mhc
MENTAL HEALTH CLINICIAN

REVIEW OF PHARMACOTHERAPY Open Access

Review of pharmacotherapy for smoking cessation in patients with schizophrenia

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How to cite: Shawen AE, Drayton SJ. Review of pharmacotherapy for smoking cessation in patients with schizophrenia. Ment Health Clin [Internet]. 2018;8(2):78-85. DOI: 10.9740/mhc.2018.03.078.

Abstract

Smoking cessation is a chronic issue surrounding individuals with schizophrenia. It is estimated that up to 90% of patients diagnosed with schizophrenia smoke cigarettes. The purpose of this article is to provide a nonsystematic review of the efficacy of smoking cessation interventions as well as to explore the potential neuropsychiatric adverse effects of these agents in patients with schizophrenia. Eighteen studies were found and included in the review. Overall, nicotine replacement therapy, bupropion, and varenicline have all proven their effectiveness at either promoting smoking abstinence or a significant reduction in cigarette use.

Keywords: schizophrenia, smoking cessation, bupropion, varenicline, nicotine replacement therapy

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Disclosures: The contributors have no disclosures of interest.

Introduction

Cigarette smoking is an epidemic that plagues the United States despite massive efforts to educate the public on its many dangers. It is estimated that one out of every six adults in the United States currently smokes.[1] Cigarette smoking is especially a concern among those diagnosed with mental illness with the prevalence being one in every five adults.[2] It is estimated that up to 90% of patients diagnosed with schizophrenia smoke cigarettes.[3] The purpose of this article is to provide a nonsystematic review of the efficacy of smoking cessation interventions as well as to explore the potential neuropsychiatric adverse effects of these agents in patients with schizophrenia.

Research has proposed that decreased nicotinic acetylcholine receptors (nAChRs) in certain brain regions may play a role in the pathogenesis of schizophrenia.[3] Nicotine functions in the brain by binding to nAChRs, stimulating the release of dopamine from neurons, which is thought to be reduced in patients with schizophrenia. Therefore, it is hypothesized that individuals with schizophrenia use nicotine as a way to self-medicate, potentially reducing the cognitive and negative symptoms of the disease.[4,5]

Another barrier faced by individuals with schizophrenia is the low success rate of smoking cessation attempts and overall decreased motivation to quit.[6] A study published in 2009 by Moss and colleagues[7] demonstrated that individuals with schizophrenia who were unsuccessful at quitting smoking had significant deficits in prefrontal cortex–related neuropsychological testing. This suggests that it may be more difficult for an individual with schizophrenia to achieve smoking cessation due to the structural and physiological abnormalities noted above as well as other factors such as affordability, access to care, and lifestyle.

It is estimated that patients with schizophrenia have a 20% reduction in life expectancy compared to the general population.[8] This reduction in life span is mostly attributed to respiratory and cardiovascular causes of death, both of which are perpetuated by cigarette use.[8]

Patients with schizophrenia have an increased risk of developing comorbidities, such as diabetes, hypertension, myocardial infarction, hyperlipidemia, and stroke over the general population.[9,10] All of these factors put patients with schizophrenia at an increased risk of death and complications, which is why an effective smoking cessation therapy is important.

Current pharmacotherapies that are Food and Drug Administration approved for smoking cessation are nicotine replacement therapy (transdermal patches, lozenges, gum, inhalers, nasal sprays), bupropion, and varenicline. Nicotine replacement therapy (NRT) functions as a direct agonist at nAChRs, providing the nicotine that is lost from a reduction in smoking.[11] Bupropion functions as a dopamine and norepinephrine reuptake inhibitor whereas varenicline is a partial nicotine agonist. The mechanism of bupropion for smoking cessation is not fully understood but is thought to be related to its ability to decrease dopamine and noradrenaline response to cessation of smoking, therefore decreasing nicotine withdrawal.[12] Varenicline functions at the nAChRs by preventing nicotine from binding to the receptor while still stimulating the receptor enough to get some release of dopamine at the presynaptic terminal.[13] These mechanisms allow for the addictive properties of smoking to have less of an effect over time, thus lessening the symptoms of nicotine craving and withdrawal. Many small studies have been conducted to determine the efficacy of these pharmacotherapies in schizophrenia because the mental health population has been excluded in the larger studies.

Methods

A literature search was conducted with the use of PubMed (limited to clinical trials) using medical subject headings (MeSH) and free text keywords: smoking cessation, bupropion, varenicline, nicotine replacement therapy, schizophrenia, psychotic, nicotine patch, and combinations of these phrases (MeSH terms used: smoking cessation AND schizophrenia AND nicotine replacement therapy, smoking cessation AND schizophrenia AND bupropion, smoking cessation AND schizophrenia AND varenicline, smoking cessation AND psychotic, schizophrenia AND varenicline, schizophrenia AND nicotine patch, schizophrenia AND bupropion). A total of 137 studies were found in the overall search criteria, and 18 studies were included. The remaining 119 studies were excluded (24 were duplicates, and the content of 94 studies was not pertinent). Scopus was utilized to confirm search results. Articles were included without regard to country of origin or study sample size. Patient age was not a specific exclusion criteria. Articles chosen included the mention of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria for diagnosis of schizophrenia or schizoaffective disorder, similar outcome measures (ie, exhaled carbon monoxide [CO], serum, and urine cotinine), analysis of adverse events, exacerbation of positive and negative symptoms of schizophrenia, and other neuropsychiatric side effects.

Results

Nicotine Replacement Therapy

Chou and colleagues[14] conducted a study to determine the effectiveness of nicotine patch therapy for smoking cessation in patients with schizophrenia. After 8 weeks, it was found that nicotine dependence, the number of cigarettes smoked per day, and exhaled CO levels were all lower to a point of statistical significance as compared to placebo.[14] Exhaled CO is easy to measure in a primary care setting and is a good indication of recent smoking activity based on its 5-hour half-life.[15] Continued abstinence was found at the 3-month follow up.[14] Dale Horst and colleagues[16] investigated the long-term effects of NRT with analyses at 3 months and 9 months. They found that 100% of patients on extended placebo therapy relapsed as compared to the 33% that were on active treatment. More recently, the varying doses of transdermal nicotine patches and their effect on smoking cessation were investigated in patients with schizophrenia.[17] It was found that there was no significant difference in a high-dose patch (31.2 mg) compared to the lower-dose (20.8 mg) patch and the effect on cessation.[17] There were no serious adverse events with this therapy that were attributed to the use of the transdermal nicotine patches other than dermal irritation.[14,16,17] More detailed results can be found in Table 1.

Bupropion

Bupropion has been studied extensively as an agent for smoking cessation. Studies[18-24] of the efficacy of bupropion on smoking cessation in patients with schizophrenia have produced conflicting data. George and colleagues[18] found a statistically significant decrease in overall smoking activity and reported 3 quitters with undetectable carbon monoxide levels as reflected in Table 1. Levels of plasma cotinine, a major metabolite of nicotine with a 16-hour half-life, were also assessed in a subset of patients from the same study.[18] Although not statistically significant, reduced cotinine levels were found in the bupropion group when compared to the placebo group.[18] A follow-up trial[19] of 17 individuals with schizophrenia showed that if individuals reduced their smoking activity during active treatment, then they would continue to do so after 2 years. A study by Evins and colleagues[24] showed a small (–4.2) decrease in positive schizophrenia and depressive symptoms on the Brief Psychiatric Rating Scale. Three studies[19,22,23] found no significance in sustained abstinence after cessation of treatment whereas 1 study[24] found significance in main-

TABLE 1: Comparison of outcomes of nicotine replacement therapy, bupropion therapy, and varenicline therapy versus placebo trials conducted in individuals with schizophrenia

Study and Intervention	Design	Cessation Outcomes	Safety
Chou et al[14] (2004) Nicotine patch (14 mg/d during weeks 1-6; 7 mg/d during weeks 7-8) vs PLA	n = 68 8 wk 3-mo follow-up Randomized, placebo controlled	• FTQ: NRT sig over PLA at end of first wk ($P < .0001$) and at 3-mo follow-up ($P < .0001$) • CPD: NRT sig over PLA at end of first wk ($P < .001$) and at 3-mo follow-up ($P < .0001$) • CO: NRT sig over PLA at end of first wk ($P < .0001$) and at 3-mo follow-up ($P < .0001$) • Abstinence rates: 6 of 26 subjects (23.1%) in NRT group abstinent at 3 months; 0% in PLA	None listed
Dale Horst et al[16] (2005) • Phase 1: NRT plus group therapy • Phase 2: NRT vs PLA	• Phase 1: n = 50, 3 mo • Phase 2: n = 18, 6 mo, single blind	• Phase 1: 18 achieved smoking cessation • Phase 2: All subjects (8/8) on PLA relapsed at 6 mo, 3 of 9 subjects on NRT relapsed ($P = .009$)	No correlation between NRT and adverse events
Chen et al[17] (2013) Nicotine patch (31.2 mg for first 4 wk then 20.8 mg for 4 wk vs 20.8 mg for 8 wk)	n = 184 8 wk Randomized, double blind, controlled	• CPD: Low-dose NRT reduced by 3.1 more cigarettes on average than high dose ($P = .005$) • Abstinence rates: No significance difference between groups ($P = .174$) • Nicotine dependence, CO levels, psychopathology: No sig differences	No sig difference in antipsychotic-induced EPS between groups
George et al[18] (2002) BUP 150 mg titrated to twice daily or matching PLA plus group therapy	n = 32 10 wk Double-blind, randomized	• BUP: Reduced CO ($P < .05$), reduced self-reported cigarette use ($P < .05$), reduced plasma cotinine levels ($P = .26$) • Trial end point abstinence in 3 quitters (BUP) with undetectable plasma cotinine	Reduction in negative sx with BUP ($P < .05$), no effect on positive sx or depression ($P = .27$)
Evins et al[19] (2004) BUP 150 mg/d All participated in CBT group for 9 wk	n = 17 Follow-up trial from Evins et al[24] (2001)	1 Abstinent at end of trial, 4 abstinent at end of 2 y ($P = .06$); 3 of these were in the BUP group Mean expired CO significantly lower for entire group ($P < .01$) 6/7 With sig reduction in smoking at end of trial maintained at least 50% reduction at 2 y (more likely to quit than those who did not significantly reduce smoking during trial; $P < .005$)	
Evins et al[23] (2005) BUP daily for 7 d then titrated to twice daily or matching PLA	n = 53 4 wk Randomized	• 7-d point prevalence abstinence: Week 4 BUP 36% and PLA 7% ($P = .016$), week 12 BUP 16% and PLA 0% ($P = .043$) • 3-mo follow-up abstinence: BUP (4%), PLA (3.6%) • Duration of abstinence: 3.05 wk (BUP), 0.7 wk (PLA); $P = .005$ • CO: Lower in BUP (0.029), not sustained in 3-mo follow-up • Reduction of cigarettes: 26.5 cigs (BUP), 10.2 cigs (PLA); $P = .002$ • 2 wk after treatment discontinuation, still sig BUP of cigs/d (0.018), but no longer sig after 6 wk	SANS scores decreased with BUP use ($P = .091$) Trend toward decreasing HDRS and PANSS with BUP

TABLE 1: Comparison of outcomes of nicotine replacement therapy, bupropion therapy, and varenicline therapy versus placebo trials conducted in individuals with schizophrenia (continued)

Study and Intervention	Design	Cessation Outcomes	Safety
Tidey et al[21] (2011) BUP 300 mg/d vs PLA, with or without CM	n = 57 22 d Double-blind, placebo controlled	CM+BUP and CM+PLA had lower CPD, CO, and cotinine ($P < .001$, $P < .01$, $P < .01$) NR+BUP and NR+PLA led to less compliance, less reported CPD but nonsignificant decrease in cotinine or CO	No difference between groups
Weiner et al[22] (2012)	n = 32 14 wk Randomized	• Sustained abstinence: BUP (4/22) compared to PLA (2/19), $P = .67$ • No overall treatment effect ($P = .29$)	No difference between groups with BPRS, SANS, positive/negative sx, anxiety or depression
Evins et al[24] (2001) BUP 150 mg/d vs PLA All participated in CBT group for 9 wk	n = 18 12 wk active treatment 6-mo follow-up Randomized, double-blind	Expired CO sig reduction in BUP ($P < .01$) at 12 and 24 wk ($P < .03$) 3 BUP and 1 PLA achieved abstinence on quit day No PLA subject achieved sustained abstinence 5 BUP and 1 PLA achieved sig reduction 3 BUP and 1 PLA maintained sig reduction	BPRS decreased in BUP and increased in PLA ($P = .03$), maintained this at 24 wk ($P = .02$) Depressive sx decreased in BUP ($P < .01$) Stable positive sx in BUP but increased in PLA ($P = .03$) but no difference at 24-wk follow-up Negative sx significantly reduced in BUP at week 4 ($P < .005$) and 8 ($P < .02$) and nonsignificant at week 12 ($P = .09$) No difference in EPS
Fatemi et al[20] (2005) BUP vs PLA	n = 10 8 wk Double-blind, crossover, randomized	• BUP: Reduction in exhaled CO, urine cotinine, and nicotine metabolites • PLA: Nonsignificant increases in all	BUP showed no increase in positive or negative sx when compared to PLA
Weiner et al[26] (2011) VAR vs PLA	n = 8 Double-blind, randomized, placebo controlled	VAR: 3/4 Individuals achieved sustained abstinence as measured by expired CO of <10 compared to placebo 0/4 ($P = .14$)	No difference in BPRS ($P = .29$), anxiety/depression score ($P = .99$), suicidal ideation remained absent throughout trial, no sig exacerbation of psychotic, depressive, or other psychiatric sx
Williams et al[31] (2012) VAR (0.5 mg daily for 3 d, 0.5 mg twice daily for 4 d, 1 mg twice daily for 11 wk) vs PLA	n = 127 12 wk Randomized, double-blind	• Week 12: 16/84 VAR achieved smoking cessation criteria, 2/43 PLA ($P = .046$) • Week 24: 10/84 VAR, 1/43 PLA maintained abstinence ($P = .09$)	Suicidal ideation: 6% VAR, 7% PLA ($P = 1.0$) Neuropsychiatric events: 36.9% VAR, 32.6% PLA
Meszaros et al[28] (2013) VAR (0.5 mg daily for 3 d, 0.5 mg twice daily for 4 d, 1 mg twice daily for 7 wk) vs PLA	n = 10 (only 4 completed) 8 wk 1-mo follow-up Randomized, double-blind, placebo controlled	• Cigarettes smoked per week decreased on average 47 in PLA and 66 in VAR ($P = .46$) • Cigarette cravings: 37% in VAR and 39% in PLA	Worsening anxiety only noted in PLA Passive suicidal ideation present in 1 patient in both VAR and PLA

TABLE 1: Comparison of outcomes of nicotine replacement therapy, bupropion therapy, and varenicline therapy versus placebo trials conducted in individuals with schizophrenia (continued)

Study and Intervention	Design	Cessation Outcomes	Safety
Smith et al[27] (2016) VAR (0.5 mg to 1 mg daily for 1 wk, then 2 mg daily for 7 wk) vs PLA	n = 87 intent to treat n = 68 completed 8 wk of study Randomized, double-blind, placebo controlled	Cigarettes smoked decreased ($P = .010$) CO levels ($P = .003$) Plasma nicotine levels decreased ($P = .045$) Plasma cotinine levels decreased ($P = .001$) Brief urge to smoke decreased ($P \leq .022$)	No effect on psychiatric rating scales
Evins et al[19] (2014) VAR (0.5 mg daily for 3 d, 0.5 mg twice daily for 4 d, 1 mg twice daily for 11 wk)	n = 203 (185 with schizophrenia spectrum disorder and 18 with bipolar disorder) 12 wk (open label), weeks 12 to 52 (relapse prevention intervention) Randomized, double-blind, placebo controlled, parallel group Weekly 1-h CBT sessions	• Relapse prevention intervention: 24 of 40 in VAR achieved 7-d point prevalence abstinence over 9 of 47 in PLA ($P < .001$) • Weeks 12-52: 18 of 40 in VAR achieved continuous abstinence over 7 of 47 in PLA ($P = .004$) • Week 76: 16 of 40 in VAR maintained abstinence an 5 of 47 in PLA ($P = .03$) • Time to relapse: VAR (358 days) sig over PLA (35 d; $P < .001$)	No effect of treatment on psychiatric sx or nicotine withdrawal sx

BPRS = brief psychiatric rating scale; BUP = bupropion; CBT = cognitive behavioral therapy; CM = contingency management; CO = exhaled carbon monoxide; CPD = cigarettes smoked/d; EPS = extrapyramidal side effects; FTQ = Fagerstrom test questionnaire; HDRS = Hamilton depression rating scale; NRT = nicotine replacement therapy; PANSS = positive and negative symptom scale; PLA = placebo; SANS = scale for assessment of negative symptoms; sig = significant; sx = symptoms; VAR = varenicline.

tained abstinence at 24 weeks. Bupropion is classified as an antidepressant agent and possesses the warning for increased risk of suicidality.[25] Yet many studies[20-22] have been conducted with bupropion in patients with schizophrenia with minimal neuropsychiatric side effects observed. Overall, bupropion has shown that it can be an effective smoking cessation tool in patients with schizophrenia, but more studies will need to be conducted to see if long-term bupropion is efficacious for sustained abstinence.

Varenicline

A small pilot study (n = 8) by Weiner and colleagues[26] showed that varenicline helped patients with sustained abstinence as measured by CO levels versus placebo. A larger study by Smith and colleagues[27] showed varenicline decreased the number of cigarettes smoked, CO levels, plasma nicotine and cotinine levels, and brief urges to smoke. Other data showed varenicline reduced the average number of cigarettes smoked per day over placebo[28] and a statistically significant longer length of smoking abstinence.[29] Varenicline for smoking cessation in individuals with schizophrenia has shown no difference between treatment and placebo groups for exacerbations or worsening symptoms of schizophrenia.[26-31] A study conducted by Williams and colleagues[31] showed a slightly higher increase in suicidality with the placebo group (7%) compared to the varenicline group (6%) with neuropsychiatric events being slightly higher with varenicline, none of which were statistically significant. A study conducted by Meszaros and colleagues[28] 2 years later also noted that depression and anxiety were worsened in the placebo group compared to the varenicline group. Altogether, varenicline has been shown to be an effective treatment option with limited adverse neuropsychiatric side effects.

Comparative and Combination Data

Two studies[32,33] found that nicotine replacement therapy is more efficacious when combined with bupropion than when used alone (Table 2). The combination of these 2 agents had no significant effect on positive or negative symptoms of schizophrenia.[33] When varenicline use was compared to bupropion, Fatemi and colleagues[34] found that there were no significant differences between the groups other than the varenicline group was more effective at lowering the urge to smoke in patients with schizophrenia.

Added Effectiveness With Antipsychotics

Some smoking cessation data suggest that second-generation antipsychotics enhance the effectiveness of bupropion or NRT. A study by George and colleagues[35]

TABLE 2: Comparisons and combinations of smoking cessation pharmacotherapies conducted in individuals with schizophrenia

Study and Intervention	Design	Cessation Outcomes	Safety
Fatemi et al[34] (2013) VAR vs BUP vs PLA	n = 17 12 wk Double-blind, placebo and bupropion controlled	• No significant reduction in number of CPD • Weeks 0-12: Trend for reduced serum and urine cotinine ($P < .09$; $P < .051$) in VAR over PLA; reduction in urge to smoke with VAR ($P < .05$) and BUP ($P < .044$)	No significant differences between groups in side effects Positive correlation with VAR and BPRS scores ($P = .014$), SAPS score ($P = .02$), and SAPS delusional score ($P = .013$)
George et al[33] (2008) BUP 300 mg/d (or PLA) plus NRT (21 mg/d) with CBT	n = 58 10 wk Double-blind, placebo controlled	• Abstinence at week 10: 34.5% (BUP) and 10.3% (PLA), $P = .056$ • Continuous abstinence (days 43-70): 27.5% (BUP) vs 3.4% (PLA), $P < .03$	No difference between groups on symptoms of schizophrenia No serious adverse events related to treatment
Evins et al[32] (2007) BUP 300 mg/d (or PLA) plus NRT with weekly CBT	n = 51 12 wk Double-blind, placebo controlled, randomized	• Abstinence: Higher in combo group at weeks 12 ($P = .036$) and 24 ($P = .039$) • CO: Mean 7.6 ppm lower in combo group from weeks 4-24 ($P = .006$) • 4-wk continuous abstinence: 52% Combo vs 19% on PLA ($P = .014$) • CPD: Mean decrease of 21 (BUP) and 11 (PLA)	Akathisia and EPS: Slightly reduced in BUP group and slightly increase in PLA No serious adverse events

BPRS = brief psychiatric rating scale; BUP = bupropion; CBT = cognitive behavioral therapy; CO = exhaled carbon monoxide; CPD = cigarettes smoked/d; EPS = extrapyramidal side effects; NRT = nicotine replacement therapy; PLA = placebo; SAPS = scale for the assessment of positive symptoms; VAR = varenicline.

found that individuals taking atypical antipsychotics in combination with the nicotine transdermal patch had greater abstinence rates than those taking typical antipsychotics alone. Evins and colleagues[23] noted that individuals taking atypical antipsychotics with bupropion had an overall reduction in expired air CO levels but not on abstinence rates versus those on typical antipsychotics alone. Two-year follow-up data published by Evins and colleagues[19] found that 4 individuals who were able to maintain abstinence, 3 on clozapine and 1 on haloperidol.

Drug Interactions

Cigarette smoke can induce cytochrome P450 isoenzyme 1A2, which increases the metabolism of certain antipsychotics.[3] For example, when patients decrease or stop smoking, serum levels of clozapine and olanzapine may increase.[3] Patients should be monitored closely for side effects of antipsychotics as smoking cessation ensues.

Safety

While bupropion and varenicline have been studied extensively as agents for smoking cessation, both agents have been linked to neuropsychiatric events. Individuals with schizophrenia have been commonly excluded from most large clinical trials of smoking cessation.[25,36] No studies included in this review resulted in significant neuropsychiatric adverse events related to smoking cessation treatment. The EAGLES trial was a large (n = 8114), double-blind, placebo-controlled trial in which the safety of NRT, varenicline, and bupropion were investigated in psychiatric versus nonpsychiatric patients.[36] Psychiatric disease states included mood disorders (major depressive disorder, bipolar disorder), anxiety disorders (panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia and generalized anxiety disorder), psychotic disorders (schizophrenia and schizoaffective disorder, borderline personality disorder). Of these individuals included, 386 were characterized as having a psychotic diagnosis. The study showed no statistical differences in neuropsychiatric adverse events in patients receiving active treatment in comparison to placebo.[37] In December 2016, the Food and Drug Administration removed the black box warning from the varenicline label about the risk of serious neuropsychiatric events and is updating the boxed warning on bupropion.[38]

Discussion

Nicotine replacement therapy, bupropion, and varenicline are all plausible options for smoking cessation in

individuals with schizophrenia. All of these agents were well tolerated in regards to neuropsychiatric events. Data[18,23,24,34] also show that bupropion and varenicline are effective in stabilizing the positive and negative symptoms that accompany schizophrenia. The relationship between bupropion or NRT and second-generation antipsychotics was also noted in which patients on both agents showed increased abstinence rates.[35]

In the combination and comparative studies,[32-34,39] it was found that varenicline may be superior to bupropion, and that combination therapy is more effective than single-agent therapy. This consequently leads to the notion that smoking cessation therapy in patients with schizophrenia is multidimensional with the need for more than 1 cessation medication to achieve sustained abstinence.

Sustained abstinence needs to be further studied in patients with schizophrenia. Current studies have found that many individuals relapse back into their previous smoking habits after discontinuation of smoking cessation pharmacotherapy. Long-term studies with extended use of both bupropion and varenicline, with or without NRT, could be beneficial in uncovering an effective course of therapy for these individuals.

It is important to keep in mind that these studies were very small and excluded many patients with unstable disease or comorbid substance abuse. This limits the generalizability of these studies to those individuals whose schizophrenia is well controlled on antipsychotics and who furthermore do not suffer from substance abuse, such as illicit drug use.

Drug-drug interactions should be kept in mind when initiating or stopping smoking cessation medications in patients with schizophrenia. Bupropion is a strong inhibitor of cytochrome P450 isoenzyme 2D6 (CYP2D6) as well as an organic cation transporter-2.[25] Serum levels of first-generation antipsychotics (eg, haloperidol) may be increased by concomitant bupropion use, and hence, these patients may require closer monitoring for side effects. Second-generation antipsychotics (eg, risperidone) may also be substrates of CYP2D6, which means that their use with bupropion should be closely monitored as well. It has been shown that nicotine can reverse the cognitive side effects of haloperidol use, and therefore, patients on haloperidol should be monitored closely for these side effects once smoking cessation is initiated.[40]

Certain patient-specific factors should be taken into account when choosing an agent, such as cost of pharmacotherapies, stability of disease, comorbid conditions, and patient compliance. Nicotine replacement therapy, bupropion, and varenicline are all effective smoking cessation therapies for patients with schizophrenia.

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