Predictors of Early Abstinence in Smokers With Schizophrenia

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Background: In patients with schizophrenia, the smoking cessation rate is low and the burden of smoking-related morbidity and mortality is high. Identification of factors associated with abstinence may allow clinicians to optimize treatment prior to a smoking cessation attempt.

Method: To identify factors associated with successful smoking cessation in patients with a DSM-IV diagnosis of schizophrenia, we analyzed baseline data from 114 stable outpatient smokers with schizophrenia who participated in 1 of 2 smoking cessation trials. The outcome of interest was 4 weeks' continuous abstinence at the end of a 12-week nicotine dependence treatment intervention. Baseline factors associated with abstinence were identified with univariate methods and entered into a manual, forward-selection multivariable regression model to identify independent predictors of abstinence. The study was conducted from March 1999 to February 2004.

Results: Fourteen of 114 participants (12%) had biochemically verified 4 weeks' continuous abstinence at week 12. We included 10 noncorrelated variables with a univariate association with abstinence in a multivariable model, controlling for pharmacotherapy, age, and gender. Age at initiation of smoking and baseline variability in attentiveness, as measured by Continuous Performance Test-AX (CPT-AX) hit reaction time standard error, were independently associated with abstinence. For every year increase in age at initiation of smoking, the OR for abstinence was 1.36 (95% CI = 1.01 to 1.83), p = .048. For every millisecond decrease in the variability of the reaction time of CPT-AX, the OR for achieving abstinence was 1.55 (95% CI = 1.07 to 2.24), p = .021.

Conclusion: Later initiation of smoking was associated with increased and baseline attentional impairment with reduced odds of abstinence. Additional research to further our understanding of the relationship between attentional impairment and cigarette smoking in schizophrenia may lead to improved nicotine dependence treatments for this group.

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Tobacco smoking is the leading preventable cause of death in the United States, a fact that results in more than $167 billion in loss of productivity and annual health-related costs and 440,000 premature deaths in the United States annually.[1] Seventy-five percent to 85% of people with schizophrenia in the United States smoke, compared with 21% of the general population.[2,3] Schizophrenia patients are not only more likely to smoke, they are more likely to smoke heavily[4] and extract more nicotine per cigarette than smokers without psychiatric illness.[5,6] Researchers have found that schizophrenia is an independent predictor of tobacco smoking after controlling for substance abuse, institutionalization, medication, and socioeconomic status.[2,3,5,7,8] People with schizophrenia die on average 10 years earlier than people in the general population,[9] and age-adjusted rates of death due to cardiac and pulmonary disease are significantly elevated in this population,[9–11] a finding that suggests that tobacco use is an important cause of the increased mortality observed in schizophrenia. An estimated 1.5 to 1.7 million smokers in the United States are diagnosed with schizophrenia.[2,3,12]

Compared with the general population, patients with schizophrenia have low smoking-cessation rates even though they can be both highly motivated and persistent in

their attempts to quit smoking[13–16] and, with nicotine dependence treatment such as nicotine replacement therapy (NRT) or bupropion sustained release (SR), can tolerate short-term tobacco abstinence without significant exacerbation in clinical or cognitive symptoms.[17–20] Identification of patient factors significantly associated with successful smoking cessation in schizophrenia patients may lead to the ability to optimize treatment decisions to increase the probability of a successful cessation in these patients who smoke heavily, have low cessation rates, and have a heavy burden of smoking-related illness.

Baseline characteristics such as older age at initiation of smoking, low level of nicotine dependence, high degree of motivation to quit, low alcohol consumption, and longer duration of previous abstinence have been associated with successful smoking cessation in the general population.[21–24] Male gender is associated with successful smoking cessation in clinical populations.[23] It is not known if these baseline characteristics are predictive of abstinence in schizophrenia patients. Smokers with schizophrenia differ from smokers in the general population in several fundamental ways. Those with schizophrenia have abnormalities in nicotinic acetylcholine receptor expression and function[25–27] and abnormalities in attention, memory, and motor speed[28–31] that may be improved with nicotine[32–36] and worsened by tobacco abstinence.[37] There is also evidence that schizophrenia patients not only smoke with greater prevalence than those in the general population but also are more likely to smoke more heavily and to smoke each cigarette more intensively, with more puffs per cigarette and shorter interpuff intervals.[2,3,5,38–41] As a result, baseline characteristics associated with successful smoking cessation for smokers with schizophrenia may differ from those in the general population. We examined the association between baseline characteristics and ability to attain 4 weeks' continuous tobacco abstinence in 114 smokers with schizophrenia in order to (1) test the strength of association of factors previously identified with abstinence in the general population in a sample of smokers with schizophrenia who participated in a smoking cessation program, (2) explore the association of baseline clinical and cognitive symptoms with tobacco abstinence in schizophrenia, and (3) create a multivariable model to identify patient characteristics independently associated with tobacco abstinence. It is hoped that identification of predictors of abstinence in this sample of smokers with schizophrenia and replication in an independent sample will eventually inform the development of appropriate smoking-cessation interventions in this population.

METHOD

Participants

Data were included from participants in 1 of the following 2 trials: (1) a double-blind, placebo-controlled trial of bupropion SR added to cognitive-behavioral therapy (CBT) in 53 patients with schizophrenia[18] or (2) a double-blind, placebo-controlled trial of bupropion SR added to NRT and CBT in 51 patients with schizophrenia.[42] An additional 10 subjects from the latter trial who were not medically eligible for bupropion SR randomization but who received open NRT and CBT (A.E.E., C.C., T.D., et al., unpublished data, 2002–2004) were included in the analysis. Patients were enrolled from 5 urban community mental health centers in Massachusetts from March 1999 to February 2004. The protocols were approved by appropriate institutional review boards. Capacity to consent was determined and documented for all participants by a doctoral-level clinician using a formal process.

Eligible subjects were adult outpatients with schizophrenia or schizoaffective disorder, depressive type, according to DSM-IV criteria, with stable psychiatric symptoms and a stable dose of antipsychotic medication for at least 30 days, who smoked ≥ 10 cigarettes/day and were willing to set a quit date within 4 weeks of enrollment. Potential subjects who met DSM-IV criteria for current major depressive disorder were not eligible. Patients with a substance use disorder other than nicotine or caffeine within 6 months of screening were not eligible, nor were patients taking bupropion SR or using NRT at the time of screening. Patients with seizure disorder, history of bulimia, history of mania, or current regimen of clozapine > 500 mg/day without a therapeutic dose of an anticonvulsant were not eligible for being randomly assigned to bupropion SR or placebo.

Interventions

All participants attended a 12-session weekly smoking cessation group program described previously.[43] Cognitive-behavioral therapy groups ranged in size from 3 to 7 participants. All subjects set a quit date before the fifth group meeting. In the second trial,[42] nicotine patches and nicotine polacrilex gum were initiated on the quit date. Nicotine patch was dosed at 21 mg/day for 4 weeks, 14 mg/day for 2 weeks, and 7 mg/day for 2 weeks and then discontinued. Nicotine polacrilex gum (2 mg) was distributed to subjects for p.r.n. use up to 9 pieces (18 mg) per day. Bupropion SR was dosed at 150 mg b.i.d.

Outcome Measure

Four weeks' continuous abstinence was the outcome of interest. This was defined as meeting criteria for 7-day point prevalence abstinence at group meetings 9 through 12 of a 12-week study intervention. Seven-day point prevalence abstinence was defined as self-report of smoking no cigarettes (not even a puff) for the past 7 days and expired air carbon monoxide < 9 ppm. Continuous abstinence for 4 weeks rather than 7 days was chosen as the endpoint because 4 weeks' continuous abstinence

is likely to be a better predictor of long-term abstinence than 7-day point prevalence abstinence. It was not possible to examine predictors of sustained tobacco abstinence at 6 or 12 months because relapse rates following discontinuation of nicotine dependence treatment was very high.

Variable Selection

Data were gathered on the following variables that have been identified in the general population as associated with tobacco abstinence: gender, age, age at initiation of smoking, stage of change, duration of previous abstinence, level of nicotine dependence, proportion of smokers in the household, and marital status.[22–24,33] Patients with schizophrenia have deficits in attention and memory functions that are improved with nicotine. Moreover, neuropsychological deficits have been associated with smoking-cessation treatment failure in patients with schizophrenia.[44] Therefore, in our study,[18,42] data were gathered on neuropsychological performance on tests of attention (Continuous Performance Test-AX [CPT-AX]), verbal learning and memory (California Verbal Learning Test), working memory (Digit Span), and executive function/inhibition (3-Card Stroop). Standard clinical data were also gathered by using the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Hamilton Rating Scale for Depression, Barnes Akathisia Scale, Simpson-Angus Scale, and Abnormal Involuntary Movement Scale. Variables that had a univariate association with the dependent variable ($p < .25$) were selected for inclusion in the multivariable analysis. Collinearity among these variables was investigated according to the guidelines of Hosmer and Lemeshow.[45] Diagnostics were run for variables with correlation coefficients greater than 0.50. Highly correlated variables with $r > 0.50$ that were also associated with the outcome with $p < .20$ were included in an automated stepwise logistic regression model. In addition, factors independently associated with the outcome of $p < .05$ were included in the multivariable model.

Multivariable Model

A manual, stepwise, forward-selection multivariable logistic-regression analysis was performed to identify factors independently associated with 4 weeks' continuous abstinence. Association with the outcome of $p < .20$ was required for entry, and association of $p < .05$ was required to remain in the model. Smoking and demographic predictors of cessation differ by gender in some samples.[46] Possible effect modification by gender was examined by adding an interaction term between gender and each of the predictor variables. The same was done for bupropion SR treatment. If the interaction term was not significant, the analysis was carried out on the pooled sample. All models were adjusted for medication treatment, age, and gender. The results are presented as effect estimates for continuous variables and ORs, with 95% CIs for dichotomous variables. All statistical analyses were performed using SAS, version 8 (SAS Institute Inc., Cary, N.C.) software.

RESULTS

Fourteen subjects (12.3%) met criteria for a greater than or equal to 4 weeks' continuous abstinence period at week 12. Seventy-nine percent (N = 11) of the 14 subjects who achieved 4 weeks' abstinence were male and 67% (N = 67) of the 100 subjects who were unable to achieve 4 weeks' abstinence were male. Of these 14 subjects, 9 (64%) received either bupropion SR or NRT, 5 (36%) received both bupropion SR and NRT, and none (0%) received placebo. Of the 100 subjects who were unable to achieve a 4-week continuous abstinence at week twelve, 54 (54%) received either bupropion SR or NRT, 18 (18%) received both bupropion SR and NRT, and 28 (28%) received placebo. These differences were not statistically significant. There were also no significant differences in race. Those who achieved 4 weeks' abstinence had slightly higher mean ratings of motivation (9.29, SD = 1.64) compared to those who were unable to achieve 4 weeks' abstinence (8.48, SD = 1.89); however, this difference was not statistically significant.

A univariate screen identified 16 variables significantly associated with continuous abstinence (Table 1). Seven variables were highly correlated: PANSS total score, PANSS cognitive symptom subscore, PANSS negative symptom subscore, SANS total score, SANS affective subscore, SANS alogia subscore, and SANS attention subscore. A stepwise logistic regression was performed with $p < .20$ for entry and $p < .05$ to select clinical variables independently associated with the outcome for inclusion in the multivariable model. From the 7 correlated variables associated with abstinence, only the SANS alogia subscore was independently associated with 4 weeks' continuous abstinence and was included in the variable list for the multivariable model.

Ten variables had univariate association with the outcome with a p value < .25; these variables were not correlated and were included in a forward-selection logistic regression model. These variables were study medication (NRT, bupropion SR, or both), baseline expired air carbon monoxide, self-report of a history of worsening of psychiatric symptoms with a past smoking cessation attempt, SANS alogia subscore, CPT-AX hit reaction time, CPT-AX hit reaction time variability, Stroop interference reaction time, age at initiation of regular smoking, and 2 variables scored with a 10-point visual analog scale: "How much do you want to quit?" and "How confident are you that you will be abstinent one year from now?"

Interactions were tested and removed if not significant. All models included the potential confounding

Table 1. Univariate Predictors of Continuous Abstinence From Smoking

	Abstinent (N = 14)		Not Abstinent (N = 100)		
Predictor	Mean	SD	Mean	SD	p Value
Male gender, N	11		67		.380
Married, N	0		7		.307
Education (highest year completed)	11.50	2.93	11.52	2.79	.979
IQ	92.31	17.67	88.09	16.98	.410
Current alcohol use (1 = 0 drinks/d; 5 = > 5 drinks/d)	1.14	0.36	1.24	0.64	.598
Level of nicotine dependence (FTND: 1 = no dependence; 10 = severe)	6.14	1.88	5.59	2.15	.362
Average baseline carbon monoxide, ppm	30.07	12.13	25.16	13.94	.213
Pack years	35.68	25.73	37.82	28.20	.789
Age at smoking initiation, y	19.86	7.08	16.80	5.95	.084
Proportion of smokers in house	0.70	0.24	0.77	0.24	.449
No. of previous quit attempts	5.31	8.38	3.89	8.04	.558
Previous quit lasted 91 days or longer, N	4		16		.250
Psychiatric problems with past quit, N	13		76		.150
Motivation: How much do you want to quit? (1 = very little; 10 = very much)	9.29	1.64	8.48	1.89	.137
How confident are you that you will be abstinent 1 year from now? (1 = very little; 10 = very much)	8.43	1.70	6.99	2.63	.051
How much do friends and family want you to quit? (1 = very little; 10 = very much)	6.00	3.40	6.97	3.40	.324
How helpful would people be if you quit? (1 = very helpful; 10 = not very helpful)	3.36	2.62	4.18	2.80	.304
Categorical medication variable (1 = bupropion SR *or* NRT only; 2 = bupropion SR *and* NRT only)	1.36	0.50	0.90	0.67	.016
PANSS					
Total	55.93	7.68	63.04	15.47	.095
Positive	9.93	4.89	10.36	4.64	.747
Negative	11.86	4.37	14.24	5.85	.147
Cognitive	9.86	2.71	11.76	3.92	.082
Excited	5.50	1.79	6.15	2.44	.336
Depressive	10.36	3.18	11.37	4.03	.372
SANS					
Total	31.14	11.51	41.46	20.04	.063
Affective	6.36	4.77	10.22	7.93	.079
Alogia	3.00	2.63	6.24	4.76	.014
Avolition	7.86	4.66	7.28	4.93	.678
Anhedonia	10.57	5.53	11.88	5.86	.434
Attention	3.79	3.81	6.11	4.02	.044
HAM-D total	9.43	5.46	9.08	5.88	.836
Barnes Akathisia Scale total	1.29	2.05	1.30	2.18	.983
Simpson-Angus Scale total	2.64	3.39	2.06	2.82	.484
AIMS total	2.29	3.93	1.86	2.73	.606
Stroop interference reaction time	1065.76	167.47	1203.23	165.87	.032
CPT-AX hit reaction time	378.56	59.39	457.12	99.78	.003
CPT-AX hit reaction time standard error	12.02	5.22	19.16	12.36	.110
Finger tapping nondominant	36.96	10.45	36.45	8.78	.862
Finger tapping dominant	42.15	9.77	41.07	8.76	.713
Digit span total forward and backward	12.69	2.75	13.74	3.81	.344
CVLT total, trials 1–5	35.00	8.16	34.06	12.01	.786

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, CPT-AX = Continuous Performance Test-AX, CVLT = California Verbal Learning Test, FTND = Fagerström Test for Nicotine Dependence, HAM-D = Hamilton Rating Scale for Depression, NRT = nicotine replacement therapy, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SR = sustained release.

variables: gender, age, and study medication (Table 2). In the multivariable model, controlling for medication, age, and gender, CPT-AX hit reaction time standard error was significantly associated with abstinence such that for every millisecond increase in the variability of the reaction time of CPT-AX, the OR for achieving abstinence was 1.55 (95% CI = 1.07 to 2.24), p = .021; because the effect size is negative, the OR reported is an inverse OR. Additionally, age at initiation of smoking was significantly associated with abstinence such that for every year increase in age at initiation of regular smoking the OR for abstinence was 1.36 (95% CI = 1.01 to 1.83), p = .048. All analyses were also run with with 7-day point prevalence abstinence at end of treatment as the dependent variable, and the results of both univariate and multivariable predictor models were identical.

Missing Data

There were 114 subjects with the outcome measure and 14 with the outcome of interest. Continuous Performance Test data were missing for 31 subjects, 6 of whom had the outcome of interest. Age at smoking initiation was missing for 3 subjects, and the outcome of interest was not missing for any subjects. To examine whether this could have confounded the results, we compared 4-week continuous abstinence rates for those with CPT-AX data with

Table 2. Demographics by Continuous Abstinence Status

	Abstinent (N = 14)		Not Abstinent (N = 100)	
Demographic	N	%	N	%
Male gender	11	79	67	67
Married	0	0	7	7
Race				
Caucasian	9	64	72	72
African American	2	14	16	16
American Indian	1	7	1	1
Hispanic	2	14	5	5
Study medication				
Placebo	0	0	28	28
NRT or bupropion	9	64	54	54
NRT and bupropion	5	36	18	18
	Mean	SD	Mean	SD
Education (highest year completed)	11.50	2.93	11.52	2.79
IQ	92.31	17.67	88.09	16.98
Level of nicotine dependence (FTND: 1 = no dependence; 10 = severe)	6.14	1.88	5.59	2.15
Baseline carbon monoxide	30.07	12.13	25.16	13.94
Pack years	35.68	25.73	37.82	28.20
Motivation: How much do you want to quit? (1 = very little; 10 = very much)	9.29	1.64	8.48	1.89

Abbreviations: FTND = Fagerström Test for Nicotine Dependence, NRT = nicotine replacement therapy.

those for subjects with missing CPT-AX data. Abstinence rates were 9 of 83 (10.8%) and 5 of 31 (16.1%), respectively (p = .52, Fisher exact test), indicating that confounding by missing data is unlikely.

DISCUSSION

This is the first forward-selection analysis to our knowledge of predictors of abstinence in nicotine dependence treatment in patients with schizophrenia. This was an exploratory analysis that included factors associated with ability to quit smoking in the general population as well as measures of psychiatric symptom severity and neuropsychological function. Factors that were associated in univariate analysis with the ability to attain abstinence during nicotine dependence treatment included factors associated with ability to quit smoking in the general population (pharmacotherapy for nicotine dependence, confidence in ability to quit, and age at initiation of smoking) as well as measures of psychiatric symptom severity (PANSS total and cognitive subscale scores and SANS total, alogia, and attention subscale scores) and measures of cognitive dysfunction (CPT-AX hit reaction time and hit reaction time standard error and Stroop interference reaction time). Factors that were identified as independently associated with tobacco abstinence in this sample of 114 schizophrenia patients were CPT-AX hit reaction time (a measure of attention) standard error and age at initiation of smoking.

These results indicate that factors associated with the ability to quit smoking in the general population are important for smoking cessation in patients with schizophrenia and that factors associated with schizophrenia such as psychiatric and cognitive symptom severity are also important factors in determining success or failure of a given smoking cessation attempt. Nicotine and nicotinic agonists improve both learning/memory and attention in animals and in humans,[47–54] while nicotinic antagonists impair cognitive performance[49,53,55] (see Levin et al.[56] for review). Some studies have shown that nicotine improves cognitive performance in nonsmokers with attentional impairment.[57–60] Other studies have shown that nicotine withdrawal produces cognitive deficits in smokers with and without psychiatric illness.[61–65] Nicotine and nicotinic agonists improve and/or normalize memory and attentional deficits, specifically in people with schizophrenia.[32,33,35,36,66,67] Furthermore, neuropsychological deficits have been implicated in smoking cessation treatment failure in people with schizophrenia but not in normal controls.[44] Our results support the hypothesis that nicotine may be therapeutic for patients with schizophrenia. Attentional deficits are strongly associated with schizophrenia, and those with greater attentional impairment were less likely to quit smoking.

Bupropion SR has been shown to be moderately effective for smoking cessation in people with schizophrenia.[18,43,68,69] In this sample, baseline attentional impairment and age at smoking initiation are more strongly associated with abstinence than is medication treatment. Studies have shown that bupropion SR may improve attentional impairment in patients with attention-deficit/hyperactivity disorder[70–73] and schizophrenia.[61] We did not find a significant interaction between bupropion SR treatment and baseline CPT-AX hit reaction time standard error.

While gender may be important in determining success of smoking cessation programs in patients with schizophrenia, illness-specific factors appear to be more important factors.

Limitations of this trial are the small sample size and the small number of patients who achieved continuous abstinence. Additionally, the predictors of abstinence reported here are data driven and may not be generalizable to the larger population of outpatients with schizophrenia who try to quit smoking. It will be important to conduct a confirmatory analysis in a separate sample. Several predictors strongly associated with abstinence in the general population were not significant predictors in this sample with schizophrenia. However, because patients with major depressive disorder and also those with concurrent substance abuse were excluded, we are not able to comment on the association between these disorders and abstinence. There was very little variability in Fagerström Test for Nicotine Dependence (FTND)[74] scores in the sample; most subjects had a FTND ≥ 5, indicating heavy dependence that is common in patients with schizophrenia. It is therefore possible that low level of dependence in patients with schizophrenia, while uncommon, may be a positive predictor of success in a smoking cessation program. Similarly, baseline smoking rate and expired air carbon monoxide were on average quite high and may not have had the variability necessary to assess an association with abstinence in the model. These factors may be significant for other groups of patients with schizophrenia. Finally, it should be emphasized that the high relapse rates in this population following termination of therapy has limited this study to examining predictors of early, 4-week abstinence, not long-term smoking cessation.

CONCLUSION

The main finding of our analysis is that attentional impairment in patients with schizophrenia is associated with failure in nicotine dependence treatment. This finding points to the need to identify treatments for cognitive impairment in patients with schizophrenia as a part of smoking cessation programs. Nicotine, nicotinic receptor agonists, and bupropion SR improve attention in those with schizophrenia and in other populations.[75] Certain cholinergic medications, such as donepezil and galantamine, have been shown to improve cognitive deficiencies in patients with Alzheimer's disease. Some trials of donepezil and galantamine in patients with schizophrenia have reported moderate improvements in memory.[76–79] Other trials have not found that donepezil or galantamine improves cognition in patients with schizophrenia compared to placebo[27,80–83]; it should be noted, however, that most of these trials included patients with nicotine dependence. It is possible that failure to respond to cholinesterase inhibitors is due to nicotinic receptor desensitization from prolonged heavy tobacco use or due to maximization of cognitive improvement from the nicotine itself and that a cholinergic medication would not provide an additional benefit over nicotine alone. However, 1 trial of galantamine was conducted in nonsmokers and found galantamine inferior to placebo.[83] Neither donepezil nor galantamine has been tested for treatment of cognitive dysfunction during nicotine withdrawal. Other cholinergic medications for potential treatment of cognitive dysfunction and nicotine dependence in patients with schizophrenia, such as anabasine, varenicline, or long-term NRT, have not yet been adequately explored.

Long-term treatment with nicotinic receptor agonists may improve success rates in nicotine dependence treatment programs for patients with schizophrenia. Further studies of cholinergic medications and long-term NRT are warranted, as are further studies of the role of learning, memory, and attention in smoking cessation and relapse prevention in schizophrenia.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), clozapine (FazaClo, Clozaril, and others), donepezil (Aricept and others), galantamine (Razadyne), varenicline (Chantix).

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REFERENCES

1. US Centers for Disease Control and Prevention. Tobacco use among adults—United States, 2005. Morbidity and Mortality Weekly Report 2006 Oct 27;55(42):1145–1148
2. de Leon J, Dadvand M, Canuso C, et al. Schizophrenia and smoking: an epidemiological survey in a state hospital. Am J Psychiatry 1995;152: 453–455
3. de Leon J, Tracy J, McCann E, et al. Schizophrenia and tobacco smoking: a replication study in another US psychiatric hospital. Schizophr Res 2002;56:55–65
4. Kelly C, Sharkey V, Morrison G, et al. Nithsdale Schizophrenia Surveys, 20: cognitive function in a catchment-area-based population of patients with schizophrenia. Br J Psychiatry 2000;177:348–353
5. Olincy A, Young DA, Freedman R. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biol Psychiatry 1997;42:1–5
6. Williams JM, Ziedonis DM, Abanyie F, et al. Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. Schizophr Res 2005;79:323–335
7. de Leon J, Diaz FJ, Rogers T, et al. Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. Schizophr Res 2002;56:47–54
8. Diwan A, Castine M, Pomerleau CS, et al. Differential prevalence of cigarette smoking in patients with schizophrenic vs mood disorders.

Schizophr Res 1998;33:113–118
9. Hannerz H, Borga P, Borritz M. Life expectancies for people with psychiatric diagnoses. Public Health 2001;115:328–337
10. Brown S. Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997;171:502–508
11. Joukamaa M, Heliovaara M, Knekt P, et al. Mental disorders and cause-specific mortality. Br J Psychiatry 2001;179:498–502
12. Narrow WE, Rae DS, Robins LN, et al. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry 2002;59: 115–123
13. Addington J, el-Guebaly N, Addington D, et al. Readiness to stop smoking in schizophrenia. Can J Psychiatry 1997;42:49–52
14. Evins AE, Cather C, Rigotti NA, et al. Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. J Clin Psychiatry 2004 Mar;65(3):307–311
15. Lader D, Meltzer H. Smoking Related Behaviour and Attitudes. London, England: Office for National Statistics, Department of Health; 2001
16. Ziedonis DM, George TP. Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. Schizophr Bull 1997;23:247–254
17. Dalack GW, Becks L, Hill E, et al. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology 1999;21:195–202
18. Evins AE, Cather C, Deckersbach T, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. J Clin Psychopharmacol 2005;25:218–225
19. Baker A, Richmond R, Haile M, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. Am J Psychiatry 2006;163:1934–1942
20. George TP, Vessicchio JC, Sacco KA, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. Biol Psychiatry 2008;63:1092–1096
21. Aubin HJ. Tolerability and safety of sustained-release bupropion in the management of smoking cessation. Drugs 2002;62(suppl 2):45–52
22. Chandola T, Head J, Bartley M. Socio-demographic predictors of quitting smoking: how important are household factors? Addiction 2004;99: 770–777
23. Ferguson JA, Patten CA, Schroeder DR, et al. Predictors of 6-month tobacco abstinence among 1224 cigarette smokers treated for nicotine dependence. Addict Behav 2003;28:1203–1218
24. Hurt RD, Wolter TD, Rigotti N, et al. Bupropion for pharmacologic relapse prevention to smoking: predictors of outcome. Addict Behav 2002;27:493–507
25. Breese CR, Lee MJ, Adams CE, et al. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 2000;23:351–364
26. Durany N, Zochling R, Boissl KW, et al. Human post-mortem striatal alpha4beta2 nicotinic acetylcholine receptor density in schizophrenia and Parkinson's syndrome. Neurosci Lett 2000;287:109–112
27. Freedman R, Hall M, Adler LE, et al. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 1995;38:22–33
28. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr Bull 1994;20:31–46
29. Liu SK, Chiu CH, Chang CJ, et al. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. Am J Psychiatry 2002;159:975–982
30. Sullivan EV, Shear PK, Zipursky RB, et al. A deficit profile of executive, memory, and motor functions in schizophrenia. Biol Psychiatry 1994;36: 641–653
31. Wiedl KH, Wienobst J, Schottke HH, et al. Attentional characteristics of schizophrenia patients differing in learning proficiency on the Wisconsin Card Sorting Test. Schizophr Bull 2001;27:687–695
32. Depatie L, O'Driscoll GA, Holahan AL, et al. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology 2002;27:1056–1070
33. Harris JG, Kongs S, Allensworth D, et al. Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 2004;29:1378–1385
34. Levin ED, Wilson W, Rose JE, et al. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 1996;15:429–436
35. Myers CS, Robles O, Kakoyannis AN, et al. Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology (Berl) 2004 Jul;174(3):334–340
36. Smith RC, Singh A, Infante M, et al. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. Neuropsychopharmacology 2002;27:479–497
37. George TP, Vessicchio JC, Termine A, et al. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. Neuropsychopharmacology 2002;26:75–85
38. US Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2000. Morbidity and Mortality Weekly Report 2002 Jul 26;51(29):642–645
39. Hughes J. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;143:993–997
40. Meltzer H, Gill B, Pettigrew M. Economic Activity and Social Functioning of Adults With Psychiatric Disorders. Rep. 3. London, England: HMSO; 1996
41. Tidey JW, Rohsenow DJ, Kaplan GB, et al. Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. Drug Alcohol Depend 2005;80:259–265
42. Evins AE, Cather C, Culhane MA, et al. 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. J Clin Psychopharmacol 2007;27:380–386
43. Evins AE, Mays VK, Rigotti NA, et al. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. Nicotine Tob Res 2001;3:397–403
44. Dolan SL, Sacco KA, Termine A, et al. Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. Schizophr Res 2004;70:263–275
45. Hosmer D Jr, Lemeshow S. Applied Logistic Regression. New York, NY: John Wiley and Sons; 1989
46. Godtfredsen NS, Prescott E, Osler M, et al. Predictors of smoking reduction and cessation in a cohort of Danish moderate and heavy smokers. Prev Med 2001;33:46–52
47. Gatto GJ, Bohme GA, Caldwell WS, et al. TC-1734: an orally active neuronal nicotinic acetylcholine receptor modulator with antidepressant, neuroprotective and long-lasting cognitive effects. CNS Drug Rev 2004;10(2):147–166
48. Lawrence NS, Ross TJ, Stein EA. Cognitive mechanisms of nicotine on visual attention. Neuron 2002;36:539–548
49. Levin ED, Rezvani AH. Development of nicotinic drug therapy for cognitive disorders. Eur J Pharmacol 2000;393:141–146
50. McClernon FJ, Gilbert DG, Radtke R. Effects of transdermal nicotine on lateralized identification and memory interference. Hum Psychopharmacol 2003;18:339–343
51. McGaughy J, Sarter M. Effects of ovariectomy, 192 IgG-saporin-induced cortical cholinergic deafferentation, and administration of estradiol on sustained attention performance in rats. Behav Neurosci 1999;113: 1216–1232
52. Puma C, Deschaux O, Molimard R, et al. Nicotine improves memory in an object recognition task in rats. Eur Neuropsychopharmacol 1999;9: 323–327
53. Rezvani AH, Bushnell PJ, Levin ED. Effects of nicotine and mecamylamine on choice accuracy in an operant visual signal detection task in female rats. Psychopharmacology (Berl) 2002;164:369–375
54. Rezvani AH, Levin ED. Nicotine-antipsychotic drug interactions and attentional performance in female rats. Eur J Pharmacol 2004;486: 175–182
55. Levin ED, Torry D. Acute and chronic nicotine effects on working memory in aged rats. Psychopharmacology (Berl) 1996;123:88–97
56. Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol 2002;53(4):633–640
57. Levin ED, Conners CK, Silva D, et al. Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder. Exp Clin Psychopharmacol 2001;9:83–90
58. Poltavski DV, Petros T. Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. Physiol Behav 2006;87:614–624
59. White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology 1999;143:158–165
60. White HK, Levin ED. Chronic transdermal nicotine patch treatment

effects on cognitive performance in age-associated memory impairment. Psychopharmacology (Berl) 2004;171:465–471
61. Evins AE, Deckersbach T, Cather C, et al. Independent effects of tobacco abstinence and bupropion on cognitive function in schizophrenia. J Clin Psychiatry 2005 Sep;66(9):1184–1190
62. Jacobsen LK, Krystal JH, Mencl WE, et al. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol Psychiatry 2005;57:56–66
63. Jacobsen LK, Slotkin TA, Westerveld M, et al. Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking. Neuropsychopharmacology 2006; 31:1550–1561
64. Sacco KA, Termine A, Seyal A, et al. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. Arch Gen Psychiatry 2005;62:649–659
65. Xu J, Mendrek A, Cohen MS, et al. Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. Biol Psychiatry 2005;58:143–150
66. Schubert MH, Young KA, Hicks PB. Galantamine improves cognition in schizophrenic patients stabilized on risperidone. Biol Psychiatry 2006 Sep;60(6):530–533
67. Smith RC, Warner-Cohen J, Matute M, et al. Effects of nicotine nasal spray on cognitive function in schizophrenia. Neuropsychopharmacology 2006;31:637–643
68. George TP, Vessicchio JC, Termine A, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. Biol Psychiatry 2002;52:53–61
69. Weiner E, Ball MP, Summerfelt A, et al. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry 2001;158:635–637
70. Barrickman LL, Perry PJ, Allen AJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1995 May;34(5):649–657
71. Conners CK, Casat CD, Gualtieri CT, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry 1996 Oct;35(10):1314–1321
72. Wilens TE, Prince JB, Spencer T, et al. An open trial of bupropion for the treatment of adults with attention-deficit/hyperactivity disorder and bipolar disorder. Biol Psychiatry 2003;54:9–16
73. 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
74. Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86(9):1119–1127
75. Barr RS, Culhane MA, Jubelt LE, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology 2008;33:480–490
76. Buchanan RW, Summerfelt A, Tek C, et al. An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. Schizophr Res 2003;59:29–33
77. Howard AK, Thornton AE, Altman S, et al. Donepezil for memory dysfunction in schizophrenia. J Psychopharmacol 2002;16:267–270
78. Risch SC, McGurk S, Horner MD, et al. A double-blind placebo-controlled case study of the use of donepezil to improve cognition in a schizoaffective disorder patient: functional MRI correlates. Neurocase 2001;7:105–110
79. Buchanan RW, Conley RR, Dickinson D, et al. Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am J Psychiatry 2008;165:82–89
80. Freudenreich O, Herz L, Deckersbach T, et al. Added donepezil for stable schizophrenia: a double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2005 Sep;181(2):358–363
81. Tugal O, Yazici KM, Anil Yagcioglu AE, et al. A double-blind, placebo controlled, cross-over trial of adjunctive donepezil for cognitive impairment in schizophrenia. Int J Neuropsychopharmacol 2004;7:117–123
82. Keefe RS, Malhotra AK, Meltzer HY, et al. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 2008;33: 1217–1228
83. Dyer MA, Freudenreich O, Culhane MA, et al. High-dose galantamine augmentation inferior to placebo on attention, inhibitory control and working memory performance in nonsmokers with schizophrenia. Schizophr Res 2008;33:480–490

