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# Treatment of Tobacco Use Disorders in Smokers with Serious Mental Illness: Toward Clinical Best Practices

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## Abstract

Addiction to tobacco-derived nicotine remains highly prevalent in the US, with 18% using daily, but 53% of those with serious mental illness smoke regularly. While smokers with serious mental illness have been excluded from most large nicotine dependence treatment studies, a growing evidence base is emerging to guide clinicians in how to assist their patients with psychiatric illness to quit smoking. The aim of this review is to present the evidence on safety and efficacy of smoking cessation interventions for those with serious mental illness.

Smokers with schizophrenia spectrum disorders should receive varenicline or bupropion with or without nicotine replacement therapy (NRT) in combination with behavioral treatment. Preliminary evidence suggests that varenicline in combination with behavioral support is efficacious and well tolerated for smoking cessation for those with bipolar disorder and major depressive disorder. More work is needed to establish treatment guidelines for smokers with major depressive disorder and bipolar disorder. Controlled trials to date have not found evidence for worsening of psychiatric symptoms or increased rate of psychiatric adverse events in this population with available pharmacotherapeutic cessation aids.

Converging evidence indicates that a majority of smokers with serious mental illness want to quit smoking and that available pharmacotherapeutic cessation aids combined with behavioral support are both effective for and well tolerated by these smokers. Most people with serious mental illness see their psychiatrist more regularly than their primary care physician, and many receive care exclusively in a psychiatric treatment setting. Psychiatrists thus have an important role to play in the recognition and treatment of tobacco use disorders in people with serious mental illness.

### Keywords

nicotine use disorder; tobacco use; smoking cessation; randomized controlled trial; schizophrenia; bipolar; depression; severe mental illness

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## INTRODUCTION

Fifty years after the first Surgeon General's report of an association between smoking and cancer, adult smoking in the United States has declined by 55% in the general population, to 18%.[1,2] Comparable decreases in smoking rates have not been realized among smokers with psychiatric illness.[3] Smoking prevalence among adults with serious mental illness (SMI) is higher today, at 53%, than it was in the general population in 1964.[4,5] Recent estimates indicate that 64%–79% of those with schizophrenia spectrum disorders smoke tobacco regularly,[5,6] as do 44–71% of those with bipolar disorder,[5–7] and 43% of those with unipolar depression.[8] People with SMI in the US die approximately 25 years earlier than those without mental illness, primarily from diseases directly attributable to tobacco smoking.[9,10] While tobacco smoking is reported to be responsible for over 18% of all deaths in the US in 2000,[11,12] a recent epidemiologic study reported that approximately half of deaths in those who had been hospitalized for schizophrenia, bipolar disorder, or major depressive disorder were due to one of nineteen diseases identified by the Centers for Disease Control and Prevention as being causally linked to tobacco use.[13]

Though smoking cessation by mid-life dramatically reduces smoking-related mortality,[14,15] tobacco dependence treatment is not routinely delivered to smokers with SMI.[16] However, converging evidence indicates that a majority of smokers with psychiatric illness want to quit smoking and that available pharmacotherapeutic cessation aids combined with behavioral support are both effective for and well tolerated by smokers with SMI.[17–29] Increased treatment intensity and longer treatment duration for smokers with specific psychiatric illnesses may improve prolonged abstinence rates.[30–32]

Despite the very high prevalence of smoking and of smoking-related illness among smokers with SMI, these individuals have been excluded from most major clinical trials of treatments for nicotine dependence.[16,33] However, there is growing evidence for safety and efficacy of specific cessation aids for specific psychiatric disorders. We summarize this evidence below, focusing on evidence from randomized controlled trials for safety and efficacy in outpatients with schizophrenia spectrum disorders, bipolar disorder, and major depressive disorder.

## METHODS

We conducted a search for all English language original reports and reviews of randomized, controlled, smoking cessation treatment intervention trials in individuals with psychiatric illness in Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and PsycINFO electronic databases. We additionally searched reference lists and asked experts for information on randomized clinical trials completed through March 2014. We focused the review on randomized, controlled, treatment intervention trials (RCTs) with biochemically-validated abstinence outcomes that compared smoking cessation interventions in adult smokers with a psychiatric illness likely meeting criteria for SMI, a federal designation based on US Public Law 102-321 which defines SMI as a diagnosable mental, behavioral, or emotional disorder (other than a substance use disorder) which includes episodic, recurrent, or persistent features and results in significant functional disability. Trials in those likely to meet the definition for SMI have been conducted to date

in smokers with schizophrenia, bipolar disorder and major depressive disorder, and we focus the review on these studies. Clinical practice guidelines recommend use of combination of medication and counseling in all individuals making a smoking cessation attempt,[34] so the review is focused on studies of combination of pharmacotherapy and behavioral treatment.[35,36] We used verified prolonged or continuous abstinence as the outcome of interest where available.

## RESULTS

Current clinical practice guidelines for smoking cessation treatment recommend that clinicians give advice to stop smoking and offer treatment with a pharmacotherapeutic cessation aid combined with behavioral treatment for regular smokers with or without psychiatric illness.[34] First line pharmacologic treatments include varenicline, bupropion, and nicotine replacement therapy (NRT).[37] Bupropion and NRT increase cessation rates over placebo, while varenicline and combination NRT (transdermal nicotine patch combined with short-acting nicotine replacement therapy (nicotine polacrilex gum, lozenge, inhaler or nasal spray) are associated with superior abstinence rates.[37]

### Schizophrenia Spectrum Disorders

Rates of smoking are 3–4× higher among individuals with schizophrenia than in the general population,[5,6] and those with schizophrenia are likely to be heavy smokers,[38] and to extract more nicotine from each cigarette.[39,4041] Despite this, smokers with schizophrenia can be motivated and persistent in attempts to quit smoking.[42,43] 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.[44,45]

In clinical trials in stable, treated, though symptomatic, outpatient smokers with schizophrenia or schizoaffective disorder, bupropion, with or without nicotine replacement therapy (NRT), and varenicline, at standard doses, dosed for 3 months in combination with behavioral support, have been associated with statistically significantly superior and clinically significant abstinence rates at the end of treatment than placebo plus behavioral support.

A meta-analysis of six randomized, placebo-controlled trials in 304 smokers with schizophrenia spectrum disorder supports the use of bupropion with or without NRT in smokers with schizophrenia.[20,22–25,46,47] Treatment with behavioral therapy and bupropion with or without NRT tripled 7-day point prevalence abstinence rates over placebo and behavioral treatment, RR=3.03, 95% CI 1.35–4.88, with an average end of treatment cessation rate of 26% for those assigned to bupropion and 7% for those on placebo bupropion with or without NRT and behavioral therapy. In four studies of bupropion vs. placebo monotherapy added to behavioral treatment, in 150 subjects with schizophrenia spectrum disorder, abstinence rates at the end of treatment ranged from 10% – 38% for those receiving bupropion and behavioral treatment and 0% – 9% for those receiving placebo and behavioral treatment.[22,23,46,47] The very low cessation rate with behavioral treatment added to placebo in these trials is notable, as the behavioral treatment was of high intensity (e.g., weekly one hour CBT group therapy) in some trials, and differs from the significant, dose

dependent benefit for behavioral treatment for smoking cessation reported for smokers in the general population.[34,48]

Though relapse rates were quite high after treatment discontinuation, in the 5 RCT's conducted in 214 subjects that evaluated abstinence rates at the 6 month follow up, 3 months after treatment discontinuation, there remained a significant effect of bupropion with or without NRT over placebo with or without NRT on abstinence, 13.2% vs. 3.7% respectively, RR=2.79, 95% CI 1.02–7.58.[20,22–25,46] Importantly, there is no evidence for worsening of positive, negative, or depressive symptoms in the pharmacotherapy group as compared to the placebo group in any of these trials individually or in aggregate, and is discussed further below.[20,22–25] In 2010, the Schizophrenia Patient Outcomes Research Team (PORT) Guidelines for the first time made an evidence-based recommendation for pharmacologic smoking cessation treatment of smokers with schizophrenia. This recommendation states that those who want to quit or reduce smoking should be advised to use bupropion SR 150 bid for 10–12 weeks with or without NRT and a smoking cessation education or support group.[21] Trials of bupropion in smokers with schizophrenia have initiated bupropion treatment 1–4 weeks prior to the quit date using standard dosing of 150 mg per day for 4–7 days then 150 mg twice daily for 11 weeks.[22–25,46,47]

While nicotine replacement therapy (NRT) monotherapy,[34,49] and combination of short and long acting NRT products in particular,[37] is first line pharmacotherapy for smokers in the general population, there are no published placebo controlled trials of the efficacy of NRT monotherapy in outpatients with schizophrenia who expressed motivation to try to quit smoking. Extended duration treatment with NRT has demonstrated promise for maintenance of abstinence among smokers with schizophrenia who attained initial abstinence with NRT in one open label study.[32] Controlled trials of NRT are needed in this population.

Varenicline has been well tolerated and effective for abstinence at the end of treatment in two RCT's of a 12-week course of varenicline or placebo added to brief individual behavioral support. In combined data from two trials in 137 smokers with schizophrenia spectrum disorder, end of treatment abstinence rates were 21% on varenicline and 4% on placebo plus behavioral support, RR=4.74, 95% CI 1.34–16.71.[20,26,27] In one trial that followed subjects for 6 months, 3 months after treatment discontinuation, the effect of the 3-month treatment course did not remain at 6-months, with 12% and 2% meeting abstinence criteria in the varenicline and placebo groups respectively.[26] Maintenance pharmacotherapy with varenicline in those who attained initial abstinence has shown promise and is discussed below.[31] In placebo-controlled and prospective trials of varenicline in smokers with schizophrenia conducted to date, varenicline has not been associated with worsening of psychiatric symptoms and is discussed further below.[20,26,27,51,52]

## Bipolar Disorder

Although half to three quarters of adults with bipolar disorder smoke cigarettes regularly,[5,6,53,54] few smoking cessation trials have been conducted in this group. Two small preliminary trials of bupropion and varenicline for smoking cessation had difficulty enrolling stable bipolar smokers and randomized 5 participants each.[55,56] In a recent smoking cessation treatment trial in stable, treated, outpatient smokers with bipolar disorder,

60 adult smokers were randomly assigned to double blind treatment with behavioral smoking cessation counseling and either varenicline or placebo for 12 weeks.[31,57] At the end of treatment, 36% of those assigned to varenicline and 10% of those on placebo attained 4-week continuous abstinence at end of treatment [OR = 4.8; 95% CI, 1.02–25.13; p = .03] (48% of those randomized to varenicline and 10% of those on placebo attained biochemically confirmed, 7-day point prevalence abstinence at the end of treatment). While varenicline added to CBT tripled 4-week continuous abstinence rates at the end of a standard 12-week course of treatment in smokers with bipolar disorder, the relapse rate in the varenicline arm was 60% within 3 months of discontinuation of pharmacotherapy, such that at 24 weeks 9% of those assigned to varenicline and 7% of those on placebo were abstinent.[57] Preliminary data on maintenance smoking cessation treatment in those with bipolar disorder is discussed below.

Fifty-four of the 60 participants (90%) had a lifetime history of suicidal ideation or behavior. Group-level data showed no evidence of psychiatric worsening in either group, and there were 6 serious adverse events in the varenicline group and 4 in the placebo group. There was a trend for more instances of treatment emergent depression in the varenicline group (n=8 of 31) than in the placebo group (n=2 of 29), and this difference was not a function of lifetime hospitalizations for depression. Weight gain was approximately 6 pounds in each condition across the study period.

With only one published RCT adequately powered to detect treatment efficacy in this population, there is currently inadequate data to form consensus guidelines for the treatment of nicotine dependence in people with bipolar disorder. However, in an online survey of 685 people with bipolar disorder who had smoked ≥100 cigarettes in their lifetime, 74% expressed an intention to quit smoking, while only 33% had been advised to quit by a mental health provider,[58] illustrating the unmet need for psychiatric treatment providers to advise and assist these smokers with cessation attempts. Emerging data suggests that mood symptoms remain relatively stable with smoking cessation in treated outpatients with bipolar disorder. In a naturalistic study in adolescent and adult smokers with bipolar disorder, mood stability did not differ for those who quit verses those who continued smoking over a randomly selected time period.[59] Psychiatric symptoms remained stable in a 52-week smoking intervention that included 20 smokers with bipolar disorder.[31]

Some smoking cessation studies in those with bipolar disorder have reported high screen fail rates.[55,56] For example, Weinberger and colleagues (2008) screened 204 smokers with bipolar disorder and determined 199 were ineligible (due to currently being on an antidepressant, not on a mood stabilizer, current drug use), 25 dropped out during screening and only 5 participants received study medication. With recent reports of psychiatric stability during smoking cessation attempts, perhaps studies can begin to enroll a more representative sample of smokers with bipolar disorder, including those who are taking antidepressant medications.

## Major Depressive Disorder

Smoking prevalence has been shown in numerous studies to be greater in those with major depressive disorders (MDD) than in the general population. While there have been many

studies of pharmacologic cessation aids in smokers with current or past depressive symptoms, nearly all of these studies have been conducted in community samples, excluding smokers requiring ongoing antidepressant or other psychotropic medications, and usually also excluding those with current MDD. These exclusion criteria have effectively excluded those smokers with more serious or chronic depressive illnesses likely to meet criteria for SMI. There have been no trials to our knowledge of smoking cessation treatments exclusively in smokers with recurrent MDD that would meet criteria for SMI.

Smokers with prior major depressive episodes, according to structured diagnostic interviews, have shown similar abstinence rates to those without MDD in treatment studies[60,61] suggesting that smokers with a prior history of clinically defined MDD can successfully stop smoking. Not surprisingly, smokers with current depression do not fare as well as non-depressed smokers in attaining abstinence,[62] and it is recommended that clinical treatment for depression be optimized before initiating a cessation attempt.

As a majority of those with recurrent MDD meeting functional criteria for SMI would likely be maintained on psychotropic medications, we have included in this review only studies in smokers with a confirmed DSM diagnosis of MDD, current or past, that did not exclude participants who were taking ongoing antidepressant medications. Thus, while these studies did not require participants to meet criteria for SMI, the population studied is more likely to include some with SMI and be more applicable to that population. Only three studies met this criterion.[18,29,63]

Hall and colleagues enrolled adults engaged in outpatient psychiatric treatment for clinically determined depression, 307 (95%) of whom met DSM-IV criteria for lifetime MDD, 268 (83%) for current MDD and 168 (52%) for recurrent MDD. Antidepressant medication use was not exclusionary. Participants were required to smoke 1 or more cigarettes per day and did not have to express a desire to quit smoking to participate. Participants assigned to the active intervention all received computerized motivational feedback at baseline and at 3, 6, and 12 months, and those who were interested in making a cessation attempt in the next 6 months (contemplation stage) were offered six 30-minute sessions of psychological counseling over 8 weeks together with transdermal nicotine patches (NRT) and the possibility of adding bupropion if NRT alone was ineffective. Control participants received a self-help guide and referral list of local smoking-treatment providers in the context of brief contact. Those assigned to active treatment were more likely to quit smoking (18% vs. 13% at 18 months), and smoked fewer cigarettes per day at the end of treatment. There were no significant relationships between abstinence and depressive symptoms as assessed with the Beck Depression Inventory (BDI), either as main or interaction effects.[18] Depressive symptoms declined significantly over time for both participants who stopped smoking and those who continued smoking, with no group differences, and those who quit smoking reported significantly lower alcohol use than those who continued smoking.[19]

Anthenelli and colleagues enrolled 525 smokers of 10 or more cigarettes per day who met DSM-IV criteria for unipolar MDD without psychotic features within their lifetime who had received treatment for an episode of MDD within the past 2 years, and randomly assigned them to 12 weeks varenicline or identical placebo together with brief individual behavioral

treatment.[29] Participants were required to be currently treated with a stable dose of an antidepressant medication or to have completed a documented successful course of antidepressant treatment within two years of enrollment, though use of bupropion, nortriptyline, medications for mania or psychosis, investigational drugs within the prior month, and previous use of varenicline was exclusionary. Of the participants enrolled, 378 (72%) were taking antidepressant medications during the study. Varenicline-treated participants were more likely to quit smoking than placebo-treated participants in all 3 periods evaluated, weeks 9–12, 36% vs. 16%; [OR, 3.35; 95% CI, 2.16 to 5.21; $p < .001$], weeks 9–24: 25% vs. 12%; [OR, 2.53; 95% CI, 1.56 to 5.21] and weeks 9 – 52: 20% vs. 10%; [OR, 2.36; 95% CI, 1.40 to 3.98; $p = .001$]. Thus, varenicline doubled continuous abstinence rates among stable smokers with current or recent MDD who were motivated to quit smoking. The relapse rate was 44% at one year in the varenicline arm. Both those assigned to varenicline and those assigned to placebo had reduction in both depression and anxiety ratings. The most frequent treatment-emergent adverse events (AE's) in the varenicline versus placebo groups were nausea (27% vs. 10%), headache (17% vs. 11%), abnormal dreams (11% vs. 8%), irritability (11% vs. 8%), and insomnia (11% vs. 5%). Depressed mood or depression was reported in 2% of those assigned to varenicline and 2.6% of those assigned to placebo. There was no treatment effect on incidence of suicidal ideation.

Van der Meer conducted a meta-analysis of smoking cessation trials in smokers with depression or depressive symptoms and reported subgroup analysis from large cessation trials that included a significant cohort of smokers with depression.[28] In one such trial, Piper and colleagues enrolled 1504 adult smokers, of which 259 had a lifetime diagnosis of MDD and 71 had past year depression. Neither current depression nor antidepressant use was exclusionary.[63] In the entire sample, abstinence rates at all time points were superior with NRT patch, lozenge, combination patch + lozenge and bupropion compared with placebo; and combination NRT was superior to NRT monotherapy. Among those with lifetime MDD, however, even though a third of participants attained abstinence, there were no significant treatment effects of any pharmacologic treatment arm (NRT monotherapy, combination NRT therapy or bupropion) compared with placebo. Seven-day point prevalence abstinence rates at the 6-month follow-up visit, 12 weeks after treatment discontinuation were 12/38 (32%) assigned to NRT lozenge, 14/46 (30%) assigned to NRT patch, 16/42 (35%) assigned to NRT patch + lozenge, 14/47 (30%) assigned to bupropion, 16/53 (30%) assigned to bupropion + NRT and 9/33 (27%) assigned to placebo. Abstinence rates at the end of the 12-week treatment were not reported.

## Duration of Treatment

Because of the high rates and rapidity of relapse observed after discontinuation of pharmacotherapeutic cessation aids in those with SMI, as well as the high smoking prevalence rates and greater severity of dependence than that observed in the general population, it has been postulated that smokers with psychiatric disorders may need maintenance pharmacotherapeutic treatment to achieve sustained abstinence needed to realize the substantial health benefits of smoking cessation.[16,24,31,57] Maintenance pharmacotherapeutic treatment has been reported to reduce relapse rates over maintenance

behavioral treatment alone among smokers with psychiatric illness in open,[30] single blind,[32] and double blind trials.[31] In a recent maintenance treatment / relapse prevention trial in 203 smokers with schizophrenia, schizoaffective or bipolar disorder, 87 (43%) attained at least 2 weeks abstinence at the end of a 12-week open label treatment phase with varenicline and group CBT and were randomized to continue CBT plus double blind varenicline or identical placebo for an additional 40 weeks. At week 52, the end of treatment, point-prevalence abstinence rates were 60% for those treated with varenicline and 19% for those treated with placebo. At week 64 and week 76 follow up visits, 45% and 30% respectively of those treated with varenicline were continuously abstinent versus 15% and 11% of those on placebo,[31] suggesting that maintenance smoking cessation pharmacotherapy may be highly beneficial in those with SMI.

A small cohort of 20 smokers with bipolar disorder was included in this maintenance varenicline trial.[31] In this trial, 9 of 20 smokers (45%) with bipolar disorder attained initial abstinence with 12 weeks of open label varenicline. Of these 9, 3 were assigned to 40 weeks of double blind varenicline and 6 to placebo added to a tapering schedule of group CBT. At 52 weeks, 3 varenicline treated smokers and 0 placebo treated smokers met criteria for 7-day point prevalence abstinence, [OR=20.3; 95% CI, 1.48 to infinity; p=0.01]. This finding suggests study of maintenance pharmacotherapy to improve sustained abstinence rates in smokers with bipolar disorder is warranted. Consonant with a chronic disease management model for tobacco dependence, more work is needed to determine not only optimal treatment type and intensity but also treatment duration for individuals with SMI.

## Behavioral Treatment

Clinical practice guidelines recommend treatment for all smokers with pharmacotherapeutic cessation aids combined with psychosocial or behavioral therapy,[34] and all of the studies reviewed here tested pharmacotherapy given in the context of a standard psychosocial treatment. These studies suggest that a concurrent psychosocial intervention may be necessary to observe the clinical benefit of pharmacotherapy in this population, but they were not designed to directly assess whether a psychosocial intervention is required, nor do they provide information on the most effective psychosocial interventions to treat smoking cessation in those with SMI. Unfortunately, there are no studies that have compared use of pharmacotherapeutic cessation aids with and without a psychosocial intervention. The few studies that have examined the efficacy of psychosocial interventions for smoking cessation in those with SMI[64–66]; reviewed in[21] support their benefit when combined with psychopharmacologic treatment but do not provide sufficient data to delineate the key components of the interventions.

Behavioral smoking cessation interventions for those with SMI have employed a range of treatment strategies including: educational (e.g., health risks of smoking, effectiveness of different treatment approaches, relationship between smoking and psychiatric symptoms), motivational enhancement (e.g., identifying personally relevant benefits of quitting, and costs of continuing to smoke) and cognitive-behavioral elements (e.g., identifying smoking triggers, developing coping strategies for these triggers, planning for high risk situations, relapse prevention). The optimal frequency, duration, and format (individual v. group) of

behavioral treatment and the active ingredients of these multi-component interventions remain unclear.

There has been a call for more work on use of incentives to reduce smoking and improve other health behaviors in people with SMI.[67] Contingency reinforcement for reduced cotinine but not for group attendance was associated with reduction in urine cotinine and expired carbon monoxide in one study in smokers with schizophrenia.[68] Some evidence suggests NRT combined with monetary reinforcement for lower expired CO concentration is superior to placebo + contingency reinforcement for smoking reduction among smokers with schizophrenia while contingencies are in place.[20] Inclusion of a mood management component may improve smoking outcomes among those with past or current depressive symptoms.[28,69]

## Treatment Adherence

Treatment adherence has been quite high (e.g. over 80% attendance at CBT group sessions) in treatment studies in combined samples of smokers with schizophrenia and bipolar disorder.[24,31,57] The majority of those who discontinue prematurely have not attained significant periods of abstinence.[23,24,29,31]

## Safety Issues

For smokers with schizophrenia, both bupropion and varenicline appear to be effective for smoking cessation and neither bupropion nor varenicline appear to increase risk of neuropsychiatric adverse effects over control treatments during a smoking cessation attempt, though the clinical trials performed to date were powered to detect efficacy and not safety with respect to rare adverse events (e.g.,[20,25,26,31,47]). In addition to concerns regarding the safety of specific medications, providers and patients may be concerned about whether smoking cessation worsens psychiatric outcomes or stability. To date, no study has identified abstinence as negatively impacting positive, negative, or depressive symptoms in people with schizophrenia.[22–26] Although several studies reported no effect of pharmacotherapeutic cessation aids or tobacco abstinence on extrapyramidal symptoms[22–24,64], one study in smokers with schizophrenia spectrum disorders reported increased muscle stiffness with bupropion plus NRT.[25] Because tobacco smoking is associated with increased hepatic clearance of many psychotropic drugs, particularly those metabolized by cytochrome P450 1A2 and 2E1,[70,71] 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.

In clinical trials of pharmacotherapeutic cessation aids in people with psychiatric illness, incidence of adverse events is often high, but not different in those assigned to active pharmacotherapy vs. placebo, as seen in trials of varenicline in those with schizophrenia[26] and depression.[29] Gibbons and Mann conducted a meta-analysis examining neuropsychiatric adverse events across 17 randomized clinical trials of varenicline with 1,004 people with psychiatric disorders and 7,023 people without psychiatric disorders.[52] In these trials, the rate of suicidal thoughts and behavior, depression, or aggression/agitation was no higher for

people assigned to varenicline than those assigned to placebo either during treatment or shortly after treatment discontinuation. A retrospective cohort study, commissioned by the FDA, conducted with Department of Defense (DOD) clinical records, reported in the same paper, compared 30-day and 60-day rates of neuropsychiatric events charted in approximately 20,000 people who used varenicline and 16,000 people who used the nicotine patch. Rates of neuropsychiatric disorders and neuropsychiatric adverse events were significantly lower overall in those prescribed varenicline than for those who had taken NRT.[52] Importantly, this chart review was conducted in records prior to the first FDA safety warning about varenicline, (August 1, 2006, to August 31, 2007), reducing the risk for selection bias and stimulated reporting of neuropsychiatric adverse events. Additionally, the study used propensity score matching to minimize the bias related to the differential selection effects for the two treatments.

Early reports raised a concern for increased risk for relapse to a depressive episode in smokers with past major depressive disorder, particularly recurrent MDD, who attained tobacco abstinence up to 6 months post cessation.[72–74] However, differential dropout by abstinence status in these studies conveyed risk for bias in ascertainment of this outcome and three more recent studies have reported that while the number and severity of prior depressive episodes was associated with risk for recurrence of MDD post cessation, this risk was independent of abstinence status.[75–77] Thus a prior history of MDD, and not recent smoking cessation, appears to be associated with risk for relapse to depression following a smoking cessation attempt.

Although the limited amount of safety data available for those with bipolar disorder severely limit our ability to draw conclusions, initial controlled studies do not provide a signal for abstinence or varenicline to be associated with worsening in psychiatric symptom severity or disease course[31,55–57,59].

## DISCUSSION

Despite gaps in the evidence, there is an adequate knowledge base to guide clinical decision-making for nicotine dependence treatment in people with schizophrenia spectrum disorders. Smokers with schizophrenia should be encouraged to use bupropion either alone or in combination with single, or dual-form NRT. Emerging evidence suggests that varenicline is effective for smoking cessation and well tolerated in smokers with schizophrenia. More research is needed in smokers with bipolar disorder and major depressive disorder. Varenicline has been effective and well-tolerated for short-term abstinence in the one published randomized controlled trial adequately powered for cessation outcomes in smokers with bipolar disorder and one trial in those with MDD to date.[29,57] Interestingly, early studies suggest that psychosocial treatment may be more effective in smokers meeting criteria for MDD[18,63] than in those with schizophrenia or bipolar disorder, where psychosocial treatment added to placebo has yielded extremely low cessation rates.[20,29,31]

Early work in the area of smoking cessation with comorbid psychiatric illness considered smoking reduction an important treatment goal, since it was unclear if people with SMI could quit smoking. Clinical trials now indicate that people with SMI can attain abstinence

at significant rates, often not differing from rates in trials of smokers without comorbid psychiatric illness. Smoking reduction may have a role for those not willing to try to quit smoking, but cessation should be the ultimate goal. Effectiveness studies are needed to evaluate cessation rates in real world settings.

Very little is known about the safety or efficacy of electronic cigarette use in this population. While electronic cigarettes are touted by some as potential smoking cessation aids, and one small open-label study of electronic cigarettes reported smoking reduction and psychiatric symptom stability at 52 weeks among smokers with schizophrenia not intending to quit,[50] it is not known whether e-cigarettes function to reduce harm from smoked tobacco or whether they delay smoking cessation attempts and allow for nicotine intake where smoking is not allowed, thus prolonging tobacco use and its attendant serious negative health effects.

One of the major take home points of our review of the literature is that outpatients with stable, treated SMI who quit smoking do not appear to suffer a worsening of their psychiatric symptoms when they quit smoking, either due to abstinence[19,59,75,77] or to pharmacotherapeutic cessation aids such as varenicline.[26,29,52] On the other hand, the risk of continued smoking is known. Half of smokers who do not quit will die from a smoking-related illness, and cessation before age 40 nearly abrogates that risk.[14,15] Those with SMI now die approximately 25 years prematurely, largely due to smoking-associated mortality.[9] The good news is that available pharmacotherapeutic cessation aids appear to be effective for smoking cessation in those with SMI; quitting smoking does not appear to jeopardize psychiatric symptom stability, and uncontrolled post-marketing reports of psychiatric worsening attributed to varenicline have not been supported by randomized controlled trials comparing neuropsychiatric adverse event incidence with varenicline to placebo or large-scale retrospective chart reviews comparing neuropsychiatric adverse event incidence with varenicline to nicotine patch.[26,29,33,52] Maintenance pharmacotherapy for one year has shown promise for longer-term abstinence in this population and appears to be well-tolerated in stable, treated outpatients.[31]

## CONCLUSION

People with SMI smoke with greater prevalence, die earlier due to smoking related illnesses but want to, can, and should be aided to quit smoking. Combined behavioral treatment and pharmacotherapy are effective for smokers with schizophrenia spectrum disorders, and we now have for the first time an evidence base to guide initial treatment of tobacco dependence in people with schizophrenia. While a number of treatment studies inform clinical practice guidelines for smoking cessation treatment in schizophrenia, far more work is needed in smokers who meet full criteria for MDD and for those with bipolar disorder, as well as those with severe PTSD and anxiety disorders who also meet criteria for serious mental illness, in order to establish an evidence base for clinical practice guidelines for smoking cessation treatment for these important subgroups of smokers. Future research is needed to address important questions such as the type of behavioral treatment that is helpful, treatment sequencing after initial treatment failure, and optimal duration of treatment for smokers with SMI. Psychiatric and primary care providers should optimize psychiatric treatment, recommend that all smokers in their care attempt to quit smoking, and aid cessation attempts

with pharmacotherapy combined with behavioral treatment, while monitoring psychiatric symptoms in an ongoing way.

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