	8 (31%)
Past depression	20 (80%)	18 (69%)
Symptomatic smoking-related physical illness	15 (60%)	9 (35%)
Percent close friends who smoke	71%	79%
Visual Analog Scales (1–10)		
How much do you want to quit?	9.1 (1.3)	8.8 (1.6)
Confidence you will quit 1 year from now	6.6 (2.6)	7.6 (2.2)
How much smoking harms your health?	8.8 (1.9)	9.5 (1.1)
How much quitting will improve your health?	8.4 (2.4)	9.2 (1.6)
How many people closest to you want you to quit?	7.1 (3.1)	7.9 (2.9)
How concerned are you about weight gain?	5.1 (3.4)	5.5 (3.2)

WSWS indicates wisconsin smoking withdrawal scale.

TABLE 2. Smoking Reduction and Cessation in a Smoking Cessation Trial in Patients With Schizophrenia

	Bupropion + NRT (n = 25)	Placebo + NRT (n = 26)	
	n (%)	n (%)	OR (95% CI)
50% or Greater reduction in smoking: seven day point prevalence			
Week 8	15 (60)	9 (35)	2.8 (0.91–8.8)
Week 12*	15 (60)	8 (31)	3.4 (1.1–10)
Week 24	8 (32)	2 (7.7)	5.7 (1.1–30)
Rates of confirmed continuous abstinence from the target quit date†			
Week 8	13 (52)	5 (19)	4.6 (1.3–16)
Week 12	9 (36)	5 (19)	2.4 (0.66–8.4)
3-Month follow-up	5 (20)	2 (8)	3.0 (0.92–7)
12-Month follow-up	3 (12)	2 (8)	1.6 (0.25–11)

*Primary outcome measure.
†Seven-day point prevalence abstinence rates were identical to continuous abstinence rates.
OR indicates odds ratio.

3 months were followed for an additional 9 months to obtain 12-month continuous abstinence rates. The Fagerstrom Test for Nicotine Dependence (FTND)[23] was administered at baseline. The Wisconsin Smoking Withdrawal Scale[24] and an adverse event checklist were administered weekly. Clinical outcomes were assessed at baseline and week 12, with the Scale for Assessment of Negative Symptoms (SANS), Positive and Negative Syndrome Scale (PANSS), HAM-D, State Trait Anxiety Inventory (STAI),[25] Simpson Angus Scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS).

Analysis

Sample size was based on the ability to detect a between-group difference at the end of treatment given a projected rate of 50% to 100% smoking reduction of 60% in the bupropion group and 20% in the placebo group. Fifty-two participants were needed to have a 2-sided α of 0.05 and 80% power to detect the difference, http://hedwig.mgh.harvard.edu/sample_size/size.html. Baseline characteristics were compared using Student *t* tests or exact tests. The primary outcome was the rate of significant smoking reduction at week 12, defined a priori as 50% to 100% reduction in cigarettes smoked per day by self-report. In previous studies, smokers with schizophrenia who reported 50% reduction in cigarettes per day had a mean 40% reduction in expired air CO,[15,17] presumably because of deeper inhalation when smoking fewer cigarettes. Thus, 40% or greater reduction of expired air CO was required for biochemical verification of self-report of 50% or greater reduction in cigarettes smoked per day. Carbon monoxide was measured twice in Week 12, and 40% or

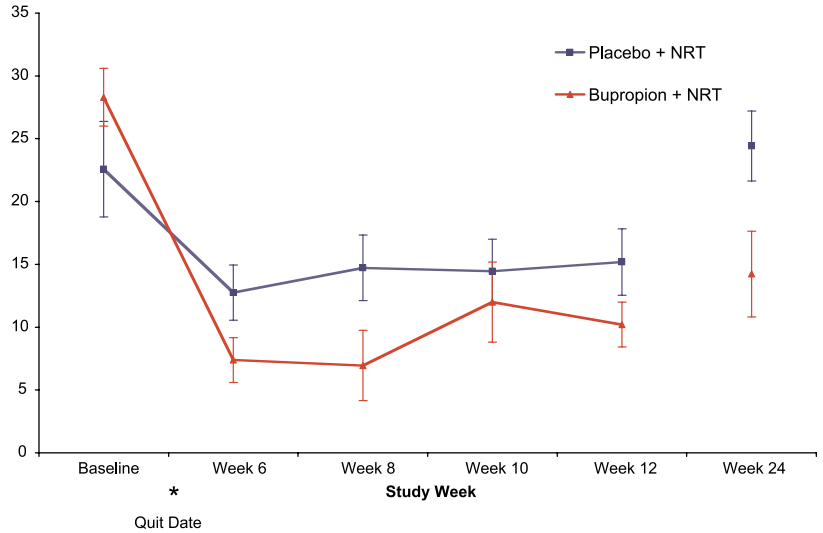

FIGURE 1. Expired air carbon monoxide in a 12-week smoking cessation study in patients with schizophrenia. *The smoking cessation date was between Weeks 4 and 5. There was a significant effect of bupropion ($F_{1,40} = 8.33$; $P = 0.006$) and of time ($F_{7,40} = 4.16$; $P = 0.002$), and the time by study medication interaction was not significant.

TABLE 3. Clinical Symptoms by Randomization and Abstinence Status

Clinical Scale		Baseline	Week 12	
SANS				
Total Score	Bupropion	43 (21)	39 (16)	
	Placebo	39 (17)	40 (16)	
PANSS				
Total Score	Bupropion	61 (14)	61 (17)	
	Placebo	67 (20)	62 (15)	
HAM-D	Bupropion	10 (5.9)	10 (6.4)	
	Placebo	10 (6.4)	11 (6.6)	
STAI	Bupropion	47 (7.2)	44 (7.0)	
	Placebo	50 (8.0)	50 (8.4)	
Barnes	Bupropion	1.4 (1.9)	0.8 (1.8)	$P = 0.005$
	Placebo	0.9 (1.5)	2.7 (2.7)	
Simpson-Angus	Bupropion	3.8 (4.2)	2.1 (2.7)	$P = 0.016$
	Placebo	2.7 (3.0)	5.0 (4.2)	
AIMS	Bupropion	3.0 (4.2)	1.4 (1.9)	
	Placebo	1.5 (2.0)	2.3 (2.8)	
SANS				
Total Score	Abstinent	34 (18)	34 (13)	
	Not abstinent	45 (20)	42 (17)	
PANSS				
Total Score	Abstinent	61 (13)	57 (14)	
	Not abstinent	65 (19)	64 (16)	
HAM-D	Abstinent	10 (5.9)	9.6 (5.2)	
	Not abstinent	10 (6.3)	11 (7.1)	
STAI	Abstinent	43 (3.9)	43 (6.5)	
	Not abstinent	51 (7.9)	49 (8.0)	
Barnes	Abstinent	1.0 (1.6)	1.9 (2.4)	
	Not abstinent	1.3 (1.8)	1.5 (2.4)	
Simpson-Angus	Abstinent	2.1 (2.7)	1.6 (1.8)	
	Not abstinent	4.1 (4.0)	4.3 (4.2)	
AIMS	Abstinent	3.1 (4.3)	0.8 (1.0)	
	Not abstinent	1.9 (2.9)	2.3 (2.7)	
Cigarettes per day	Quit	27 (12)	0.0 (0.0)	$P < 0.0001$
	Not quit	22 (13)	13 (11)	

greater reduction from baseline was required on both measurements for criteria for significant reduction at Week 12 to be met. Comparisons of reduction rates were performed with Pearson χ^2 test. As a secondary measure of smoking reduction, expired air CO measurements from the quit date to the 3-month follow-up were analyzed by treatment with a repeated-measures mixed model analysis of variance using ProcMixed in Simpson Angus Scale. Other secondary outcomes were biochemically validated point prevalence and continuous abstinence at Weeks 8, 12, 24, and 52 and change from baseline in symptom ratings. Seven-day point prevalence abstinence was defined as self-report of smoking no cigarettes in the prior 7 days confirmed by expired air CO of less than 8 ppm. Subjects who met the criteria for 7-day point prevalence abstinence at every assessment after the target quit date were considered to have continuous abstinence at that time point. Dropouts were considered smokers for analyses of binary outcomes. As no subjects met criteria for significant reduction at the time of dropout, the potential for bias with this method of handling missing data in this study is low. Effects were considered significant if 2-sided $P < 0.05$.

RESULTS

After study description and written informed consent, 110 subjects were screened for enrollment. Twenty-four subjects were not eligible, and 35 did not return after screening or withdrew consent. Fifty-one subjects were randomized, received at least 1 week of treatment, completed at least 1 postbaseline assessment, and were included in the analysis. At baseline, subjects reported smoking over 1 pack of cigarettes per day and had a mean FTND score of 7.1 (SD, 1.7), consistent with heavy smoking. Subjects reported that they had initiated smoking at age 17 (SD, 6.2) and had smoked for 26 (SD, 10.6) years, and 51% reported a current smoking-related illness. Subjects reported a median of 2 (range, 0–50) previous smoking cessation attempts. There were no differences between groups in baseline demographic characteristics or clinical symptoms (Tables 1 and 3).

Five of 25 subjects in the bupropion group and 8 of 26 on placebo dropped out before Week 12; all were smoking at their baseline level at the time of dropout. All subjects who were abstinent at end of treatment completed the 12-month follow-up. Subjects in the bupropion + NRT group missed an average of 0.52 (SD, 0.73) doses of study medication per week, and those in the placebo + NRT group missed 0.57 (SD, 0.79) doses per week by self-report, confirmed by pill count (ns). Subjects reported using an average of 18 mg of nicotine gum per day from Weeks 4 to 8, 15 mg/d in Weeks 9 to 10, and 13 mg/d in Weeks 11 to 12. There were no between-group differences in NRT dose at any week. Assessment of treatment assignment was at the level of chance for both participants and staff at Weeks 4 and 12 for both treatment assignments.

Smoking Reduction and Cessation

Subjects on bupropion + dual NRT had a higher rate of 50% to 100% reduction in smoking at Weeks 12 (60% vs. 31%; $\chi^2 = 4.4$; $P = 0.036$) and 24 (32% vs. 8%; $P = 0.039$; Fisher exact) (Table 2). In subjects with 50% to 100% reduction, the average change in CO at Week 12 was 82% reduction (95% confidence interval [CI], 73–91). From Weeks 4 to 24, those on bupropion had a mean 7.6 (2.6) ppm lower CO than those on placebo, $F_{1,40} = 8.33$; $P = 0.006$ (Fig. 1). There was a significant effect of treatment on CO at each time point, $F_{7,40} = 4.16$; $P = 0.002$.

Fifty-two percent of those on bupropion + dual NRT achieved 4-week continuous abstinence at Week 8, compared with 19% of those on placebo ($\chi^2 = 5.99$; $P = 0.014$). Continuous abstinence rates did not differ between groups after Week 8 (Table 2). Of interest, 31% (4 of 13) of those in the bupropion group who had been abstinent for 4 weeks at Week 8 resumed low-level smoking (<5 cigarettes per day) during the taper of NRT between Weeks 8 and 12.

From baseline to Week 12, subjects on bupropion + NRT had a mean change of −21 (95% CI, 29–15) cigarettes per day, and those on placebo had a mean change of −11 (95% CI, −26 to 4.8) cigarettes per day. At Week 24, those

in the bupropion NRT group had a change from baseline of −9.5 (95% CI, −19 to −0.4) cigarettes per day, and those in the placebo + NRT group reported a mean change of−2.9 (95% CI, −24 to 18) cigarettes per day.

Effect of Antipsychotic Type on Abstinence

There was no detectable effect of type of antipsychotic (atypical vs. conventional) on abstinence outcomes. Six (38%) of 16 clozapine-treated subjects and 8 (23%) of 35 nonclozapine-treated subjects were abstinent at Week 12, ns.

Psychiatric Symptoms

There were no effects of study medication or abstinence on psychiatric symptoms. Akathisia and extrapyramidal symptom (EPS) scores were slightly decreased in the bupropion group and somewhat increased in the placebo group at Week 12 relative to baseline measures, and the between-group effects were significant (Table 3).

Adverse Events

There were no serious adverse events. Four subjects discontinued study medication because of adverse events. Two subjects in the bupropion and NRT group discontinued study medications, 1 during the fourth week because of insomnia and the other in the ninth week because of dizziness. Two subjects in the placebo group discontinued study medications, 1 at Week 2 because of insomnia and palpitations and the other at Week 11 because of insomnia, indigestion, and weight loss. None of the participants who discontinued study medications were abstinent at the time of dropout.

DISCUSSION

This is the first report of combination pharmacological treatment for nicotine-dependence treatment in schizophrenia, a group with a high prevalence of nicotine dependence and low rate of smoking cessation. We report a significantly superior effect of bupropion versus placebo added to short- and long-acting NRT on 50% to 100% smoking reduction, the primary outcome measure, and on smoking reduction as a continuous measure. Combination of bupropion and dual NRT was also superior for 4-week continuous abstinence, whereas NRT was maintained at approximately 40 mg/d. Importantly, the incremental benefit of bupropion for smoking cessation and reduction was only evident during the 12-week treatment period.

As in previous nicotine-dependence treatment studies in schizophrenia, the rate of relapse to smoking was high during taper and discontinuation of pharmacological treatment.[16,17] Those on bupropion SR, nicotine patch 21 mg/d, and prn nicotine gum up to 18 mg/d had a 4-week continuous abstinence rate of more than 50%. The relapse rate during taper of NRT from approximately 40 to 20 mg/d in this group was 31%, and the relapse rate after treatment discontinuation was 77%, suggesting that bupropion may improve abstinence rates in smokers with schizophrenia the most when combined with high-dose dual NRT. The abstinence rate on combination pharmacotherapy was higher than that reported with either bupropion or NRT alone.[14−17] Because the health benefit of smoking cessation increases with longer duration of abstinence and because the abstinence rate on combination pharmacotherapy and CBT was high but the relapse rate during taper and discontinuation of treatment was very high, a longer trial of combination pharmacotherapy and CBT is warranted for prevention of relapse in those who are able to quit smoking on this regimen.

Although relapse rates are also high in the general population after discontinuation of short-term, 8 to 12 weeks, smoking cessation treatment,[20,26] nicotinic receptor expression is expected to return to normal after smoking cessation in smokers without schizophrenia. In schizophrenia, nicotinic activity is abnormally low at baseline,[27−29] is increased by smoking or NRT,[30−32] and is not expected to return to a normal baseline after smoking cessation. Smoking and NRT may ameliorate nicotinic receptor hypofunction by providing exogenous agonist and by increasing nicotinic receptor expression, even if this increase is modest.[28,33,34] Low-affinity nicotinic receptors desensitize rapidly,[35] and increased nicotinic transmission with long acting NRT may be limited by tachyphylaxis at these receptors.[36] However, nicotine seems to improve sensory gating deficits and attention deficits in schizophrenia by improving inhibition of responses to sensory input and inhibition of impulsive responses in tasks of attention,[30−32,37−39] effects that may become more robust over time.[40] Based on these data and the high rate of relapse to smoking during NRT taper and immediately after treatment discontinuation observed in this study, we postulate that longer term, perhaps chronic, nicotine-dependence treatment that includes NRT or a nicotinic agonist may result in improved sustained abstinence rates in recently abstinent smokers with schizophrenia.

A significant medication effect on EPS was observed, with EPS decreasing in the bupropion + NRT group and increasing in the placebo + NRT group. This finding was in the opposite direction of what was expected because bupropion is a weak cytochrome p450 (CYP)2D6 isozyme inhibitor[41,42] and can increase concentrations of antipsychotic substrates of CYP2D6. Additionally, smoking, but not NRT, is associated with higher doses but not serum levels of antipsychotic medications.[43,44] Polycyclic aromatic hydrocarbons present in cigarette smoke induce hepatic aryl hydrocarbon hydroxylases and CYP450 isozymes, primarily CYP1A1, 1A2, and 2E1, thereby increasing metabolic clearance of medications such as clozapine that are substrates for these enzymes.[45−47] Smoking cessation is associated with a 30% to 42% reduction in activity of CYP1A2; the half-life of this reduction is 27 to 54 hours; thus, therapeutic drug monitoring and dose reduction of 10% over the first 4 days of tobacco abstinence has been recommended to avoid toxicity.[47] Although participants in the bupropion group had greater reduction in smoking, which may have resulted in slower metabolism and higher serum concentrations of concomitant medications, mild dopaminergic properties of bupropion may have protected against a potential increase in EPS resulting from increased serum levels of antipsychotic medications.[48]

Limitations of this trial include small sample size that limits our ability to draw conclusions about the effect of

combination bupropion + dual NRT compared with placebo + dual NRT on abstinence measures after taper of NRT. Despite this limitation, we found a significant effect of the combination of bupropion and NRT on rate of 50% to 100% reduction in smoking at trial end point and on reduction in expired air CO during the study intervention.

In summary, smokers with schizophrenia in this trial showed considerable motivation to quit smoking and achieved significant smoking reduction. During treatment, more smokers on combination of bupropion + NRT patch and gum + CBT achieved 50% to 100% reduction in smoking compared with those on placebo + NRT patch and gum + CBT. Relapse rates were very high after treatment discontinuation, and the incremental benefit of bupropion was not apparent after treatment discontinuation. Because schizophrenia patients have decreased nicotinic receptor expression and function, longer duration treatment with tailored nicotine dependence treatment with high-dose NRT, combination of short- and long-acting NRT, and/or combination bupropion and NRT may improve sustained abstinence rates.

ACKNOWLEDGMENTS

The authors thank Beth Ewy for her assistance with the Tobacco Treatment Specialist training and Drs Kenneth Duckworth and Joan Kerzner from the Massachusetts Department of Mental Health for supporting this work.

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