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A Review of Varenicline's Efficacy and Tolerability in Smoking Cessation Studies in Subjects with Schizophrenia

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Abstract

Schizophrenia is a severe psychiatric disorder affecting 1% of the world's population. Nicotine addiction is one of the most important health concerns for patients with schizophrenia. An extensive body of evidence points to a high prevalence rate of comorbid nicotine addiction in people with schizophrenia (70–90%), which contributes to significant cardiovascular and cancer risks in this vulnerable population. Therefore, effective smoking cessation strategies could play a major role in preventing significant morbidity and mortality in this population. Two of the most common pharmacological approaches to smoking cessation, bupropion and nicotine replacement therapy (NRT), have been used in psychiatric patients to reduce their smoking. In 2006, varenicline, a partial agonist of α4β2 acetylcholine receptor, was approved for smoking cessation by the FDA. This drug not only has the beneficial effects on withdrawal symptoms, but also reduces craving and rewarding effects of smoking. While varenicline has been shown to be an effective, safe medication for the general population, its efficacy and safety for subjects with schizophrenia is less well characterized. A number of case studies have prompted FDA warnings about the potential exacerbation of psychiatric symptoms. However, other case studies and pilot studies have shown varenicline to be a safe and effective treatment for smoking cessation in subjects with schizophrenia. Varenicline has the potential to reduce smoking in subjects with schizophrenia, however, clinicians should carefully monitor patients receiving varenicline for potential exacerbation of psychiatric symptoms.

Keywords

Schizophrenia; Schizoaffective disorder; Smoking cessation; Varenicline; Bupropion

Schizophrenia and Nicotine Addiction

Schizophrenia is a major debilitating and neurodevelopmental [1] disorder which affects an estimated 1% of the world's population. Subjects with schizophrenia present with a variety of characteristic symptoms, such as delusions, hallucinations, disorganized speech and

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behavior (positive symptoms), and/or affective flattening, poverty of thought, and avolition (negative symptoms) [2]. There is a high prevalence of substance abuse in subjects with schizophrenia [3,4]. Several reports find a strong association between smoking and schizophrenia with prevalence rates ranging from 74% [5] to as high as 90% [6–8], as compared to national average of 20% in individuals who do not have a diagnosis of schizophrenia [9]. Smoking cessation rates among patients with schizophrenia are considerably lower than for other psychiatric disorders [10,11]. Not surprisingly, people with schizophrenia have an increased risk for at least three of the most important respiratory diseases: Chronic obstructive pulmonary disease (COPD), pharyngeal cancer, and lung cancer [12–14]. However, others have found reduced rates of cancer among subjects with schizophrenia [15,16].

A number of hypotheses have been proposed to explain the relationship between high smoking rates and schizophrenia [7,17,18], mostly relating to self-medication. Dalack et al. [17] reviewed preclinical and clinical literature and suggested that subjects with schizophrenia were using nicotine as a way of self-medicating, primarily for the negative symptoms of schizophrenia [17]. Similarly, Patkar et al. [7] found significant correlations between smoking and negative symptoms, including blunted affect, social withdrawal, difficulty in abstract thinking, and stereotyped thinking. In contrast, they found no correlation to positive symptoms [7]. Other researchers have hypothesized self-medication of anxiety, depression, and psychotic symptoms [19,20], self-medication to reduce extrapyramidal side effects [5], and to enhance cognition and normalizing attentional and information processing deficits [20,21]. Patients who smoke require a higher dosage of antipsychotics because they metabolize their medication more rapidly than nonsmokers [22].

Psychosocial factors also influence the high rate of smoking in subjects with schizophrenia. Several social factors that increase the risk of smoking in this population are low educational attainment, unemployment, peer influence and the mental health care system [23]. It has been hypothesized that the rewards patients with schizophrenia receive from smoking, particularly the reduction of negative symptoms, might increase the patients' interactions with others, reducing feelings of isolation [22]. Others have pointed out that mental health settings, including group homes where other smokers live and where smoking is accepted, has possibly contributed to the increased rates of smoking [24]. Indeed, supplying cigarettes has been used to reward positive behavior in psychiatric treatment units [25]. It has only been recently that some psychiatric treatment facilities have begun to address smoking cessation strategies [23].

Nicotine has been shown to increase the release of dopamine in the nucleus accumbens and prefrontal cortex [26–28] via alteration in firing of ventral tegmental dopamine cells from a regular pattern to a burst-firing format. The consequent release of dopamine in nucleus accumbens has been associated with reward mechanisms in the brain [29–31]. Additional studies provide evidence for nicotine stimulation of dopamine release via activation of nicotinic receptors localized on dopaminergic neurons in the mesolimbic system [17], and smoking results in a reduction in activity of the monoamine oxidase B enzyme and the consequent decrease in degradation of dopamine in the brain [32]. Recent evidence [7] links high smoking rates with negative symptoms in subjects with schizophrenia. Negative symptoms are related to a hypodopaminergic state of the brain and are thus relieved by nicotinic stimulation of dopamine release via increased smoking. Finally, nicotine also enhances glutamatergic and GABAergic function in brains of subjects with schizophrenia [33] helping in better transmission of these neurotransmitters implicated in pathophysiology of schizophrenia.

Smoking Cessation Studies in Schizophrenia

Due to the use of nicotine for self-medication by patients with schizophrenia, it may be that the smoking cessation agents which work well for smokers that do not have a diagnosis of schizophrenia may have reduced efficacy among patients with schizophrenia who smoke. For the patients with schizophrenia who smoke and are unwilling or unable to quit, a smoking reduction approach may have benefits, as described by Dalack and Meader-Woodruff's study on the use of nicotine patch [10]. An alternative approach involves use of psychotropic medications, which affect the dopamine and norepinephrine systems. One such agent is bupropion HCl, a unicyclic aminoketone atypical antidepressant.

A number of reports [34–39], as well as a recent metaanalysis [40], now suggest that bupropion HCl is a safe medication for treatment of smoking in subjects with schizophrenia, although its effectiveness is inconclusive. Evins et al. [35] examined the effect of bupropion HCl combined with cognitive behavioral therapy (CBT) on smoking cessation. They found that subjects treated with bupropion HCl and CBT were more likely to be abstinent a week after the quit date, as well as four weeks of continuous abstinence [35]. Treatment with bupropion HCl also displayed a trend towards improvement in depressive and negative symptoms [35]. However, Evins et al. [35] found a high relapse rate at the end of treatment. More recently, a study by George et al. [38] found that smokers with schizophrenia that received bupropion HCl combined with transdermal nicotine patch were significantly more likely to achieve continuous smoking abstinence than those with the transdermal nicotine patch alone [38]. Importantly, the combination of bupropion HCl and transdermal nicotine patch was well tolerated by smokers with schizophrenia and did not alter positive or negative symptoms of schizophrenia [38].

Several studies have shown an impact of antipsychotics on the smoking behavior of subjects with schizophrenia. Haloperidol has been shown to increase smoking among subjects with schizophrenia and results in a worsening of some of the symptoms ameliorated by nicotine [41–43]. A report by de Leon et al. [44] has shown that, in contrast to earlier studies [45–46], clozapine had no significant effect on smoking cessation. Another study has shown that atypical antipsychotics combined with a nicotine patch had an enhanced rate of smoking cessation [47]. Moreover, George et al. [37] demonstrated that antipsychotic medication (clozapine, risperidone, or olanzapine) and bupropion HCl enhanced smoking cessation outcomes when compared to placebo [37].

Varenicline

Varenicline is a new smoking cessation aide that was approved by the FDA on May 11, 2006. Varenicline is a partial α4β2 and full α7 nicotinic acetylcholine receptor agonist. Animal studies have established that the α4β2 receptor is necessary and sufficient to establish nicotine addiction [48–52]. Stimulation of this receptor by its agonist causes a release of dopamine from the nucleus accumbens and prefrontal cortex [53]. In addition, studies of knockout mice suggested that α5, α7, and β4 acetylcholine receptor subunits have some essential roles in the expression of somatic signs of nicotine withdrawal, and that β2 subunits were instrumental in showing affective aspects of the nicotine withdrawal [48]. As a partial agonist of the α4β2 receptor, varenicline allows for the release of some dopamine, which causes a lessening of withdrawal and craving, while blocking the effects of nicotine in cigarette smoke.

To date, there have been several smoking cessation and maintenance of cessation studies [57–63] to test varenicline's efficacy. These studies have found varenicline to be more effective than placebo and bupropion as measured by consistently higher continuous abstinence rates both at the end of the initial study periods as well as up to a year following

the end of treatment. Furthermore, subjects on varenicline reported reduced craving, withdrawal symptoms, and smoking satisfaction when compared to subjects on nicotine replacement therapy [54,64].

Nausea has been reported as the most common side effect with varenicline [57,59]. Other common side effects include sleep disturbance and constipation [65]. A recent case study has shown that varenicline may trigger severe hyperglycemia in subjects with Type 1 diabetes suggesting that further investigation of the use of varenicline in subjects with diabetes is warranted [66]. Also, a review study has documented 78 adverse events related to aggression/ violence associated with use of varenicline including assault (10 events), homicidal ideation (nine events), and other thoughts or acts of violence and aggression (seven events) [67]. Of these cases, 93% of them were resolved following discontinuation of varenicline [67]. Finally, the FDA has recently issued a statement that "varenicline may be associated with a small increased risk of certain cardiovascular adverse events" in patients with cardiovascular disease [68]. Table 1 summarizes physical side effects associated with varenicline in selected publications.

Thus far, there are no published studies that have shown an interaction between varenicline and antipsychotic medications. Indeed, varenicline's pharmacokinetic properties suggest that there would not be an interaction with antipsychotic medications. It has been demonstrated that 92% of varenicline is excreted unchanged in urine [69]. In vitro studies in human liver microsomes have demonstrated that varenicline does not induce or inhibit human cytochrome P450 activities, thus having no effect on CYP1A2, CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A [70]. Therefore, it is unlikely that varenicline would interact with any medication that is primarily cleared by P450 enzymes. Consequently, drugs like clozapine and olanzapine, that are primarily cleared by CYP1A2 [71], and haloperidol, perphenazine, risperidone, thioridazine, and zuclopenthixol, that are cleared by CYP2D6 [71], are unlikely to interact with varenicline. It is important to emphasize, however, that as a result of smoking cessation, plasma levels of CYP1A2 metabolized drugs may increase to potentially toxic levels [72,73]. Therefore, it is important for clinicians to carefully monitor plasma levels of these drugs for patients undergoing treatment with varenicline or other smoking cessation programs.

Varenicline and Schizophrenia

The use of varenicline to treat smokers with schizophrenia and other psychiatric disorders has been and continues to be considered controversial due to a number of case studies and a small pilot study which showed exacerbation of psychiatric symptoms including psychosis, mania, anxiety, and depression [74–83] (Table 2). An FDA warning, issued February 1, 2008, stated that serious neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide, have occurred in patients taking varenicline [84]. Because of these case studies and the FDA warning, it is important that people with schizophrenia receiving outpatient care receive close monitoring, especially early in treatment, to ensure that there are no physical or psychiatric side-effects are manifested as a result of varenicline.

A recent study involving subjects without psychiatric illnesses found no difference between subjects receiving placebo and subjects receiving varenicline on measures of depression, anxiety, or aggression and hostility [85]. Additionally, separate case studies have found that varenicline was effective in reducing smoking in individuals with schizophrenia with no exacerbation of symptoms [86,87]. Moreover, a case series showed lack of worsening in psychosis in 13 subjects with schizophrenia successfully treated with varenicline [88]. Finally, a study by Stapleton et al. [89], has demonstrated that there is no exacerbation of

symptoms of mental illness in subjects diagnosed with depression, bipolar disorder, psychosis, psychosis and depression, and eating disorders following treatment with varenicline combined with group support.

More recently, a number of pilot studies have examined the efficacy and safety of varenicline for subjects with schizophrenia (Table 2). Smith et al. [90] found that treatment with varenicline led to some cognitive improvement as measured by RBANS subscores for list learning, list recall, and language index. The same patients significantly reduced the number of cigarettes smoked as well as reduced CO expired and cotinine levels [90]. A small pilot study comparing varenicline to placebo in subjects with schizophrenia (n=4 each) found significantly increased smoking abstinence, verified by significantly lower carbon monoxide levels, in subjects in the varenicline group following 12 weeks of treatment [91]. Importantly, varenicline had no effect on psychotic, depressive, or other psychiatric symptoms [91]. Similarly, a study involving patients with schizophrenia undergoing a mandatory smoking cessation intervention showed that patients receiving varenicline had no exacerbation of depression or anxiety [92]. A larger study of 53 subjects with schizophrenia treated with varenicline and cognitive behavioral therapy (CBT) for 12 weeks found that 60.4% attained 14-day point prevalence abstinence at week 12, which was verified by significantly reduced expired CO [93]. Varenicline treatment has recently been shown to improve executive function and reduce startle reactivity, regardless of smoking status in subjects with schizophrenia [94]. Moreover, gradual titration of varenicline did not lead to increased psychosis, suicidal ideation, or depression [94]. Thus, emerging data suggests that varenicline has the potential to be safe and effective for subjects with schizophrenia. However, large-scale controlled studies are needed to provide a more accurate picture of varenicline's efficacy and safety in subjects with schizophrenia.

The efficacy of varenicline in subjects with schizophrenia may be related to its effect on induction of dopaminergic signaling and on induction of gene expression. Dutra et al. [93] found that subjects with lower baseline scores of affective flattening were more likely to attain abstinence with varenicline and CBT. Studies have shown that affective flattening is related to dysfunction of the dopamine D2 receptor (DRD2) [95], while in a rodent model, varenicline has been shown to increase DRD2 binding in striatum [96]. Thus, the authors posit that striatal DRD2 stimulation by varenicline may be one way in which it aids smoking cessation [93].

While the recent studies cited above provide preliminary evidence that varenicline may be safe and effective for subjects with schizophrenia, concerns remain regarding possible exacerbation of psychiatric symptoms such as mania, psychosis, and suicidal ideation. Clinicians are advised to carefully discuss the pros and cons of varenicline treatment with their patients who wish to reduce or quit smoking and to closely monitor patients for any changes in behavior. Finally, a recent review has indicated an increase in suicidal ideation in subjects treated with varenicline [109].

Conclusions

Nicotine addiction remains an important health concern for subjects with schizophrenia due to the resulting increased morbidity and mortality in this population. Smoking cessation strategies in subjects with schizophrenia using nicotine replacement therapy or bupropion have been inconclusive. Due to its success in the general population, varenicline has the potential to dramatically increase smoking cessation and improve the overall health of subjects with schizophrenia. A number of case studies have demonstrated adverse psychiatric changes in healthy as well as patients diagnosed with mental illness as a result of treatment with varenicline. Other studies, however, have found no psychiatric side-effects.

Careful monitoring of patients with schizophrenia receiving varenicline by clinicians is warranted. There are currently few controlled studies of varenicline to determine its safety and efficacy in subjects with schizophrenia. Further large-scale studies are required, as well as research into varenicline's mode of action to determine if widespread use in this population is warranted.

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Table 1

Commonly reported physical side effects of varenicline.

Study	Population	Dosage	Side Effects (including percentage experiencing a given side effect)
Boudrez et al. [56]	Non-psychiatric	Not specified	Nausea (8.9%), insomnia (2.9%), and sleep disorder (2.2%)
Gonzales et al. [57]	Non-psychiatric	1 mg BID	Nausea (28%), insomnia (14%), dry mouth (6.7%), headache (15.5%), and dizziness (6%)
Jorenby et al. [59]	Non-psychiatric	1 mg BID	Nausea (29.4%), insomnia (14.2%), abnormal dreams (13.1%), headache (12.8%), and dry mouth (5.5%)
Nides et al. [61]	Non-psychiatric	1 mg BID	Nausea (52%), insomnia (35.2%), headache (24%), abnormal dreams (15.2%), and taste perversion (15.2%)
Garza et al. [85]	Non-psychiatric	1 mg BID	Nausea (37.7%), insomnia (30.9%), somnolence (20%), and abnormal dreams (9.1%)
Evins and Goff, [88]	Schizophrenia	1 mg BID	Nausea and vomiting (21.1%)
Stapleton et al. [89]	Depression, bipolar disorder, psychosis, psychosis and depression, eating disorders	Not specified	Nausea (32.1%), and sleep disturbances (32.1%)
Smith et al. [90]	Schizophrenia, schizoaffective	1 mg BID	Mild nausea, shaking, dry mouth, and tiredness-sleepiness (57% of all patients experienced at least one side effect)
Weiner et al. [91]	Schizophrenia	1 mg BID	Constipation (50%), insomnia (75%), and nausea (75%)
Liu et al. [92]	Schizophrenia	1 mg BID	Nausea (10%), vomiting (10%), fatigue (5%), dry mouth (5%), muscle stiffness (5%), and headache (5%)
McClure et al. [97]	Depression	1 mg BID	Tension/agitation (51%), nausea (61.6%), sleep disturbance (46.4%), irritability (47.1%), confusion (19.3%), and difficulty concentrating (33.4%)
Philip et al. [98]	Depression	1 mg BID	GI problem (21.4%), sleep disturbances, and irritability (7.1%)
Tonstad et al. [99]	Non-psychiatric	1 mg BID	Sleep disturbance (19.9%)

GI: Gastrointestinal

Table 2

Psychiatric side effects of varenicline.

Study	Underlying disorder (N)	Methods and Dosage	Outcome	Concomitant medication
Ahmed et al. [74]	Bipolar disorder (1)	Case report; Duration: 7 days (1mg/day)	Acute manic episode	mianserin (90 mg/day), oxazepam (10 mg/day), acetylsalicylic acid (80 mg/day), barnidipine (20 mg/day), hydrochlorothiazide (12.5 mg/day), perindopril (8 mg/day) and rosuvastatin (5 mg/day)
Francois et al. [75]	None (1)	Case report; Duration: 7 days (dose not specified)	Grandiose delusions, agitation, insomnia, rapid speech	None
Freedman, [76]	Schizophrenia (1)	Case report; Duration: 5 days (1 mg BID)	Exacerbation of psychotic symptoms	Thiothixene (10–15mg/day)
Hussain et al. [77]	History of mild depression (1)	Case report; Duration: approximately three weeks (0.5mg/day)	Manic episode	Oxycodone (up to 12 pills/day), diazepam (10mg/day)
Ismail et al. [78]	Schizophrenia (1)	Case report; Duration: 20 days (1 mg BID)	Significantly reduced smoking and self-reported craving to smoke. Polydipsia and hyponatremia	Depot risperidone (25mg/2 weeks)
Kohen and Kremen, [79]	Bipolar disorder (1)	Case report; Duration: 7 days (2mg/day)	Exacerbation of manic episode	valproic acid (dose not specified)
Morstad, [81]	Bipolar II disorder, poly-substance abuse (1)	Case report; Duration: approximately one month (2mg/day)	Hypomanic episode with suicidal ideation	bupropion XL (300 mg/day), clonazepam (1 mg/day), oxcarbazepine (450 mg/day), quetiapine (100 mg/day), montelukast (10 mg/day), pantoprazole (40 mg/day)
Popkin, [82]	Major depression (1)	Case report; Duration: 6 weeks (2mg/day)	Hypersomnia, unusual dreams, decreased appetite, irritability, sadness and guilt	Fluoxetine (20mg/day), aspirin, niacin and metoprolol
Waldo et al. [83]	Schizophrenia (6)	Pilot study; Duration: 2 hours (1 mg, once)	Varenicline did not improve P50 gating. Study discontinued due to emergence of suicidal ideation, aggressive, erratic behavior	Atypical APDs
Anghelescu, [86]	Schizophrenia (1)	Case report; Duration: 2 weeks (1 mg BID)	Complete abstinence confirmed with expired CO level, improvement of negative symptoms 45 to 22 via PANSS	Depot risperidone (37.5mg/2 weeks)
Fatemi, [87]	Schizophrenia (1)	Case report; Duration: >24 weeks (1 mg BID)	Meaningful reduction in number of cigarettes smoked	Clozapine (700mg/day) and citalopram (40 mg/day)
Evins and Goff, [88]	Schizophrenia (16)	Case series; Duration: 12 weeks (1 mg BID)	Reduced craving to smoke, 13 patients quit smoking (expired CO level <9 ppm), self-reported abstinence ≥ 12 weeks	Various antipsychotics
Smith et al. [90]	Schizophrenia (9); Schizoaffective (3)	Case series; Duration: 9 weeks (1 mg BID)	Significant decrease in plasma cotinine ($p < 0.01$), expired CO level ($p < 0.05$), self-reported smoking urges, number of cigarettes smoked and	Various antipsychotics

Study	Underlying disorder (N)	Methods and Dosage	Outcome	Concomitant medication
			nicotine level. Improvement in some cognitive test score	
Weiner et al. [91]	Schizophrenia (8)	Double blind randomized trial; Duration: 12 weeks (1 mg BID)	Sustained abstinence and significant reduction in CO level <10 ppm (p=0.02) in Varenicline group	Atypical antipsychotics
Dutra et al. [93]	Schizophrenia or Schizoaffective disorder (53)	Trial combined with CBT; Duration: 12 weeks (1 mg BID)	60.4% attained abstinence, significantly reduced CO levels (p<0.001) compared with baseline	Various antipsychotics
Pirmoradi et al. [100]	Alcohol abuse and MDD (1)	Case report; Duration: 7 days (1mg/day)	Experience of severe anxiety	eszopiclone (2 mg/day), fluoxetine (20 mg/day), bupropion hydrochloride (300 mg/day), lisinopril (10 mg/day) and hydrochlorothiazide 12.5 mg/day)
Pumariega et al. [101]	MDD (1)	Case report; Duration: 90 days (dose not specified)	Creation of manic episode	Sertraline (dose not specified)
DiPaula and Thomas, [102]	Bipolar disorder (1)	Case report; Duration: 2 days (2mg/day)	Exacerbation of psychotic symptoms and agitation	Haloperidol, olanzapine, lorazepam and diphenhydramine (dose not specified)
Liu et al. [103]	Schizoaffective disorder (1)	Case report; Duration: 13 days (dose not specified)	Exacerbation of mania episode with psychotic features	clothiapine (160 mg/day) and lithium (1,200 mg/day)
Lyon, [104]	MDD, GAD, BLPD and marijuana use (1)	Case report; Duration: One month (2mg/day)	Paranoia and irritability	Topiramate (200 mg/day), duloxetine (120 mg/day), modafinil (400 mg/day) and clonazepam (2mg/day)
Alhatem et al. [105]	Bipolar and Adult ADHD disorder (1)	Case report; Duration: 2 weeks (dose not specified)	Exacerbation of mania	Quetiapine and amphetamine salts (dose not specified)
Kutscher et al. [106]	None (1)	Case report; Duration: 10 weeks (dose not specified)	Paranoia, anxiety and suicidal ideation	Oral contraceptive
Raidoo et al. [107]	PTSD, depression, alcohol dependence (1)	Case report; Duration: 19 days (2mg/day)	Visual hallucination	fluoxetine (20 mg/day), nortriptyline (25 mg/day), quetiapine (50 mg/day), prazosin (1 mg/day), pramipexole (0.5 mg/day), terazosin (5 mg/day), atenolol (50 mg/day) and spironolactone (50 mg/day)
Cinemre et al. [108]	Brief episode of atypical psychosis (1)	Case report; Duration: 30 days (dose not specified)	Creation of psychotic symptoms	None

ADHD: Attention deficit hyperactivity disorder; BLPD: Borderline personality disorder; GAD: Generalized anxiety disorder; MDD, Major depressive disorder; PTSD, post-traumatic stress disorder.