Published in final edited form as:

J Dual Diagn. 2013 ; 9(1): 87–93. doi:10.1080/15504263.2012.749559.

An Open Trial of Relapse Prevention Therapy for Smokers With Schizophrenia

Corinne Cather, Ph.D.^{1,2,3}, Michael A. Dyer, M.D.^{1,3}, Heather A. Burrell, B.A.², Bettina Hoepfner, Ph.D.², Donald C. Goff, M.D.^{1,3}, and A. Eden Evins, M.D., MPH^{1,2,3}

¹Schizophrenia Program, Massachusetts General Hospital and Harvard Medical School

²Center for Addiction Medicine, Massachusetts General Hospital and Harvard Medical School

³Department of Psychiatry of the Massachusetts General Hospital and Harvard Medical School

Abstract

Objective—Following successful smoking cessation, smokers with schizophrenia are vulnerable to relapse shortly after treatment discontinuation. Our objective was to assess the feasibility and effectiveness of a 12-month relapse prevention intervention in recently abstinent smokers with schizophrenia.

Method—Adult outpatient smokers with schizophrenia received weekly cognitive behavioral therapy groups, bupropion slow release, transdermal nicotine patch, and nicotine gum or lozenge for three months. Subjects with seven-day point prevalence abstinence at month 3 received an additional 12 months (months 4–15) of therapy with bupropion, transdermal nicotine patch, and nicotine gum/lozenge in conjunction with relapse prevention-based cognitive behavioral therapy groups that were held weekly in month 4, biweekly in months 5–6, and monthly in months 7–15.

Results—Seventeen of 41 participants (41.5%) attained biochemically verified self-report of seven-day point prevalence abstinence at the end of three months of treatment and entered relapse prevention treatment. There was an 81% attendance rate at relapse prevention groups. At the end of the 12-month relapse prevention phase (month 15 overall), 11 of 17 (64.7%) demonstrated biochemically verified seven-day point prevalence abstinence, and 10 of 17 (58.8%) reported four-week continuous abstinence. Almost one quarter of the sample (23.5%) demonstrated long-term prolonged abstinence through the end of the trial. There were no clinically detected cases of psychiatric symptom exacerbation. One participant, who was managed as an outpatient, self-reported psychiatric symptom exacerbation in the interim period between study visits.

Conclusions—Extended duration smoking cessation treatment is well-tolerated and may improve smoking outcomes for recently abstinent smokers with schizophrenia. Controlled trials are warranted.

Corresponding Author: Corinne Cather, Ph.D. Schizophrenia Program of the Massachusetts General Hospital Freedom Trail Clinic 25 Staniford Street Boston, MA 02114 Tel: 617-912-7891 Fax: 617-723-3919 ccather@partners.org. Michael A. Dyer, MD [MDyer@iroc.harvard.edu], Heather A. Burrell, BA [HBurrell@partners.org], Bettina Hoepfner, Ph.D [bhoepfner@partners.org], Donald C. Goff, MD [Donald.goff@nyumc.org], A. Eden Evins, MD, MPH [A_eden_evins@hms.harvard.edu].

DISCLOSURES

Dr. Dyer, Ms. Burrell, and Dr. Hoepfner report no financial relationships with commercial interests. Dr. Cather has received consulting income from United Biosource Inc. Dr. Goff has served as a consultant or advisor to: Bristol-Myers Squibb, Indevus Pharmaceuticals, H. Lundbeck, Schering-Plough, Eli Lilly, Takeda, Biovail, Solvay, Hoffman-LaRoche, Cypress, Danippon Sumitomo, Abbott Laboratories, Genetech, and Endo Pharmaceuticals. He served on a DSMB for Otsuka, and has received research funding from Pfizer, Janssen, Novartis, PamLab, and GlaxoSmithKline. Dr. Evins reports receipt of grant support from Pfizer, GlaxoSmithKline, and Envivo, and receives consulting income from Pfizer and Boehringer-Ingelheim.

Keywords

schizophrenia; severe mental illness; smoking cessation; nicotine replacement therapy; bupropion; cognitive behavioral therapy; relapse prevention

It has long been recognized that rates of smoking and smoking-related morbidity and mortality are dramatically higher among individuals with schizophrenia compared with those in the general population (de Leon et al., 1995; Fiore, Bailey, & Cohen, 1996; Hughes, 1986; Olincy, Young, & Freedman, 1997; Strasser et al., 2002; Tidey & Colby, 2011; Williams et al., 2010). Mortality from smoking-related diseases such as pulmonary and cardiovascular disease are two to six times higher among individuals with schizophrenia than among age-matched controls (Brown, Inskip, & Barracough, 2000; Curkendall, Mo, Glasser, Rose Stang, & Jones, 2004; Enger, Weatherby, Reynolds, Glasser, & Walker, 2004; Goff et al., 2005; Joukamaa et al., 2001; Sudders, 2002). Improving sustained smoking abstinence outcomes is essential if we are to respond to this major neglected public health problem.

A substantial proportion of smokers with schizophrenia are able to quit smoking with cognitive behavioral therapy and bupropion, with or without nicotine replacement therapy (Evins et al., 2007; Evins et al., 2005; George et al., 2008; George et al., 2002; George et al., 2000). A meta-analysis that evaluated abstinence rates at six months following a three-month treatment intervention with cognitive behavioral therapy and bupropion alone, or combined with nicotine replacement therapy, found a clear benefit at the end of treatment, with a risk ratio of 2.78 [1.02, 7.58] for the bupropion compared to placebo groups (Tsoi, Porwal, & Webster, 2010). An additional meta-analysis and a consensus guideline of evidence-based treatments has recommended combination therapy with cognitive behavioral therapy and bupropion, with or without nicotine replacement therapy, for people with schizophrenia who are interested in quitting smoking (Buchanan, et al., 2009; Tsoi, et al., 2010; Weiner et al., 2012). However, relapse rates upon discontinuation of smoking cessation treatment are very high, with only 14% of those initially abstinent with cognitive behavioral therapy, bupropion, and nicotine replacement therapy remaining abstinent from smoking six months following treatment discontinuation in one study (George et al., 2008) and 28% remaining abstinent 12 months after nicotine taper in another (Evins et al., 2007). Perhaps most striking is the rapidity with which individuals relapse. The relapse rate was 50% within two weeks of discontinuation of pharmacotherapy with bupropion in one study (Evins et al., 2005) and 31% during nicotine replacement taper in another (Evins et al., 2007). Although interventions to improve sustained smoking abstinence rates among all smokers are needed, there is great urgency to address high relapse rates among smokers with schizophrenia (Hajek, Stead, West, Jarvis, & Lancaster, 2009). Extended duration pharmacotherapy reduces relapse rates among smokers in the general population who successfully attain smoking abstinence (Hall, Humfleet, Reus, Munoz, & Cullen, 2004; Hays et al., 2001) but extended duration pharmacotherapy does not improve abstinence rates at end of extended treatment among those who do not achieve initial abstinence at the end of a standard 12 week treatment period (Hall et al., 2004). Horst and colleagues (2005) randomized 17 smokers with schizophrenia who successfully attained abstinence after three months of treatment with the transdermal nicotine patch to nine months of continuation single blind transdermal nicotine patch or placebo. After nine months of continuation treatment (month 12), thirty three percent of those receiving the nicotine patch were abstinent whereas none of those who received placebo patch were abstinent.

The aim of the current study was to evaluate the feasibility and effectiveness of continuation of cognitive behavioral therapy, short and long-acting nicotine replacement therapy, and

bupropion for prevention of relapse in recently abstinent smokers with schizophrenia or schizoaffective disorder. We predicted that continuation treatment would be well-tolerated and would result in higher abstinence rates at 12 months than previously reported following completion of 10-12 weeks of smoking cessation treatment.

METHODS

Study Design

The study was approved and monitored by the Metro Boston Department of Mental Health Central Office Research Review Committee Institutional Review Board. Following a complete discussion of the study with potential participants, participants provided written informed consent prior to initiation of study procedures. The study was conducted in accordance with the Declaration of Helsinki. Participants who met inclusion criteria were offered three months of combination pharmacotherapy and group cognitive behavioral therapy for smoking cessation. Participants who achieved biochemically confirmed seven-day point prevalence abstinence at the final smoking cessation treatment visit (month 3) were eligible to receive one year of combination pharmacotherapy and relapse prevention-oriented group cognitive behavioral therapy (see Figure 1).

Participants

Participants were diagnosed with schizophrenia or schizoaffective disorder by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria as per chart review, reported smoking 10 or more cigarettes per day for at least the prior year, expressed a desire to quit smoking and a willingness to set a smoking cessation date within 4 weeks of enrollment, were psychiatrically stable on a fixed dose of an antipsychotic for the past 30 days or more, and reported no active substance use disorder other than nicotine or caffeine within 6 months of enrollment. Participants ineligible for bupropion treatment due to neurologic risk factors were eligible to participate and receive short- and long-acting nicotine replacement therapy and cognitive behavioral therapy only.

Assessments

Baseline assessments included a smoking behavior questionnaire on which participants reported prior cessation attempts in which they attained at least 24 hours abstinence, the Fagerström Test for Nicotine Dependence (Fagerström, 1978), a self-report questionnaire with total scores ranging from 0 to 10 with higher scores indicating higher levels of nicotine dependence, and expired carbon monoxide. Smoking self-report and expired carbon monoxide were also collected at each weekly study visit. Expired carbon monoxide was measured using a MicroSmokerlyzer (Bedfont Scientific Ltd, Kent, UK). Participants provided a self-report of whether they had been hospitalized, had visited an emergency room, or had an unscheduled (emergency) psychiatric visit since their previous assessment.

Interventions

Smoking cessation phase—Treatment in the smoking cessation intervention consisted of transdermal nicotine patch 21 mg per day, either nicotine polacrilex gum or nicotine lozenge (2-18 mg per day) as needed for craving, bupropion slow release 150 mg per day for seven days then 150 mg twice per day, and a 12-session, weekly, manualized group cognitive behavioral therapy program that has been previously described (Evins et al., 2007; Evins et al., 2005) (smoking cessation manual available from the first author). All participants were asked to set a quit date between the third and fourth group.

Relapse prevention phase—The relapse prevention phase consisted of continued pharmacotherapy and group cognitive behavioral therapy focused on understanding relapse and learning and applying key cognitive and behavioral skills to high-risk situations. This included refusal skills, problem-solving, identifying and responding to permission-giving beliefs, and developing and implementing personalized relapse prevention plans (relapse prevention manual available from the first author). Participants identified their unique high risk situations, such as specific routines or smoking cues, and the group used a structured problem-solving approach to generate possible ways of handling these triggers to resume smoking. Participants would then choose a solution or combination of solutions to implement, evaluate, and report on in the next group. In the majority of groups, written individualized relapse prevention plans prompted participants to identify what (s)he would do in the coming week to: reduce stress, avoid purchasing or borrowing cigarettes, increase support for not smoking, etc. Relapse prevention cognitive behavioral therapy groups were held weekly for the first month, biweekly for two months and then monthly for the remaining nine months, for a total of 17 groups over a 12-month period. Groups were led by a staff psychologist and included up to seven participants. Participants were encouraged to continue bupropion, transdermal nicotine patch and nicotine gum/lozenge without dose reduction during the relapse prevention phase.

Analysis

We used descriptive analyses exclusively to compile results. Specifically, percentage of relapse prevention groups attended, as well as rates of 12-month continuous abstinence, four-week continuous abstinence, and seven-day point prevalence abstinence at the end of the 12-month relapse prevention phase were the primary outcomes of interest. For these descriptive analyses, participants who dropped out were considered to be smokers. To examine the rate of relapse, we calculated the proportion of the sample who was abstinent at each month of the relapse prevention treatment. We used SAS 9.3 for all analyses.

RESULTS

Forty-one participants enrolled in open treatment (study months one through three); 17 (41.5%) attained biochemically verified self-report of seven-day point prevalence abstinence at the end of the three-month smoking cessation phase and entered the relapse prevention phase of 12 months of continued pharmacotherapy and a tapering schedule of relapse prevention-focused cognitive behavioral therapy groups (study months four through 15). Sixteen participants received pharmacotherapy with transdermal nicotine patch, nicotine gum/lozenge and bupropion, and one participant received transdermal nicotine patch and nicotine gum/lozenge (no bupropion).

As shown in Table 1, the sample was predominantly male, Caucasian, and heavily nicotine dependent (mean Fagerström score in the heavily dependent range), with almost half of the sample (47.1%) smoking more than a pack a day. At the beginning of the relapse prevention phase, mean expired carbon monoxide was less than one part per million (ppm); participants had been abstinent for an average of 35 days, 14 (82%) had attained at least 14 days of continuous abstinence, and 12 (71%) had attained at least 28 days of continuous abstinence.

Smoking outcomes

During the relapse prevention phase, 15 of 17 (88.2%) participants attended at least 75% of relapse prevention groups (12 of 17 group sessions). Group attendance was not associated with 4-week continuous abstinence ($r = 0.4$, $p = .13$) nor sustained continuous abstinence ($r = 0.2$, $p = .39$) at the end of the 12-month relapse prevention phase. Six of the 17 participants terminated the relapse prevention phase early (35.3%). At the end of the 12-

month relapse prevention phase (month 15), 11 participants (64.7%) had biochemically verified self-report of seven-day point prevalence abstinence and 10 of these participants (58.8%) reported four weeks of continuous abstinence (See Figure 2). Visual inspection of the survival curve (Figure 3) shows rapid relapse during the first month of relapse prevention treatment, followed by fewer participants relapsing per month until month six. After month 6, those who were abstinent (23.5%) remained abstinent through the end of the trial.

Expired carbon monoxide at month 15 was 1.2ppm in those who reported abstinence and 12.75 in those who were not abstinent at that time point. See Figure 2 for mean expired carbon monoxide values over the course of the relapse prevention intervention.

Adverse events

Participants did not report any psychiatric hospitalizations during the course of the study. One participant went to the emergency room for worsening of psychiatric symptoms during week 24; this participant was not admitted, and a change in antipsychotic medication was made by the outpatient psychiatrist. According to clinical assessment by the group leader (CC), participants remained psychiatrically stable throughout the 15-month intervention. The only adverse event that was probably related to the study intervention was an allergic reaction in one participant during the smoking cessation phase. There were two medical hospitalizations that were likely related to smoking status and not study interventions. These were for asthma and for breathing difficulties of unspecified cause.

DISCUSSION

Previous studies of standard smoking cessation interventions in outpatients with schizophrenia have documented a clear benefit of smoking cessation treatment with moderate cessation rates during treatment but high relapse rates following discontinuation of smoking cessation interventions. In this sample of smokers with schizophrenia or schizoaffective disorder who had a long history of heavy smoking and an average of five prior smoking cessation attempts, 17 of 41 (41.5%) attained seven-day point prevalence abstinence at the end of a three-month treatment regimen with bupropion, transdermal nicotine patch, nicotine polacrilex gum and weekly group cognitive behavioral therapy. All those who attained abstinence with this intervention participated in a relapse prevention program consisting of continuation of pharmacotherapy and a tapering schedule of cognitive behavioral therapy groups for 12 months. Participants attended 81% of groups throughout the 12-month relapse prevention phase suggesting relapse prevention treatment is likely to be well-tolerated and feasible in this population. The findings replicate the work of Horst and colleagues (2005) who randomized 17 smokers with schizophrenia who successfully attained abstinence after three months of treatment with the transdermal nicotine patch to nine months of continuation single blind transdermal nicotine patch or placebo. After nine months of continuation treatment (month 12), thirty three percent of those receiving the nicotine patch were abstinent whereas none of those who received placebo patch were abstinent.

At the end of 12 months of relapse prevention treatment, 65% had biochemically confirmed seven-day point prevalence abstinence and 59% reported four or more weeks of continuous abstinence. This 35% relapse rate is less than half the 77% relapse rate at 12-months after discontinuation of a similar 12-week smoking cessation intervention of cognitive behavioral therapy, bupropion and dual nicotine replacement therapy in a previous study (Evins et al., 2007) and the 75% relapse rate three months after discontinuation of cognitive behavioral therapy and bupropion in another study (Evins et al., 2005). While a relapse rate of 36% at 6 months has been reported in smokers with mental illness following a 12-week smoking

cessation intervention (Baker et al., 2006), this was in a sample in which only 57% had a schizophrenia or schizoaffective disorder, which may account for the lower relapse rates following treatment discontinuation. In the current study, almost one quarter (23.5%) demonstrated prolonged continuous abstinence with continuation therapy, a rate that compares favorably to rates of prolonged abstinence in the general population which rarely exceed 30% with approved pharmacologic and behavioral treatments (Fiore et al., 2008).

Although existing research has generally indicated that relapse prevention interventions consisting of extended duration pharmacological and behavioral therapies are not efficacious (c.f., Agboola et al., 2010) in promoting sustained abstinence in the general population (Hajek et al., 2009), abnormalities in neuronal nicotinic acetylcholine receptor expression and function in individuals with schizophrenia suggest a neurobiological rationale for better efficacy of extended duration pharmacotherapy in schizophrenia. Nicotinic acetylcholine receptor expression and function are abnormally low in individuals with schizophrenia, independent of smoking status (Breese et al., 2000; Durany et al., 2000). Thus, though these receptors are upregulated to some extent with nicotine exposure, nicotine receptor number and function are not expected to return to a normal baseline after smoking cessation among individuals with schizophrenia who attain abstinence. Nicotine has been shown to ameliorate cognitive and neurophysiologic abnormalities associated with schizophrenia (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992; Adler, Hoffer, Wiser, & Freedman, 1993; Avila, Sherr, Hong, Myers, & Thaker, 2003; Barr, et al., 2007; Julbelt et al., 2009, Smith et al., 2008). Because nicotine may confer greater cognitive benefit to smokers with schizophrenia than to smokers without this psychiatric illness, there may be a stronger drive to return to smoking once abstinent among individuals with schizophrenia than in the general population. Longer-term nicotine dependence treatment could potentially compensate for these abnormalities and by doing so, promote continued abstinence among individuals with schizophrenia. This hypothesis will need to be tested in future trials.

The major limitations of this study are the small sample size and lack of control groups. Another limitation is reliance on self-report for 4-week continuous abstinence rates later in the study when group sessions were less frequent, as biochemical validation of abstinence was performed only at group sessions. In addition, because the intervention had multiple components, it is not possible to identify which component(s) contributed to the sustained abstinence rates. Also, information was not systematically collected on factors that contributed to relapse, such as exposure to smoking-related cues, permission-giving beliefs, or suboptimal adherence to psychiatric or smoking cessation medications. Although we assessed self-report of medication adherence and attempted to count pills and unused nicotine replacement therapy, participants were poorly compliant with this component of the protocol. Additionally, although we did not choose to focus on smokers with other co-occurring substance use disorders in the current study, future work should consider this group given evidence that this group: comprises a large percentage of individuals with schizophrenia, is motivated to stop smoking cigarettes, and rarely receives evidence-based interventions for smoking cessation (Ferron et al., 2011). Notwithstanding these limitations, the results suggest that relapse prevention treatment may be feasible and may result in higher sustained abstinence rates and lower relapse rates in recently abstinent smokers with schizophrenia. Larger, controlled trials are warranted to further investigate the effect of extended duration treatment for prevention of relapse to smoking in individuals with schizophrenia, as well as to better estimate the optimal components and duration of this treatment in order to maximize sustained smoking abstinence rates and improve health outcomes in this population. If confirmed in larger trials, the results of this study may provide a rational treatment that in clinical practice could reduce the heavy burden of smoking-related morbidity and mortality in this population.

Acknowledgments

We would like to thank the members of the Center for Addiction Medicine Manuscript Review Group for their suggested edits to the manuscript (Suzanne Hoeppner, PhD, John Kelly, PhD., Gladys Pachas, MD, Sungwon Roh, MD, Zev Schuman-Olivier, MD, and Luke Stoeckel, PhD). This work was supported by a grant from the Sidney R. Baer Foundation (Drs. Cather, Evins, and Goff), NIMH 5K24MH002025-10 (Dr. Goff) and the National Institutes of Drug Abuse 1K23DA00510 Nicotine and smoking cessation in schizophrenia (Dr. Evins).

REFERENCES

- Adler L, Hoffer L, Griffith J, Waldo M, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biological Psychiatry*. 1992; 32:607–616. doi: 10.1016/0006-3223(92)90073-9. [PubMed: 1450287]
- Adler L, Hoffer L, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *American Journal of Psychiatry*. 1993; 150(12):1856–1861. [PubMed: 8238642]
- Agboola S, McNeill A, Coleman T, Bee JL. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. *Addiction*. 2010; 105:1362–1380. doi: 10.1111/j.1360-0443.2010.02996.x. [PubMed: 20653619]
- Avila MT, Sherr JD, Hong E, Myers CS, Thaker GK. Effects of nicotine on leading saccades during smooth pursuit eye movements in smokers and nonsmokers with schizophrenia. *Neuropsychopharmacology*. 2003; 28(12):2184–2191. doi:10.1038/sj.npp.1300265. [PubMed: 12968127]
- Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, Wilhelm K. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *American Journal of Psychiatry*. 2006; 163(11):1934–1942. doi: 10.1176/appi.ajp.163.11.1934. [PubMed: 17074945]
- Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, Evins AE. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology*. 2007; 33(3):480–490. doi: 10.1038/sj.npp.1301423. [PubMed: 17443126]
- Breese CR, Lee MJ, Adams CE, Sullivan B, Logel J, Gillen KM, Leonard S. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. *Neuropsychopharmacology*. 2000; 23(4):351–364. doi: 10.1016/S0893-133X(00)00121-4. [PubMed: 10989262]
- Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *British Journal of Psychiatry*. 2000; 177:212–217. [PubMed: 11040880]
- Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophrenia Bulletin*. 2009; 36(1):71–93. doi:10.1093/schbul/sbp116. [PubMed: 19955390]
- Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *Journal of Clinical Psychiatry*. 2004; 65(5):715–720. [PubMed: 15163261]
- de Leon J, Dadvand M, Canuso C, White AO, Stanilla JK, Simpson GM. Schizophrenia and smoking: An epidemiological survey in a state hospital. *American Journal of Psychiatry*. 1995; 152(3):453–455. [PubMed: 7864277]
- Durany N, Zochling R, Boissl KW, Paulus W, Ransmayr G, Tatschner T, Riederer P. Human post-mortem striatal alpha4beta2 nicotinic acetylcholine receptor density in schizophrenia and Parkinson's syndrome. *Neuroscience Letters*. 2000; 287(2):109–112. doi: S0304-3940(00)01144-7. [PubMed: 10854724]
- Eger C, Weatherby L, Reynolds RF, Glasser DB, Walker AM. Serious cardiovascular events and mortality among patients with schizophrenia. *Journal of Nervous and Mental Disease*. 2004; 192(1):19–27. doi: 00005053-200401000-00004. [PubMed: 14718772]
- Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, Goff DC. 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. *Journal of Clinical*

- Psychopharmacology. 2007; 27(4):380–386. doi: 10.1097/01.jcp.0b013e3180ca86fa. [PubMed: 17632223]
- Evins AE, Cather C, Deckersbach T, Freudenreich O, Culhane MA, Olm-Shipman CM, Rigotti NA. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology*. 2005; 25(3):218–225. doi: 00004714-200506000-00004. [PubMed: 15876899]
- Fagerström K. Measuring degrees of physical dependence to tobacco smoking with reference to individuation of treatment. *Addictive Behaviors*. 1978; 3:235–241. [PubMed: 735910]
- Fiore, M.; Bailey, W.; Cohen, S. Smoking cessation. clinical practice guideline no. 18. Agency for Health Care Policy and Research; Rockville, MD: 1996. (No. AHCPR publication no. 96-0692)
- Fiore, MC.; Jaén, CR.; Baker, TB. Treating tobacco use and dependence: 2008 update. Clinical practice guideline. US Department of Health and Human Services; Public Health Service; Rockville, MD: 2008.
- Ferron JC, Brunette MF, He X, Xie H, McHugo GJ, Drake RE. Course of smoking and quit attempts among clients with co-occurring severe mental illness and substance use disorders. *Psychiatric Services*. 2011; 62:353–359. doi:10.1176/appi.ps.62.4.353. [PubMed: 21459985]
- George T, Vessicchio J, Sacco K, Weinberger A, Dudas M, Allen T, Jatlow PI. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation. *Biological Psychiatry*. 2008; 63:1092–1096. doi: 10.1016/j.biopsych.2007.11.002. [PubMed: 18096137]
- George T, Vessicchio J, Termine A, Bregartner T, Feingold A, Rounsaville B, Kosten TR. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*. 2002; 52(1):53–61. doi: S0006322302013392. [PubMed: 12079730]
- George T, Ziedonis D, Feingold A, Pepper W, Satterburg C, Winkel J, Kosten TR. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *American Journal of Psychiatry*. 2000; 157(11):1835–1842. [PubMed: 11058482]
- Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, Sacks FM. Medical morbidity and mortality in schizophrenia: Guidelines for psychiatrists. *Journal of Clinical Psychiatry*. 2005; 66(2):183–194. [PubMed: 15705003]
- Hajek P, Stead LF, West R, Jarvis M, Lancaster T. Relapse prevention interventions for smoking cessation. *Cochrane Database of Systematic Reviews*. 2009; (1) CD003999. doi: 10.1002/14651858.CD003999.pub3.
- Hall SM, Humfleet GL, Reus VI, Munoz RF, Cullen J. Extended nortriptyline and psychological treatment for cigarette smoking. *American Journal of Psychiatry*. 2004; 161(11):2100–2107. doi: 10.1176/appi.ajp.161.11.2100. [PubMed: 15514412]
- Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, White JD. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. *Annals of Internal Medicine*. 2001; 135(6):423–433. doi: 200109180-00011. [PubMed: 11560455]
- Horst WD, Klein MW, Williams D, Werder SF. Extended use of nicotine replacement therapy to maintain smoking cessation in person with schizophrenia. *Neuropsychiatric Disease and Treatment*. 2005; 1(4):349–355.
- Hughes J. Prevalence of smoking among psychiatric outpatients. *American Journal of Psychiatry*. 1986; 143:993–997. [PubMed: 3487983]
- Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. *British Journal of Psychiatry*. 2001; 179:498–502. [PubMed: 11731351]
- Julbelt LE, Barr RS, Goff DC, Logvinenko T, Weiss AP, Evins AE. Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. *Psychopharmacology*. 2008; 199(1):89–98. doi:10.1007/s00213-008-1133-8. [PubMed: 18548234]
- Olinicy A, Young DA, Freedman R. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. *Biological Psychiatry*. 1997; 42(1):1–5. doi: 10.1016/S0006-3223(96)00302-2. [PubMed: 9193735]
- Smith RC, Lindenmayer JP, Davis JM, Cornwell J, Noth K, Gupta S, Sershen H, Lajtha A. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder.

- Schizophrenia Research. 2009; 110(1-3):149–155. doi: 10.1016/j.schres.2009.02.001. [PubMed: 19251401]
- Strasser K, Moeller-Saxone K, Meadows G, Hocking B, Stanton J, Kee P. Smoking cessation in schizophrenia. General practice guidelines. Australian Family Physician. 2002; 31(1):21–24. [PubMed: 11840883]
- Sudders, M. Massachusetts Department of Mental Health Mortality Report 2000. Commonwealth of Massachusetts Executive Office of Health and Human Services Department of Mental Health; 2002.
- Tidey J, Colby S. Characterization of 72-hr abstinence effects in smokers with schizophrenia and controls. Preliminary result. Paper presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Toronto, Canada. 2011
- Tsoi D, Porwal M, Webster A. Interventions for smoking cessation and reduction in individuals with schizophrenia. Cochrane Database of Systematic Reviews. 2010; (6) CD007253. doi: 10.1002/14651858.CD007253.pub2.
- Weiner E, Ball MP, Buchholz AS, Gold JM, Evins AE, McMahon RP, Buchanan RW. Bupropion sustained release added to group support for smoking cessation in schizophrenia: A new randomized trial and a meta-analysis. Journal of Clinical Psychiatry. 2012; 73(1):95–102. doi: 10.4088/JCP.10m06143gre. [PubMed: 21535998]
- Williams J, Gandhi K, Lu S, Kumar S, Shen J, Foulds J, Benowitz NL. Higher nicotine levels in schizophrenia compared with controls after smoking a single cigarette. Nicotine & Tobacco Research. 2010; 12:855–859. doi: 10.1093/ntr/ntq102. [PubMed: 20584771]

Note: In the cessation phase, subjects received bupropion (BUP), transdermal nicotine patch (TNP) and/or nicotine gum/lozenge (NG/NL) in conjunction with weekly cognitive behavioral therapy (CBT) groups for 3 months. Subjects with 7-day point prevalence abstinence at month 3 received an additional 12 months (months 4-15) of therapy with BUP, TNP, and NG/NL in conjunction with relapse prevention based CBT groups that were held weekly in month 4, biweekly in months 5 - 6, and monthly in months 7-15. BSL = baseline.

Figure 1.
Schema of Study Visits

Figure 2. Abstinence Rates and Expired CO over 12-Month Intervention ($N=17$). *Note.* CO = carbon monoxide; ppm = parts per million.

Figure 3. Survival function showing abstinence among participants using bupropion and nicotine gum/lozenge in the 12 month relapse prevention phase (starting at month 3 of the trial).

Table 1Baseline Characteristics ($N=17$)

Characteristic	Mean (SD; Range) or n (%)
Age (years)	47.1 (4.7; 38-54)
Gender (male)	13 (76.5%)
Diagnosis	
Schizophrenia	13 (76.5%)
Schizoaffective Disorder	4 (23.5%)
Ethnicity	
Caucasian	13 (76.5%)
African American	3 (17.6%)
Other	1 (5.9%)
Education (years)	12.4 (2.7; 6-16)
Pack Years (yrs smoked*avg amount smoked/day)	26.6 (9.9; 10.5-38)
Expired CO (ppm)	18.1 (10.4; 8-45)
Cigarettes smoked per day	23.2 (8.0; 9-60)
% Smoked > 1 pack/day	47.1%
FTND total score	7.0 (1.5; 4-10)
Number of prior cessation attempts	4.8 (5.8; 1-25)

Note: CO = carbon monoxide; ppm = parts per million; FTND = Fagerström Test for Nicotine Dependence.