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Achieving Smoking Cessation in Individuals with Schizophrenia: Special Considerations

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Abstract

Premature mortality due to cardiovascular disease in those with schizophrenia is the largest lifespan disparity in the US and is growing; adults in the US with schizophrenia die on average 28 years earlier than those in the general population. Smoking prevalence among individuals with schizophrenia is estimated to be from 64–79%. Smokers with schizophrenia have historically been excluded from most large nicotine-dependence treatment studies. Converging evidence, however, indicates that a majority of smokers with schizophrenia want to quit smoking and that available pharmacotherapeutic smoking cessation aids are well tolerated by this population of smokers and effective when combined with behavioral treatment. The aim of this review is to present updated evidence for safety and efficacy of smoking cessation interventions for those with schizophrenia spectrum illness. We also highlight implications of the very low abstinence rates for smokers with schizophrenia who receive placebo plus behavioral treatment in randomized trials and review treatment approaches to address the high rate of rapid relapse observed upon pharmacologic treatment discontinuation in this population. Recommendations for monitoring for treatment-emergent nicotine withdrawal symptoms, side effects and effects of cessation on antipsychotic medication are also provided. Smokers with schizophrenia spectrum disorders should be encouraged to quit smoking and should receive varenicline, bupropion with or without nicotine replacement therapy, or nicotine replacement therapy, all in combination with behavioral treatment for at least 12 weeks. Maintenance pharmacotherapy may reduce relapse and improve sustained abstinence rates. Controlled trials in smokers with schizophrenia consistently show no greater rate of neuropsychiatric adverse events with pharmacotherapeutic cessation aids than with placebo.

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Compliance with Ethical Standards

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1. Introduction

Addiction to tobacco is highly prevalent among those with schizophrenia. Individuals with schizophrenia are more likely to smoke, smoke more heavily, extract more nicotine and carbon monoxide (CO) from each cigarette, and are more likely to be physically nicotine dependent than those without psychiatric illness [1–5]. 50 Years after the first United States (US) Surgeon General's report of an association between smoking and cancer in 1964 [6], adult smoking in the US has declined by 55% in the general population, to 18%, [7, 8] but despite availability of smoking cessation treatments shown to be effective specifically in this population, comparable decreases in smoking rates have not been observed among smokers with schizophrenia [9]. Smoking prevalence among adults with serious mental illness (SMI), such as schizophrenia, is higher today, at 53%, than it was in the general population in 1964 [10, 11]. Recent estimates indicate that 64%–79% of those with schizophrenia spectrum disorders smoke tobacco regularly [11–13] and most state they would like to quit [14–18].

People with schizophrenia in the US suffer physical diseases at younger ages and die approximately 28 years earlier than those without mental illness, primarily from diseases directly attributable to tobacco smoking [19]. Age-adjusted mortality from smoking-related pulmonary and cardiovascular disease is 2 to 6 times higher among individuals with schizophrenia than in age-matched samples without schizophrenia [20, 21]. While tobacco smoking is responsible for over 18% of all deaths in the US [22, 23], it was recently reported that, among those who had been hospitalized for schizophrenia in the state of California from 1990 to 2005, over half subsequently died from one of 19 diseases identified by the Centers for Disease Control and Prevention as causally linked to tobacco use [24].

The benefits of smoking cessation are dramatic for all age groups [25, 26]. Those who quit smoking between 25 and 34 years of age live 10 years longer than those who do not quit; those who quit between 35 and 44 years of age gain 9 years of life, those who quit between 45 and 54 years of age gain 6 years, and those who quit between 55 and 64 years of age gain 4 years compared to those who do not quit smoking [25]. Smoking cessation in those with schizophrenia has been reported to drive reduced 10-year risk for cardiovascular morbidity and mortality despite abstinence-associated weight gain [27].

Despite the epidemic of tobacco dependence among those with schizophrenia and the associated large and growing mortality disparity, available smoking cessation aids with proven efficacy and tolerability in those with schizophrenia exist and are vastly underutilized in this population [28]. Reluctance to prescribe cessation aids, particularly non-nicotine pharmacotherapies, to aid smoking cessation, may be due to continuing concerns about safety of the pharmacotherapy itself, low expectancies regarding patient follow-through or success with quit attempts, or simply lack of knowledge about the evidence base for smoking cessation pharmacotherapies for smokers with schizophrenia. Although a recent meta-analysis reported that smokers with schizophrenia are as likely as those without schizophrenia to receive physician advice to quit smoking [29], cessation advice or even behavioral therapy alone alone has a low success rate with this population [11, 30, 31], and effective pharmacotherapies, particularly varenicline, are less likely to be prescribed to smokers with schizophrenia than to smokers without psychiatric illness [32]. Reluctance by

treaters to recommend and prescribe effective smoking cessation therapies may contribute to the disparity in the rates of successful cessation in smokers with schizophrenia at the population level [33].

2. Effectiveness of initial pharmacotherapy

Although smokers with schizophrenia have been excluded from most major clinical trials of nicotine dependence treatments [34, 35], a growing body of evidence supports the safety and efficacy of first-line smoking cessation pharmacotherapies for smokers with schizophrenia, including varenicline, bupropion with and without nicotine replacement therapy (NRT), and nicotine patch monotherapy [36–46]. We summarize the evidence from randomized, placebo-controlled trials published from 2000 through 2016 of pharmacotherapies added to behavioral treatment, with biochemically-validated abstinence outcomes in adult outpatient smokers with schizophrenia spectrum disorders. Articles were identified in a Pubmed literature search of English language manuscripts and a search of the citations in each identified manuscript (see Table 1 for a summary of study methodologies and outcomes). Because clinical practice guidelines recommend use of a combination of medication and counseling in all individuals making a smoking cessation attempt [47], and because the abstinence rate with behavioral treatment alone is approximately 4% across smoking cessation trials randomizing one group to behavioral treatment and placebo [30, 31], this review focuses on trials of combined pharmacotherapy and behavioral treatment. Biochemically verified self report of prolonged or continuous abstinence is the outcome of interest where available.

First line pharmacologic treatments in the general population include varenicline, bupropion, and NRT either alone or in combination [48]. In general population smokers, varenicline and combination NRT (transdermal nicotine patch combined with short-acting NRT [nicotine polacrilex gum, lozenge, inhaler or nasal spray]) are associated with abstinence rates superior to bupropion, single form NRT, and placebo, while bupropion and single form NRT both significantly increase cessation rates over placebo [48].

3. Safety and efficacy of bupropion monotherapy or combined with NRT

There is consistent clinical trial evidence for efficacy and tolerability of bupropion, either alone or in combination with NRT, for smoking cessation specifically for those with schizophrenia [36, 39–41, 43]. This has been confirmed in independent, systematic reviews and meta-analyses [37, 49–51] and incorporated into clinical practice guidelines.

These studies support the use of bupropion with or without NRT in smokers with schizophrenia, with active treatment increasing abstinence rates 2–5 fold over placebo or treatment as usual [36, 37, 40, 43, 49, 52, 53]. Importantly, there is no evidence for worsening of positive, negative, or depressive symptoms in those assigned to receive bupropion with or without NRT as compared to placebo in any of these trials individually or in aggregate [36, 37, 39–41, 43]. Consensus guidelines for treatment of schizophrenia, the revised Schizophrenia Patient Outcomes Research Team (PORT) Guidelines recommend that providers prescribe bupropion pharmacotherapy with or without NRT for smoking

cessation with behavioral support for all smokers with schizophrenia spectrum disorders who wish to try to quit [38].

4. Safety and efficacy of varenicline

Since the revised PORT guidelines were published, evidence has emerged consistently and strongly supporting the safety and efficacy of varenicline for smoking cessation and maintenance of abstinence in schizophrenia [44–46, 54–56]. Varenicline in combination with behavioral support has been found to be efficacious in promoting abstinence in smokers with schizophrenia interested in quitting [37, 44] and maintenance treatment with varenicline among successful quitters has been shown to protect against relapse in those with schizophrenia and bipolar disorder [42, 56].

5. Neuropsychiatric Safety of Cessation Aids and Weighing Risks and Benefits

Contrary to anecdotal reports of serious neuropsychiatric adverse events with pharmacotherapeutic cessation aids, particularly varenicline, and particularly in those with psychiatric illness, much emphasized in the press, and highlighted in a boxed warning for neuropsychiatric adverse events for both bupropion and varenicline, no controlled trial to date, alone or in aggregate, in smokers with psychiatric illness in general or schizophrenia in particular has shown a signal for increased neuropsychiatric adverse events other than sleep disturbance with varenicline or bupropion compared to placebo or NRT [37, 42, 44–46, 54, 57–61].

Due to concern raised by case reports and post-marketing pharmacovigilance reports suggesting the possibility of new-onset/worsened psychiatric symptoms including, irritability, depressive symptoms, suicidality, and behavioral dyscontrol associated with varenicline and bupropion, particularly in smokers with psychiatric illness, the Federal Drug Administration (FDA) mandated the makers of varenicline and bupropion to conduct a randomized, controlled, post-marketing trial to compare and quantify the risk of neuropsychiatric adverse events and abstinence rates with varenicline and bupropion compared to placebo and nicotine patch (NRT) in a large, international sample of smokers. This trial, termed the Eagles trial enrolled approximately 4000 smokers with and 4000 without psychiatric illness, including 390 with schizophrenia or schizoaffective disorder. This was the first placebo-controlled head to head comparison of the three first line smoking cessation treatments (varenicline, bupropion and NRT monotherapy), all combined with brief counseling, for smoking cessation and for smoking cessation in schizophrenia.

Comparison of safety across those with schizophrenia or schizoaffective disorder assigned to varenicline, bupropion, nicotine patch or placebo in the Eagles trial revealed nearly identical psychiatric adverse event rates in each group. In the psychotic disorders subgroup in Eagles, the rate of moderate to severe neuropsychiatric adverse events was 6.3% in the varenicline, bupropion, and placebo arms and 5.1% in the nicotine patch arm [54]. The finding that neuropsychiatric adverse events are not more common with varenicline or bupropion than placebo or nicotine patch led to the removal of the boxed warning for bupropion and

varenicline from both FDA and European Medicines Agency (EMA) prescribing instructions.

Further informing the risk to benefit assessment of prescribing smoking cessation treatment for those with schizophrenia, Eagles confirmed previous studies demonstrating efficacy of bupropion and varenicline in this population [35–41, 43, 44, 46, 55]. In the 390 smokers with psychotic disorders, the 4-week continuous abstinence rate at the end of treatment was highest with varenicline at 23.2%, similar with bupropion and nicotine patch at 11.2% and 13.1% respectively, and lowest with placebo, 4.1% [46, 54]. As the first placebo-controlled trial of NRT in this population, this study also provides new evidence for safety and efficacy of nicotine patch compared to placebo in smokers with schizophrenia [54]. Prior to this, there were no published placebo controlled trials of NRT in smokers with schizophrenia, although maintenance NRT has been effective in preventing relapse among smokers who attained initial abstinence with NRT in one small open trial [62] and one single-blind extension phase trial [63]. While dual NRT has been shown to be superior to single form NRT in the general population [48], there are no placebo-controlled trials to our knowledge testing the efficacy of dual NRT for smoking cessation in those with schizophrenia.

6. Low Placebo Quit Rates: Smoking Cessation Pharmacotherapy may be Essential

While those with psychiatric illness appear to quit smoking at a lower rate than those without psychiatric illness [46], the odds of end of treatment abstinence with pharmacotherapy appear to be *greater* in those with psychotic disorders than those observed in general population smokers [46, 54]. Smokers without a psychiatric illness had an abstinence odds ratio of 4.0 and 4-week continuous abstinence rate of 38.0% on varenicline (vs 13.7% on placebo), whereas, those with schizophrenia had an abstinence odds ratio of over 5 and 4-week continuous abstinence rate of 23.2% with varenicline and 4.1% with placebo[30]. This is likely due to the low cessation rate with placebo plus behavioral treatment that is consistently observed in those with psychotic disorders [37, 54].

The low placebo quit rate (approximately 4%) observed across trials [37, 54] suggests behavioral treatment alone is ineffective for regular, daily smokers of 10 or more cigarettes per day with schizophrenia. Neurobiological abnormalities observed among individuals with schizophrenia, such as regulation and affinity of nicotinic acetylcholine receptors [64, 65] may underlie low smoking cessation rates without pharmacotherapy in this population of smokers. In addition, social determinants, such as a higher density of smokers in the smoker with schizophrenia's social environment and attentional deficits have been implicated in predicting success of smoking cessation treatment in this population [66, 67] and may play a role in necessitating smoking cessation pharmacotherapy.

7. Rapid Relapse after Discontinuation of Smoking Cessation Pharmacotherapy Is Common in this Population: The Role of Maintenance Therapy

While relapse is an important problem for all smokers, a particularly high rate of rapid relapse after discontinuation of pharmacotherapy has been observed for those with schizophrenia [52, 68–70]. Among those who attained abstinence with a standard, 12-week course of pharmacotherapeutic treatment, maintenance pharmacotherapeutic and behavioral treatment has been reported to dramatically reduce relapse rates over maintenance behavioral treatment alone among smokers with schizophrenia illness in open, [62] single blind [63], and double blind trials[42].

With use of maintenance varenicline, an additional 12 weeks of treatment among those who attained abstinence with an initial 12-week course of varenicline plus behavioral treatment [71] those with schizophrenia spectrum disorders appear to derive particular benefit. A recent analysis comparing the relapse curves in abstinent smokers with and without schizophrenia assigned to maintenance treatment varenicline or placebo found that without maintenance treatment, recently abstinent smokers with schizophrenia relapsed significantly faster than those without psychiatric illness, while for those who received maintenance varenicline, the relapse rate over 12 weeks of maintenance treatment was no different, suggesting that maintenance pharmacotherapy for prevention of relapse confers greater benefit for smokers with schizophrenia than for smokers without psychiatric illness [56]. After three months of maintenance treatment, those with schizophrenia assigned to placebo had abstinence rates fully 30% lower than those without psychiatric illness. Among those assigned to maintenance varenicline, however, there was no difference in abstinence rates by diagnosis, abstinence rates were over 80% in those with and without schizophrenia. Maintenance pharmacotherapy may be a particularly important intervention to aid smokers with schizophrenia in achieving the sustained tobacco abstinence needed to realize the substantial health benefits of smoking cessation [34, 40, 42, 58].

8. Many Nicotine Withdrawal Symptoms are Common for Those with Schizophrenia: Treatment of Emergent Adverse Events and a Rationale for Separating of Initiation of Pharmacotherapy from the Quit Date

Anxiety, dysphoria, and insomnia are common nicotine withdrawal symptoms [72] and are also quite high in smokers with schizophrenia even in the absence of nicotine withdrawal [73]. It can be difficult to establish whether these symptoms, if they worsen during a smoking cessation attempt, are attributable to the initiation of pharmacotherapeutic smoking cessation aids, to nicotine withdrawal, to the stress of trying to quit smoking, or due to fluctuation of symptoms of schizophrenia over time in general or during a smoking cessation attempt specifically. The 6.3% rate of moderate to severe neuropsychiatric adverse events observed in the placebo arm in the Eagles trial [30] can be reasonably understood to be nicotine withdrawal symptoms and/or symptom fluctuations in the underlying psychotic illness observed during a smoking cessation attempt.

In accordance with this conceptualization of non-specific withdrawal symptoms in this population, we have found it useful to separate the initiation of smoking cessation pharmacotherapy from the target quit date by 4 weeks [74]. This practice allows patients and treaters to establish the tolerability of the new pharmacotherapeutic smoking cessation aid prior to the quit date. This allows both patients and treaters to separate potential medication-related neuropsychiatric adverse events from nicotine withdrawal symptoms and is consistent with the flexible quit approach outlined in FDA prescribing information for varenicline [75, 76]. The result of separating initiation of pharmacotherapy from the quit attempt by several weeks, in our experience, is to increase treatment acceptance and adherence, leading to increased duration of treatment with the smoking cessation pharmacotherapy and increased abstinence rates. Further, it may be that 4 weeks of pretreatment helps smokers with schizophrenia consolidate learning from reduced nicotine withdrawal symptoms, craving, and reduced reward from smoking prior to the target quit date.

9. Tobacco Smoking and Smoking Cessation Impact Hepatic Metabolism of Psychotropic Medications

Because tobacco smoking is associated with increased hepatic clearance of many psychotropic drugs, particularly those metabolized by cytochrome P450 1A2 [77, 78], it is recommended that clinicians monitor patients who reduce or quit smoking for evidence of reduced clearance of psychotropic medications metabolized by these enzymes and consider dose adjustment accordingly [79]. In smokers with schizophrenia, monitoring for increased side effects of the antipsychotic medications including olanzapine, clozapine, haloperidol, and fluphenazine is particularly relevant [80, 81]. Conversely it is important to monitor for effects of resumption of smoking in those who have had medications stabilized during a period of abstinence, since therapeutic efficacy of these medications can decrease with relapse to smoking. It is important to note that the effect is induced by the products of tobacco smoke rather than nicotine, thus neither NRT nor electronic cigarettes affect hepatic cytochrome enzyme activity [81].

We recommend monitoring for medication side effects when smoking is reduced significantly (i.e., 50%), rather than with less marked reduction, since smokers are expected to make compensatory changes in smoking topography (e.g., puff volume) to extract higher amounts of nicotine with fewer cigarettes [82] which will likely compensate for smaller reductions in cigarettes smoked per day. One clear implication of this recommendation is that regular monitoring of smoking is indicated as part of every clinical visit..

10. Group Behavioral Smoking Cessation Treatment for Smokers with Schizophrenia

Treatment adherence has been quite high in treatment studies in samples of smokers with schizophrenia and bipolar disorder [40, 42, 58]. These favorable adherence rates may be partly attributable to the standard practice of providing weekly visits during the initial

treatment phase. Given the central role of smoking cessation pharmacotherapy in favorable cessation outcomes particularly for smokers with schizophrenia, it may be important to establish weekly check-ins in clinical practice to monitor and address any barriers to medication adherence, medication tolerability, psychiatric symptoms and abstinence success.

There is insufficient data from combined smoking cessation pharmacotherapy and behavioral trials to inform choice of one behavioral treatment or format (i.e., group vs. individual) for smokers with schizophrenia over any other [83]. An early study showed no difference in end of treatment 4-week continuous abstinence between a behavioral treatment tailored for smokers with schizophrenia and the same intensity behavioral treatment developed for general population smokers by the American Lung association [69]. Recent studies of combined smoking cessation medication and behavioral treatment have differed quite a bit in terms of the intensity of behavioral treatment provided, with some studies providing 10 minutes of counseling per visit [46, 84] and others providing approximately 1 hour of group cognitive behavioral smoking cessation treatment per visit [42, 68]. Cost-effectiveness and efficacy of behavioral treatments of varying intensity and format, including smartphone/telephone/internet-based treatment would be of value, particularly in terms of potentially extending the reach of behavioral treatment in this population.

In our own work, we have found a group format for behavioral smoking cessation treatment to provide a number of benefits for those with schizophrenia, including enhancing peer support for quitting, providing many opportunities for repetition of material, and organizing efforts to quit around a group target quit date. We also routinely incorporate peers with a serious mental illness who have successfully quit smoking with pharmacotherapy and behavioral treatment in our group treatments (see also [11]). Peers who have successfully quit smoking are especially helpful for increasing positive expectancies about the treatments. They serve as role models who provide first-hand experience of the ancillary benefits of quitting smoking in terms of finances, health and decreased pressure from others to quit, all of which are important reasons to quit for smokers with schizophrenia [18].

11. Future Directions

RCTs that include those with low motivation to quit, those with active substance use disorders, and light smokers are needed. Study of incentive-based interventions for initiation of abstinence are warranted in this population. Finally, study of interventions to improve system-level, provider-level and patient-level factors that impede delivery of evidence-based smoking cessation interventions may hold promise for increasing rates of known effective smoking cessation treatments in this population of smokers.

Although it is true that many smokers with schizophrenia want to quit smoking, there is a need for treatment models that address the needs of smokers who are not ready to quit. Minimal treatment interventions, such as brief physician advice to quit may enhance motivation to make a quit attempt in this population of smokers [85]. Similarly, brief behavioral interventions (single session of 40–45 minutes), comprised of motivational enhancement including personalized feedback regarding smoking behavior and consequences have increased rates of pursuing nicotine dependence treatment compared to

psychoeducation in this population [86–88]. Finally, in smokers with schizophrenia not ready to reduce or quit, a brief course of smoking cessation pharmacotherapy may increase willingness to try to quit as a result of reduced withdrawal symptoms or rewarding effects of smoking. This has been postulated to be the mechanism at work in the effective gradual quit attempt strategy in general population smokers in which smoking reduction is the therapeutic goal for the first 12 weeks of therapy prior to a quit date at week 12 [89]. Because of converging evidence that behavioral treatments alone are ineffective for smoking cessation in this population, it is important to identify methods of enhancing motivation not only to quit, but also to more widely utilize evidence-based smoking cessation pharmacotherapies together with behavioral support.

Despite recommendations from the European Psychiatric Association [90] and the Schizophrenia Patient Outcomes Research Team (PORT) [38] that smokers with schizophrenia be offered specific treatments to help them to quit smoking, provider factors may be a barrier to wide implementation of evidence-based smoking cessation treatment for smokers with schizophrenia [91, 92]. Patient behavior also likely impedes use of smoking cessation pharmacotherapy; in one study of 1577 general population smokers more than half (55.7%) of those prescribed varenicline did not fill their prescription [93].

There may be a role for using incentives to directly reduce smoking in people with schizophrenia [94] and/or to reinforce intermediary behavioral targets (e.g., medication or behavioral treatment adherence, brief abstinence) that could increase abstinence rates. Contingent reinforcement for reduced cotinine but not for group attendance was associated with reduced urine cotinine and expired CO in smokers with schizophrenia [95]. Some evidence suggests NRT combined with monetary reinforcement for lower expired CO concentration is superior to placebo + contingent reinforcement for abstinence among smokers with schizophrenia and results in high rates of abstinence (56.3% versus 27.8%) while contingencies are in place [37, 96]. We are particularly encouraged by the prospect of improved outcomes with contingent reinforcement combined with evidence-based smoking cessation pharmacotherapy. This work should be extended to test, for example, whether combined contingent reinforcement for early abstinence along with varenicline for prevention of relapse in this population results in higher end of treatment/long term abstinence rates [55, 95]. We know very little about the safety or efficacy of first line smoking cessation treatments for individuals with schizophrenia with active substance use disorders other than nicotine and for individuals smoking less than 10 cigarettes per day, some of whom are not nicotine dependent. The inclusion of these subgroups of smokers with schizophrenia in future clinical trials is important.

12. Conclusion

Low rates of provision of guideline-concordant smoking cessation treatment to smokers with schizophrenia in the community contributes to the abysmally low rates of smoking cessation and the large and growing disparity in expected lifespan for those with schizophrenia [21, 34, 97–100]. Studies conducted to date indicate that smoking cessation medications that work for the general population work for those with schizophrenia with the same relative efficacy as in other populations [54]. As in the general population, varenicline appears to be

the most effective treatment, followed by bupropion plus NRT, followed by bupropion or NRT monotherapy. Pharmacotherapy appears to play a more critical role for smokers with schizophrenia than in other populations of smokers, increasing the odds of quitting by a factor of 4–5 times, likely because of the low quit rate with behavioral treatment alone, approximately 4% across studies [37, 54]. Maintenance treatment also appears to differentially improve relapse rates for smokers with schizophrenia [56], possibly related to the high rate of relapse after treatment discontinuation identified in laboratory studies [101] and clinical trials [56] among smokers with schizophrenia who attain abstinence. There is evidence for maintenance varenicline as protecting against relapse in one RCT [55] and preliminary findings in an open trial of NRT with or without bupropion [62].

Population-wide smoking cessation rates among adults with SMI are less than half those in the general population [102]. However, abstinence rates of 20–48% are reported in clinical trials of standard pharmacotherapies and behavioral treatment in those with SMI [37, 42, 44, 57, 58]. Achievement of the abstinence rates in those with SMI observed in clinical trials in the community through improved delivery of effective, evidence-based, smoking cessation treatments would result in the elimination of tobacco use among 1.4 to 3 million people. This achievement is possible with tools available to us today and would dramatically impact the 28-year reduction in lifespan observed in those with schizophrenia [19] largely due to smoking-related disease [103].

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Key Points

- Low rates of provision of guideline-concordant smoking cessation treatment to smokers with schizophrenia contributes to the abysmally low rates of smoking cessation and the near 30-year disparity in expected lifespan for those with schizophrenia.
- Varenicline appears to be the most effective treatment for smoking cessation in this population.
- Pharmacotherapy appears to play a more central role for smokers with schizophrenia, increasing the odds of quitting by a factor of 4–5 times, likely because the quit rate with behavioral treatment alone is so low.

Table 1
Efficacy of Placebo-Controlled Randomized Controlled Trials of Combination Smoking Cessation Pharmacotherapy and Behavioral Treatment among Smokers with Schizophrenia

Study	N	Clinical Outcome	Intervention	Control/Comparison	Primary Outcome	Abstinence Rates End of Tx (Tx vs. Control)	Follow-up (Tx vs. Control)
George et al. (2000)	45	Cessation	ALA program (1hr x 10wks) + TNP (21mg x 6wks; 14mg x2wks; 7mg x2wks)	Specialized group therapy for schizophrenia (1hr x10wks) + TNP (21mg x 6wks; 14mg x2wks; 7mg x2wks)	7-day PPA	Wk 10: 35.5% vs. 35.7%	Wk 24: 17.6% vs. 10.7%
Evins et al. (2001)	19	Cessation	Bupropion (150mg/d x12wks) + group CBT (1hr x9wks)	Placebo + group CBT (1hr x9wks)	4-week CA	Wk 12: 11% vs. 0%	Wk 24: 11% vs. 0%
George et al. (2002)	32	Cessation	Bupropion (150mg/d x3d, 300mg/d x10wks) + group therapy (1hr x10wks)	Placebo + group therapy (1hr x10wks)	7-day PPA	Wk 10: 50% vs 12.5%	n/a
Evins et al. (2005)	57	Cessation	12 weeks bupropion (300mg/d x11wks) + group CBT (1hr x12wks)	Placebo + group CBT (1hr x12wks)	4-week CA	Wk 12: 16% vs 0%	3mos; 4% vs. 3.6%
Horst et al. (2005)	18	Relapse prevention	Following 12 wks open tx with TNP; participants received 6 mo TNP (range 14–63mg/d x6mo) + biweekly group	Following 12 weeks open treatment with TNP; participants received placebo + biweekly group education/motivation	7-day PPA	Wk 24: 66% vs. 0%	n/a
Evins et al. (2007)		Cessation	Bupropion SR (150mg/d x1wk, 300mg/d x11wks) + TNP (21mg wk 4–8; 14mg wk 9–10, 7mg wk 11–12) + CBT (1hr x12wks)	Placebo + TNP (21mg wk 4–8; 14mg wk 9–10, 7mg wk 11–12) + CBT (1hr x12wks)	4-week CA	Wk 12: 36% vs. 19%	Wk 24: 20% vs. 8%, Wk 52: 12% vs. 8%.
George et al. (2008)	59	Cessation	Bupropion (150mg/d x3d, 300mg/d x10wks) + TNP (21mg day 15–70) + group therapy (50min x10wks)	Placebo + TNP (21mg day 15–70) + group therapy (50min x10wks)	7-day PPA	Wk 10: 27.6% vs 3.4%	Wk 24: 13.5% vs 0%
Weiner et al. (2011)	9	Cessation	Varenicline (1mg BID x12wks) + ALA program counseling (2 sessions)	Placebo + ALA program counseling (2 sessions)	4-week CA	Wk 12: 75% vs. 0%	n/a
Weiner et al. (2012)	46	Cessation	Bupropion (300mg/d x12wks) + Fresh Start therapy (x9wks)	Placebo + Fresh Start therapy (x9wks)	7-day PPA	Wk 12: 18% vs 11%	n/a
Williams et al. (2012)	128	Cessation	Varenicline (0.5mg/d x3d, 0.5mg BID x4d, 1mg BID x11wks) + counseling (<30min weekly)	Placebo + counseling (<30min weekly)	End tx: 7-day ppa; F/u: CA end of tx to f/u	Wk 12: 19% vs 4.7%	Wk 24: 11.9% vs 2.3%
Evins et al. (2014)	61	Relapse prevention	Following 12 wks varenicline open tx, participants with 2 wks abstinence received varenicline (1mg BID wks 12–52) + relapse-prevention CBT (weekly x4wks, biweekly x2mo, monthly x8mo)	Following 12 wks varenicline open tx, participants with 2 wks abstinence received placebo + relapse-prevention CBT (weekly x4wks, biweekly x2mo, monthly x8mo)	4-week CA	Wk 52: 60% vs 19% [OR 6.2]	Wk 64: 45% vs. 15% [OR 4.6]; Wk 76: 30% vs 15% [OR 3.4]

Study	N	Clinical Outcome	Intervention	Control/Comparison	Primary Outcome	Abstinence Rates End of Tx (Tx vs. Control)	Follow-up (Tx vs. Control)
Evins et al. SRNT (2016)	390	Cessation	12 wks of varenicline (1.0 mg BID x 12 wks) or bupropion (300mg BID x12wks) or TNP (21mg with taper) + brief CBT	12 wks of placebo + brief behavioral smoking cessation counseling	4-week CA	Wk 12: Varenicline 23.2%, bupropion 11.2%, TNP 13.1%, placebo 4.1%	Wk 24: Varenicline 16.8%, bupropion 10.2%, TNP 10.1%, placebo 4.1%

PPA = Point Prevalence Abstinence; CA = Continuous Abstinence; TNP = transdermal nicotine patch