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Combination Extended Smoking Cessation Treatment Plus Home Visits for Smokers With Schizophrenia: A Randomized Controlled Trial

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Abstract

Introduction: The majority of people with schizophrenia have a diagnosis of tobacco dependence during their lifetime. A major obstacle to reducing the burden of cigarette smoking in this population is that these smokers have lower quit rates when undergoing standard treatment compared to smokers with no mental illness. We sought to determine if combination extended treatment (COMB-EXT) and home visits (HV) would lead to improved outcomes in smokers with schizophrenia.

Methods: Thirty-four cigarette smokers with schizophrenia completed either COMB-EXT with HV, COMB-EXT without HV, or treatment as usual (TAU) (random assignment). COMB-EXT consisted of group cognitive-behavioral therapy (CBT), bupropion, nicotine patch, and nicotine lozenge, which were initiated within 2 weeks and continued for 26 weekly visits. HV consisted of biweekly visits to the home with assessment of secondhand smoke (SHS) exposure and brief behavioral therapy with participants and others in the home environment. TAU consisted of group CBT plus serial single or combination medication trials as per standard care.

Results: Smokers with schizophrenia who received COMB-EXT (with or without HV) had greater reductions in cigarettes per day than those treated with TAU (both *p*s < .01). In addition, 7-day point prevalence abstinence rates for the three groups were 45%, 20%, and 8%, respectively, which was significantly higher for COMB-EXT plus HV than TAU ($\chi^2(1) = 4.8$, $p = .03$). Groups did not differ significantly in the number of adverse events, and HV were easily scheduled.

Conclusion: COMB-EXT improves outcomes for smokers with schizophrenia. HV appeared to provide additional benefit for smoking cessation in this treatment-resistant population.

Implications: The clear benefit found here of rapidly initiated, combination, extended treatment over TAU suggests that aggressive and extended treatment should be considered in clinical practice for smokers with schizophrenia. Furthermore, HV to address SHS exposure showed initial promise for assisting smokers with schizophrenia in maintaining abstinence, indicating that this intervention may be worthy of future research.

Introduction

The majority of people with schizophrenia have a diagnosis of tobacco dependence during their lifetime (approximately 64%–79%),[1–3] primarily from cigarette smoking. People with schizophrenia have a lifespan that is shortened by an average 28.5 years,[4] and the elevated rate of smoking is a major contributing factor to this decreased life expectancy.[5,6] Moreover, smoking is a considerable financial burden to patients with schizophrenia[7] and interferes with maintenance of stable levels of some antipsychotic medications.[8–11] Therefore, cigarette smoking poses considerable risks to people with schizophrenia, making smoking cessation in this population a high public health priority.

A major obstacle to reducing the burden of smoking in people with schizophrenia is that these smokers have less success at smoking cessation during a quit attempt than smokers with no mental illness.[3,12] A naturalistic review by our group of gold-standard smoking cessation treatment (including medication plus group psychotherapy) revealed the lowest rates of successful abstinence in smokers with schizophrenia (compared to smokers with other mental illness or substance abuse diagnoses).[13] This relatively poor prognosis occurs despite the fact that smokers with schizophrenia have the same distribution of "stages of change" and are equally likely to make a quit attempt as smokers without schizophrenia.[14]

Current treatment approaches for smokers with schizophrenia are moderately effective compared to control conditions,[3,12,15] and include both medication and psychotherapy. First-line medications for smoking cessation in the general population are commonly used in smokers with schizophrenia,[16] and include nicotine replacement therapies (such as patch, lozenge, and gum), bupropion HCl, and varenicline HCl,[15,17–19] with the standard of care in most treatment settings being to choose specific medications based on availability, ease of use, side effect profile, and patient preference.[19,20] A very large recent medication trial[15] demonstrated clear superiority of these commonly used medications compared to placebo in smokers with psychiatric illness (including a subgroup with schizophrenia). Among psychotherapies, cognitive-behavioral therapy (CBT) is the most widely studied and used technique,[21] and has been shown, in at least some studies, to be effective in smokers with schizophrenia.[22] However, an attempt to increase efficacy of psychotherapy by adding schizophrenia-related techniques (eg, social skills training and psychoeducation) did not show additional benefit over standard CBT for achieving smoking cessation,[23] and a recent meta-analysis did not find "convincing evidence" of a benefit of using CBT for smoking in schizophrenia.[16] Medications and talk therapy have been tested alone and in combination, and commonly-used medications have been found to be well-tolerated in smokers with schizophrenia.[16,24,25] A recent thorough review by the European Psychiatric Association reported that current smoking cessation treatments are useful, but not highly efficacious, for smokers with schizophrenia.[26]

Based on these prior studies, recommendations for treating smoking in schizophrenia include the use of bupropion or varenicline (with or without nicotine replacement therapy [NRT]) in combination with behavioral treatment[24,27–29]; we sought to support and expand upon these recommendations. Specifically, we performed a pilot study to examine the rapid (within 2 weeks) initiation of a combination of first-line treatments (COMB) administered for an extended period of time (EXT; 6 months) with or without home visits (HV) for smokers with schizophrenia. HVs included attempts to minimize secondhand smoke (SHS) exposure, based on prior research demonstrating that smokers exposed to SHS have higher markers of nicotine exposure[30] and are less likely to initiate or maintain abstinence[31–33] than smokers without such exposure. We hypothesized that COMB-EXT would be more efficacious for smoking reduction and cessation than treatment as usual (TAU). We further hypothesized that HVs would provide additional benefit.

Methods

Participants

Adult male smokers with schizophrenia were recruited via flyer advertisements from the smoking and schizophrenia treatment programs at the VA Greater Los Angeles Healthcare System. The primary inclusion criteria were diagnoses of tobacco use disorder and schizophrenia (by *DSM IV* criteria[34]), smoking 10 to 40 cigarettes per day, and an expressed desire to obtain smoking cessation treatment and quit smoking during the initial screening interview. Diagnoses were confirmed by reviewing each participant's chart and contacting their primary psychiatrist if further corroboration was warranted. For all study participants, exclusion criteria included having contraindications for study medications (eg, known hypersensitivity, significant renal/hepatic impairment, unstable cardiovascular disease for NRT, or a seizure disorder), changes in psychiatric medications or significant suicidality within the past 6 months, substance abuse/dependence within the past 6 months, or other current psychiatric illness. Smokers who smoked more than 40 cigarettes per day were excluded because much prior research[35–40] demonstrates that greater nicotine dependence (which is partly established by a higher number of cigarettes per day) is associated with worse treatment outcome, and we wanted to limit the effect of this potential confound.

Thirty-four participants had usable data for study analyses, while an additional eight potential participants signed the informed consent form but dropped out of the study prior to initiating treatment the following week and were not included in study analyses (Figure 1). All participants signed an informed consent form approved by the local institutional review board at the initial study visit, and understanding of the contents of the consent form was confirmed by having participants state to us the basic study procedures after they were done reviewing the form.

Baseline and Treatment-Related Assessments

At a baseline assessment visit, demographic, smoking-related, and psychiatric symptom-related information was collected. For demographic and smoking-related information, the Smokers' Profile Form was administered, as in past studies of smoking cessation treatment.[41–43] Smoking behavior was assessed with an exhaled carbon monoxide (CO) level (MicroSmokerlyzer, Bedfont Scientific Ltd, Kent, United Kingdom) and the Fagerström Test for Nicotine Dependence (FTND).[44,45] While some investigators have questioned the use of the standard FTND in smokers with schizophrenia,[46,47] there is considerable support in the literature for its use.[48–52] Psychiatric symptom-related information was collected using the Brief Psychiatric Rating Scale (BPRS),[53] Scale for Assessment of Negative Symptoms (SANS),[54] Clinical Global Impression (CGI)[55] scale, and Beck Depression Inventory (BDI-II).[56] To evaluate issues related to safety, the Columbia-Suicide Severity Rating Scale (C-SSRS)[57] and Abnormal Involuntary Movement Scale (AIMS)[58] were also administered.

At weekly treatment visits, participant reports of cigarettes per day, exhaled CO levels, and FTND scores were obtained, as measures of smoking behavior. These measures were obtained by study staff between 1 and 1:30 PM, prior to medication management and CBT administration. At 12 weeks of treatment, the BPRS, SANS, CGI, BDI-II, C-SSRS, and AIMS were re-administered, in order to monitor psychiatric symptoms and safety issues.

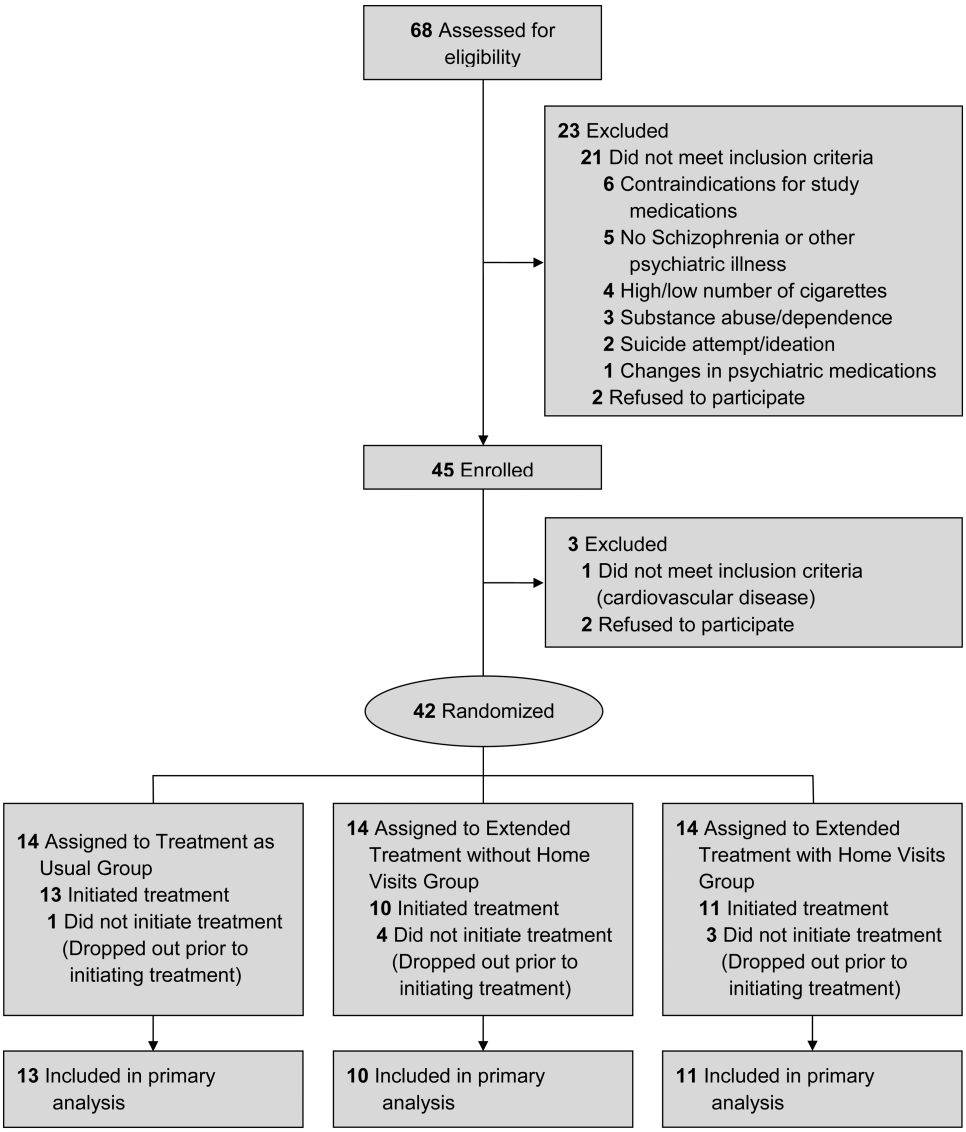

Figure 1. Consolidated standards of reporting trials diagram of flow of participants from screening to analysis.

Study Treatments

At the baseline visit, participants were randomly assigned (via simple randomization, www.randomization.com) to either rapidly initiated combination extended treatment plus home visits (COMB-EXT+HV), COMB-EXT without HV, or TAU, and treatment was initiated 1 week later. COMB-EXT consisted of a rapidly initiated (within 2 weeks) combination of three medications (bupropion plus nicotine patch plus nicotine lozenge) and CBT, which was provided via weekly visits for 6 months. Medication dosages were commonly used ones,[17] with bupropion HCl SR 150 mg po qd being initiated at the first treatment visit, and increased to 150 mg po BID on day 4 of treatment. Nicotine replacement with both 21 mg nicotine patch and 2 or 4 mg nicotine lozenge (depending on whether morning smoking occurred less than or greater than 30 minutes after waking) was initiated at week 2, which was also the assigned quit date. Participants were instructed to take a lozenge every 2 hours as needed, and were maintained on the same strength of nicotine lozenge throughout their participation in the study (other than two participants who had the dosage increased from 2 to 4 mg due to breakthrough craving). Participants met weekly with a study physician (ALB or TZ) for 15-minute medication management visits, which consisted of assessment of adherence to the medication regimen, monitoring of smoking behavior,[59–61] and evaluation of side effects.

CBT (group format) was administered for 1 hour each week for all three study groups by an experienced psychologist (CM), using a manualized intervention that has been described in past reports by our group.[13,42,62] Psychotherapy consisted of 12 rotating sessions focused on: education about smoking addiction, withdrawal, and relapse prevention; recognizing danger situations (triggers) that could lead to relapse; developing new coping skills, such as avoiding triggers, coping with negative affective states, reducing overall stress, and distracting attention from smoking using thought-stopping techniques; developing lifestyle changes; and social support.[63,64] Participants had exhaled CO levels monitored at each session, and were encouraged to taper off cigarettes.

HVs were designed to assess and reduce SHS exposure in the home environment, and consisted of scheduled bi-weekly 20–30 minutes visits by a study investigator (RH or SB). HV were initiated with greeting the participant (and significant others or staff in the home environment). The study investigator then walked through

the home environment with participants and filled out a SHS Observation Form (SOF), which included yes/no questions regarding visible signs of smoking activities both outdoors and indoors (eg, areas of smoking restriction with "no smoking" signage, cigarette butts visible, ashtrays visible, and the smell of smoke). Information from the Surgeon General's office on SHS exposure was provided to participants and others in the home. In addition, brief behavioral counseling was given to encourage minimization of SHS exposure and promote abstinence, such as suggesting behavioral strategies for avoiding SHS and other smoking triggers. The focus of these visits was consistent over time, and visits were performed in the same manner for participants who lived in independent or supervised housing.

TAU consisted of weekly CBT and medication management visits, in which CBT was initiated at the first visit and a single first-line smoking cessation medication (nicotine patch, bupropion, or varenicline) was initiated at the first or second treatment visit (patient preference, in consultation with a study physician) as is common practice. Medication monotherapy was typically continued for at least 2–4 weeks at which point the need to add additional medication or switch medications was assessed and carried out. As with COMB-EXT, a quit date was set for week 2 of treatment. Length of treatment and medication type was flexible and based on participant preference and treatment response.[19,20]

At week 26, 7-day point prevalence abstinence rate was determined as a participant report of more than 7 days of continuous abstinence from any tobacco use and an exhaled CO level less than or equal to 3 parts per million. These criteria are similar to recent recommendations for documenting smoking abstinence[65,66] and are comparable to criteria used in other treatment studies.[67–69] Participants who initiated treatment, but dropped out of the study, were classified as non-abstinent, in accordance with recent recommendations[65,70] and use of this classification in smoking cessation treatment research.[71] After the final study treatment visit, participants were treated as per common practice, with continued access to CBT and tapering off of smoking cessation medications, as indicated.

Statistical Analysis

Means (±*SD*s) were determined for baseline and treatment-related variables for the study groups. Baseline characteristics were compared between study groups using analyses of variance (ANOVAs) for continuous variables and chi-square tests for the categorical variable.

The primary outcome measures for the study were reductions in cigarettes per day and 7-day point prevalence abstinence rates at 6 months. To determine if there were differences over time in cigarettes per day between the three treatment groups (COMB-EXT with HV, COMB-EXT without HV, and TAU), a generalized linear mixed model (GLMM) was used with cigarettes per day as the dependent variable. The GLMM accounts for within subject associations in this longitudinal dataset, and also provides unbiased parameter estimates even in the presence of missing data that is missing at random. Based on significant results of the GLMM, we conducted post hoc analyses to determine the structure of these effects. As the changes over time in this sample were nonlinear, we treated the trajectories over time as unstructured. While this approach reduced power, it ensured that we avoided problems due to misspecification of the model for the trajectories. Seven-day point prevalence abstinence rates at 6 months were compared between groups using chi-square tests. For completeness, GLMM analyses with the same structure as the preceding one were also performed for other measures of smoking behavior (exhaled CO levels and FTND scores). We additionally analyzed these outcomes at the study endpoint (week 26) using an analysis of covariance and covarying for baseline scores.

In addition to between-group comparisons of treatment effects on smoking-related variables, GLMMs were performed for all symptom/safety measures (BPRS, SANS, CGI, BDI-II, C-SSRS, and AIMS) separately, with the symptom/safety measure as the dependent variable, time as a within-subject factor, and group as a between-subject factor, to determine if these measures changed over time during treatment and if different treatments resulted in different trajectories over time. In addition, a chi-square test was performed to compare the proportion of participants with adverse events in the treatment groups, in order to determine if groups significantly differed on the tolerability of treatments.

Results

At baseline, the study sample was late middle-aged (56.7 ± 8.3 years old), 53% black, smoked a moderate number of cigarettes per day (19.0 ± 8.2), and was moderately nicotine dependent (FTND 6.2 ± 2.1). BPRS, SANS, CGI, and BDI-II scores (42.5 ± 11.8, 47.6 ± 17.1, 4.3 ± 1.0, and 11.5 ± 13.2, respectively) indicated mild-to-moderate psychiatric symptoms (Table 1).[56,72–74] All participants were taking antipsychotic medication, with 79% of the study sample taking atypical antipsychotics. No significant between-group differences were found in these baseline measures. In examining changes in symptom/safety measures (BPRS, SANS, CGI, BDI-II, AIMS, and C-SSRS) with treatment, no significant changes were found in the study sample as a whole over time ($F(1,19) = 0.03$ to 2.39, ps = .14 to .87) and there were no group by time interactions ($F(2,19) = 0.09$ to 1.96, ps = .17 to .91).

Regarding feasibility of study treatments, participants who did not drop out of the study completed 19 ± 4, 22 ± 3, and 10 ± 2 CBT/medication management visits for the COMB-EXT with HV, COMB-EXT without HV, and TAU treatments, respectively. Participants in the COMB-EXT with HV group who did not drop out had 10 ± 4 HV, and only 3 HV total had participant no-shows. Participants in both COMB-EXT groups were treated with bupropion, nicotine patch, and nicotine lozenge (mean of 6.5 lozenges/d), while participants in the TAU group were treated with either all three medications ($n = 4$), nicotine patch plus lozenge ($n = 4$), bupropion plus patch ($n = 1$), or monotherapy with bupropion, nicotine patch, nicotine lozenge, or varenicline ($n = 1$ each). Adherence rates (defined as completing the assigned length of CBT, reporting good compliance with medication, and being evaluated at 6 months) were 73%, 60%, and 62% for the three study groups, respectively.

The overall GLMM analysis examining cigarettes per day showed a significant difference in the pattern of change over time between the three study groups ($F(52,391) = 1.8$, $p < .01$) (Figure 2). Post hoc analyses showed that this effect was due to significant differences in the trajectory between the groups treated with COMB-EXT+HV and TAU ($F(26,267) = 2.5$, $p < .01$) and between the groups treated with COMB-EXT without HV and TAU ($F(26,248) = 2.4$, $p < .01$). The COMB-EXT groups with and without HV did not differ in their trajectories over time ($F(26,267) = 0.4$, $p = 1.0$). At 26 weeks, the COMB-EXT+HV, COMB-EXT without HV, and TAU groups smoked a mean of 2.5, 4.5, and 12.2 cigarettes per day, which was significantly different between both COMB-EXT groups and the TAU group (Student t tests, $p < .05$) (Table 2).

Seven-day point prevalence abstinence rates at 6 months for the COMB-EXT+HV, COMB-EXT without HV, and TAU groups were

Table 1. Baseline Demographic Variables and Rating Scale Scores for the Three Treatment Groups

Variable	Treatment as usual (n = 13)	COMB-EXT (n = 10)	COMB-EXT+HV (n = 11)
Age	57.5 (±7.6)	56.3 (±10.6)	56.1 (±7.2)
Racial group			
Asian	7.7%	10.0%	9.0%
Black	61.5%	60.0%	45.5%
White	30.8%	30.0%	45.5%
Living arrangements (independent/supervised)	6/7	6/4	4/7
Cigarettes per day	19.6 (±8.5)	18.5 (±7.5)	18.6 (±9.2)
Exhaled carbon monoxide (parts per million)	11.5 (±5.1)	12.3 (±9.9)	12.0 (±4.8)
Fagerström Test for Nicotine Dependence	6.5 (±2.5)	5.9 (±1.6)	6.2 (±2.1)
Brief Psychiatric Rating Scale	39.6 (±7.5)	38.7 (±11.2)	49.4 (±14.4)
Scale for Assessment of Negative Symptoms	45.3 (±19.4)	47.1 (±13.7)	50.9 (±17.9)
Clinical Global Impression	4.5 (±1.2)	4.0 (±0.7)	4.2 (±1.1)
Beck Depression Inventory	10.2 (±12.0)	10.3 (±10.9)	14.2 (±16.9)

COMB-EXT = combination extended treatment; COMB-EXT+HV = combination extended treatment plus home visits. All values are presented as means (±*SD*) or percentages. All variables were compared between the three study groups, and no significant differences were found at the $p < .05$ level on analyses of variance or t tests for continuous variables, or a chi-square test for the categorical variable.

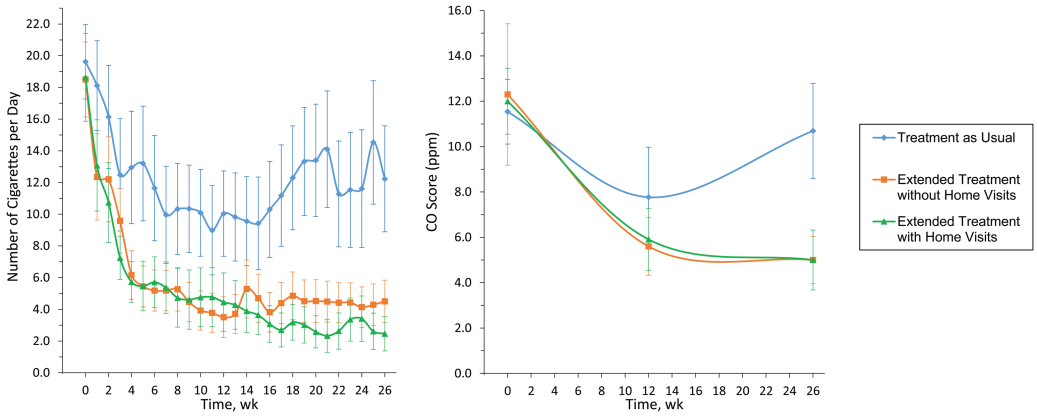

Figure 2. Effect of Combination Extended Treatment (COMB-EXT) with or without home visits (HV) compared to treatment as usual (TAU) on measures of smoking behavior.

45%, 20%, and 8%, respectively. These rates of abstinence were significantly different between the COMB-EXT+HV and TAU groups ($\chi^2(1) = 4.8$, $p = .03$), but not between the COMB-EXT without HV and TAU groups ($\chi^2(1) = 0.7$, $p = .4$) or between the COMB-EXT with and without HV groups ($\chi^2(1) = 1.6$, $p = .2$).

For exhaled CO levels, the difference in trajectories of the three groups over time did not reach significance ($F(4,62) = 2.0$, $p = .1$), but the data showed a similar pattern to the preceding overall analysis, with the COMB-EXT+HV group being significantly different from the TAU group ($F(2,44) = 5.0$, $p = .01$), the COMB-EXT without HV versus TAU group being non-significant, but trending ($F(2,42) = 2.2$, $p = .1$), and the two COMB-EXT groups not being significantly different from each other ($F(2,38) = 0.05$, $p = .9$). While the means of the COMB-EXT groups appear similar in Figure 2 at the various time points, the difference in magnitude of the treatment effects between COMB-EXT+HV and COMB-EXT without HV (compared to TAU) was due to group differences in variability. After correction for multiple testing, the difference between the trajectories of the COMB-EXT+HV and TAU groups remained significant. When comparing exhaled CO of the three treatment groups at week 26 using an analysis of covariance with the baseline measurement as a covariate, the three groups were significantly different from each other (5.2, 5.0, and 10.5, respectively; $F(2,30) = 5.1$, $p = .01$). Post hoc tests showed that this omnibus effect was due to significant differences between COMB-EXT+HV and TAU ($p = .01$) and COMB-EXT without HV and TAU ($p = .01$), while there was no significant difference between COMB-EXT with and without HV ($p = .9$) (Table 2). Similarly, there was no overall difference in the participants' trajectories of FTND scores ($F(2,62) = 1.4$, $p = .5$), and pairwise comparisons between group trajectories were not significant ($F(2,38) = 0.5$, $p = .6$; $F(2,44) = 1.6$, $p = .2$; and $F(2,42) = 0.4$, $p = .6$, respectively). When comparing FTND scores at week 26 using an analysis of covariance and controlling for the baseline measurement there was a nonsignificant trend for an overall difference between the three treatment groups ($F(2,30) = 2.76$, $p = .08$). These results indicate that biochemical and rating scale measures of smoking behavior decreased over time and these reductions were greater for the COMB-EXT groups than the TAU group. Results also show that the pattern of changes for exhaled CO and FTND scores are consistent with effects observed in the analysis of cigarettes per day.

For the COMB-EXT+HV, COMB-EXT without HV, and TAU groups, the percentages of participants reporting adverse events were

Table 2. Effect of Treatments on Smoking-Related Variables For Treatment as Usual (TAU), Combination Extended Treatment (COMB-EXT) Without Home Visits (HV), and COMB-EXT With HV

Variable/group	Week 0	Week 12	Week 26
Cigarettes per day			
TAU	19.6 (±8.5)	10.0 (±9.7)	12.2 (±12.1)
COMB-EXT without HV	18.5 (±7.5)	3.5 (±4.1)*	4.5 (±4.2)*
COMB-EXT with HV	18.6 (±9.2)	4.5 (±6.1)	2.5 (±3.6)*
Exhaled carbon monoxide level			
TAU	11.5 (±5.1)	7.8 (±7.9)	10.7 (±7.6)
COMB-EXT without HV	12.3 (±9.9)	5.6 (±4.0)	5.0 (±3.3)*
COMB-EXT with HV	12.0 (±4.8)	5.9 (±4.5)	5.0 (±4.4)*
Fagerström Test for Nicotine Dependence			
TAU	6.5 (±2.5)	4.1 (±2.4)	4.3 (±2.6)
COMB-EXT without HV	5.9 (±1.6)	3.5 (±2.1)	2.9 (±2.4)
COMB-EXT with HV	6.2 (±2.1)	2.8 (±2.5)	2.0 (±2.0)*

All values are presented as means (±*SD*). All variables were compared between study groups at each time point.
*$p < .05$ for *t* test between the specified COMB-EXT group vs. TAU at the time point listed.

27%, 30%, and 46%, respectively (all between-group chi-square tests were not significant). For the study sample, the most common adverse event was insomnia ($n = 4$), with vivid dreams ($n = 2$), nausea ($n = 2$), rash (with patch) ($n = 2$), and agitation ($n = 1$) also being reported. There were no serious adverse events.

Discussion

This study had two central findings that were novel. First, the rapid initiation of four first-line smoking cessation treatments (bupropion HCl, nicotine patch, nicotine lozenge, and CBT) provided for an extended period of time (COMB-EXT) was clearly more effective than TAU for reducing cigarette usage and abstaining from smoking in smokers with schizophrenia, with no evidence for greater risk of adverse events. While each of the treatments (and some combinations) have been studied in the past in smokers with schizophrenia, the research presented here is novel in that it examined both combination and extended treatment in a controlled manner. Second, though the COMB-EXT and COMB-EXT plus HV groups had similar results for smoking levels, the addition of HV resulted in a significantly higher 7-day point prevalence abstinence rate than TAU at 6 months. These results suggest that HV focusing on minimizing SHS (or a more extensive behavioral therapy program) may be worthy of future research as an adjunct for initiating and maintaining abstinence in smokers with schizophrenia.

For the overall effect of COMB-EXT found here, prior research has examined combination and extended treatment, but we are unaware of controlled studies comparing this approach to TAU. To our knowledge, only two studies have used combinations of treatments similar to the ones administered here in smokers with schizophrenia, and these studies provided treatment for a standard (not extended) amount of time. In one such study,[75] CBT, bupropion, and NRT were administered in typical dosages, with NRT started at week 4 and study medications tapered (and CBT stopped) at week 12. In that study, smokers with schizophrenia in the experimental group had a higher quit rate than the control group at week 8, but not at week 24 after acute treatment was discontinued. In the second such study,[24] CBT, bupropion, and nicotine patch were administered within 15 days of study initiation and continued for 10 weeks, with abstinence rates of 27.6% at 10 weeks and 13.8% at 6 months of follow-up. Taken together, these studies demonstrate an advantage of combination treatment over regimens including placebo, which could (at least partly) account for the primary results here, but extended treatment was not administered, which may have resulted in the lower quit rates found in these studies at approximately 6 months of treatment.

Prior studies using extended treatment (6 months or more) have demonstrated the utility of maintenance treatment with a single medication, such as NRT[76] or varenicline,[77] once a smoker with schizophrenia has attained an initial period of abstinence. In addition, a prior open-label study with CBT (for 12 weeks), bupropion, and NRT for 1 year demonstrated the feasibility of this approach, with a substantial quit rate of 23.5%,[78] but no control group using TAU. The present study is consistent with this prior research and the clearly significant differences between COMB-EXT and TAU, along with the absence of evidence for increased adverse events with COMB-EXT, point to the advantage of rapidly initiated, combined, and extended treatment for smoking in schizophrenia over standard care.

Study results also give a preliminary indication that HV targeted to minimize SHS exposure, which were straightforward to implement, result in additional benefits above and beyond those provided by COMB-EXT treatment without HV. This research builds upon prior studies aimed at decreasing SHS exposure in the home environment. Such studies have typically used one or two HV for pregnant women,[79,80] postpartum women who had recently quit smoking,[81] or children at risk for respiratory diseases[82,83] to attempt to decrease SHS exposure. The present suggests that a larger number of visits over a longer period of time may be useful to encourage smoking abstinence. We speculate that the HV intervention increased awareness of behavioral smoking-related triggers in the home environment, leading to an actual decrease in exposure to these triggers. Given that the COMB-EXT with and without HV had similar decreases in cigarettes per day, but the COMB-EXT with HV were more likely to quit smoking, this additional behavioral intervention may have helped smokers with schizophrenia overcome a significant hurdle to quitting, namely environmental influences that interfere with cessation.

The primary limitation of the study was the modest sample size, which lacked sufficient power to more fully detect statistical differences between the COMB-EXT groups with and without HV. A larger sample would be needed to determine if COMB-EXT+HV indeed results in an improved quit rate over COMB-EXT alone in smokers with schizophrenia. A related limitation is the absence of control groups other than TAU. This absence led to the study being unable to differentiate which components of the COMB-EXT were essential in leading to improved outcomes (though both the combination and extended parts of the treatment can clearly be inferred as being helpful for relapse prevention, based on prior studies[24,75]). The study was also limited by the absence of a motivation to quit rating scale, though all participants expressed a desire to obtain smoking cessation treatment and quit, so we speculate that they fell within a relatively narrow range of motivation levels. The use of the standard FTND to measure severity of nicotine dependence is a potential limitation, since this scale may not have as much internal consistency as other proposed instruments for measuring tobacco dependence in people with schizophrenia. Another limitation was the absence of plasma, salivary, or urinary cotinine (or nicotine) levels. While 7-day point prevalence rates are commonly defined

using participant reports and exhaled CO levels in smoking cessation treatment trials[84–87] as was done here, additional biochemical measures would have improved sensitivity for verifying smoking abstinence.[88] The fact that the sample was all male was also a limitation, given that study results may not be applicable to women with schizophrenia.

In conclusion, rapidly initiated combination and extended treatment improves smoking reduction/cessation outcomes compared to TAU in smokers with schizophrenia. In addition, HV appear to be a promising adjunct to encourage smoking reduction and abstinence, and may be worthy of future research.

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Declaration of Interests

None declared.

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