Does Varenicline Worsen Psychiatric Symptoms in Patients With Schizophrenia or Schizoaffective Disorder? A Review of Published Studies

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ABSTRACT

Objective: To review published cases and prospective studies describing the use of varenicline in patients with schizophrenia and schizoaffective disorder.

Data Sources: PubMed, PsychINFO, and the Cochrane Database were searched in July 2011 using the key words *schizophrenia, schizoaffective disorder, psychosis, positive symptoms, negative symptoms, aggression, hostility, suicidal ideation* AND *varenicline* to identify reports published between January 2006 and July 2011 in English.

Study Selection: Five case reports, 1 case series, 1 retrospective study, 10 prospective studies (17 publications), and 1 meeting abstract describing the use of varenicline in patients with schizophrenia or schizoaffective disorder were identified. Review articles and articles describing findings other than the use of varenicline in patients with schizophrenia or schizoaffective disorder were excluded. Thirteen reports were included in the final analysis.

Data Extraction: Information on each study's patient population, age, diagnosis, medication treatment, tobacco use history, adverse effects, and outcome was collected from the published reports.

Results: Of the 260 patients with schizophrenia or schizoaffective disorder who received varenicline in these published reports, 13 patients (5%) experienced the onset or worsening of any psychiatric symptom, although 3 of the 13 patients experienced a very brief negative effect after 1 dose. No patients experienced suicidal ideation or suicidal behaviors.

Conclusions: Published reports suggest that, in most stable, closely monitored patients with schizophrenia or schizoaffective disorder, varenicline treatment is not associated with worsening of psychiatric symptoms. Current, prospective studies are assessing effectiveness and further assessing safety in this population.

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Patients with psychiatric disorders commonly use tobacco.[1] The prevalence of smoking among patients with psychiatric illness ranges from 40% to 60% in patients with major depressive disorder to as high as 88% in patients with schizophrenia, compared to a prevalence of 19.8% in the general population.[1,2] Reducing patients' use of cigarettes is crucial, as the most common preventable diseases in the United States are related to smoking.[3] Abstinence from tobacco could be even more critical for patients with schizophrenia, as these patients already have a shortened life expectancy due partly to the substantial burden of cardiometabolic risk factors and disorders they experience and to problems in health service delivery and utilization.[4,5]

Interventions for tobacco use disorders include motivational interviewing and other psychotherapeutic approaches, nicotine replacement therapy, and medication therapy specifically targeting smoking cessation.[6] Despite the high prevalence of smoking in this population, patients with psychiatric illness are often excluded from studies evaluating strategies for smoking cessation.[7] This is unfortunate, as many patients with psychiatric disorders want to quit smoking.[8] More recently, studies looking at interventions for tobacco use both alone and in combination have included patients with schizophrenia and other severe mental illness.[9] The results show many patients with schizophrenia continue smoking, even after numerous interventions targeting tobacco cessation have been implemented.[9] For example, in 1 study of patients with schizophrenia treated with 12 weeks of bupropion and cognitive behavior therapy, 66% of patients reduced overall tobacco use, but only 11% achieved abstinence from tobacco at the 6-month follow-up.[10] At the 2-year follow-up, 22% of patients originally enrolled in the 12-week treatment trial ultimately achieved abstinence, while 78% of patients continued to smoke.[11] These results suggest that additional interventions may be needed to treat the remaining patients using tobacco.[12]

Varenicline is a nicotinic acetylcholine $\alpha_4\beta_2$ receptor partial agonist and an α_7 full agonist with US Food and Drug Administration (FDA) approval for the treatment of tobacco dependence.[13] Varenicline is administered orally and is usually initiated at 0.5 mg daily for 3 days, followed by 0.5 mg twice daily for 4 days, then 1 mg twice daily on day 8 through week 12, which is the usual target dose and treatment duration, although some patients can remain on varenicline therapy for longer durations.[13] Nausea is the most common adverse effect of varenicline dosing, with 30% to 50% of treated patients experiencing nausea at the target dose of 1 mg by mouth twice daily. This effect can be lessened with dose reduction or coadministration with food.[13] Paralleling the course of other tobacco cessation strategies, Phase III clinical studies of this medication excluded those with underlying psychiatric illness[14,15] and focused on maintaining abstinence from tobacco.[16] Varenicline was found to be effective in treating tobacco dependence and superior to other treatments.[7,14–16] Spurred by these promising findings in the general population, investigators and clinicians began using varenicline in patients with psychiatric disorders. However, concern about the use of varenicline and other antismoking agents in patients with psychiatric disorders developed when researchers and clinicians noted

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Clinical Points

- In most stable, closely monitored patients with schizophrenia or schizoaffective disorder, varenicline treatment is not associated with worsening of psychiatric symptoms.
- Over half of patients with schizophrenia or schizoaffective disorder and tobacco dependence reduced daily cigarette use after treatment with varenicline.

the association of varenicline initiation or discontinuation with psychiatric symptoms (eg, hostility, aggression, psychosis) and suicidal behavior in some patients, prompting the FDA to issue a black box warning in July 2009.[17] Some of the original reports were of the emergence of psychiatric symptoms in patients without previously diagnosed mental illness,[18,19] although other reports described worsening or onset of symptoms in patients with chronic psychiatric disorders.[20–24]

A subsequently published Cochrane Review[25] of studies published through October 2010 on the effectiveness of nicotine receptor partial agonists (eg, varenicline) in treating tobacco dependence in the general population noted that "possible links with serious adverse events, including depressed mood, agitation and suicidal thoughts, have been reported but are so far not substantiated."[25(p4)] Harrison-Woolrych and Ashton[26] obtained survey data on patient self-reported psychiatric adverse effects for 1,394 of 3,415 patients prescribed varenicline for smoking cessation in New Zealand between April 2007 and March 2008. The authors found that 56 people (4.3%) experienced insomnia, the most common adverse effect, 39 people (2.98%) reported symptoms of depression, and 6 people (0.18% of the total cohort) reported self-harm events (1 fatal and 5 nonfatal).

Recently, Moore et al[27] reviewed serious case reports from the FDA's Adverse Event Reporting System (AERS) to examine the comparative safety profiles of varenicline, bupropion, and nicotine replacement products compared to commonly prescribed antibiotics (comparison group) on suicidal behavior and depression. Overall, the investigators found that, of 13,243 reported cases of adverse effects associated with 1 of the 3 smoking cessation interventions, 3,249 (25%) were of suicidal behavior or depression. In comparison, the antibiotic groups had 4,047 cases of reported adverse effects, of which 48 (1%) were reports of suicidal behavior or depression. Ninety percent (2,925 cases) of the cases from the smoking cessation group were reported in association with varenicline. Patients attempting tobacco cessation who received varenicline were more than 8 times as likely (odds ratio [OR] = 8.4, 95% CI, 6.8–10.4) to be reported as having experienced suicidal behavior or depression compared to nicotine replacement therapy and almost 3 times as likely (OR = 2.9, 95% CI, 2.5–3.4) compared to bupropion. The authors concluded that their findings "render [varenicline] unsuitable for first-line use in smoking cessation."[27(p1)]

Of the Cochrane Review, the New Zealand review, and the FDA AERS review, none focused on the population of patients with schizophrenia receiving varenicline, leaving clinicians uncertain about the risk of using this agent in this population. To our knowledge, no published article has reviewed the reports on the use of varenicline in this group of patients. Our aim is to review the existing literature on the use of varenicline in patients with schizophrenia or schizoaffective disorder and to determine how commonly these patients experience worsening psychiatric symptoms in association with varenicline treatment.

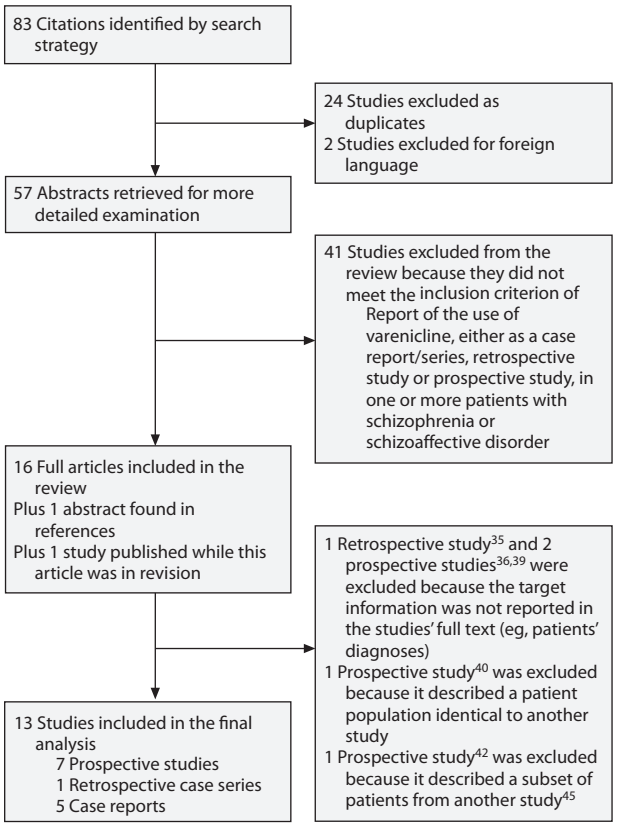
METHOD

We searched Medline, PsychINFO, and the Cochrane Database in July 2011 using the following term combinations: *schizophrenia*, *schizoaffective disorder*, *psychosis*, *positive symptoms*, *negative symptoms, aggression, hostility, suicidal ideation* AND *varenicline* to obtain case studies, case series, retrospective studies, and prospective studies of the use of varenicline in patients with schizophrenia or schizoaffective disorder published between January 2006 and July 2011. We identified articles describing the use of varenicline in patients with schizophrenia or schizoaffective disorder. Studies examining the use of varenicline as a tobacco cessation agent as well as studies examining the role of varenicline in treating other symptoms of schizophrenia or schizoaffective disorder (eg, cognitive symptoms) were included. We excluded review articles, articles in languages other than English, and articles describing findings other than those related to the use of varenicline in patients with schizophrenia or schizoaffective disorder. Resulting abstracts were searched for studies describing the use of varenicline in patients with schizophrenia or schizoaffective disorder. Full articles were then retrieved, and the references of these articles were searched for additional reports fulfilling our criteria. Relevant information (patient population, age, diagnosis, medication treatment, tobacco use history, adverse effect, and outcome) was collected from each published report. For case reports of adverse effects, the Naranjo Adverse Drug Reaction (ADR) Probability Scale[28] was used (using the information reported in the published case reports) to assess the probability that the reported adverse effect was caused by varenicline. Patient characteristics and outcomes were extracted from each report.

RESULTS

Our process for study selection is shown in Figure 1. Our search yielded 5 case reports,[29–33] 1 case series,[34] 1 retrospective study,[35] and 9 prospective studies[36–44] (16 publications) describing cases or studies examining the use of varenicline in patients with schizophrenia or schizoaffective disorder. One additional prospective study presented in a meeting abstract[45] was identified by examining the references of these publications. One study[46] was also identified while this

Figure 1. Selection of Reported Studies From the Literature Search



article was undergoing revision, making the total number of studies 18. Five of these 18 studies were excluded from the analysis for reasons described in Figure 1, leaving us with 13 total studies for analysis. The results of our search and data extraction are shown in Table 1.

Case Reports

Three case reports described varenicline-associated adverse effects in patients with schizophrenia or schizoaffective disorder and tobacco dependence.[29,31,33] All cases reported the onset of adverse effects subsequent to varenicline dosing. Freedman[29] described the worsening of psychotic symptoms over a 5-day time course in an ambulatory woman with schizophrenia. Based on the reported information, an ADR score of 2 was assigned to this case. Total scores greater than 9 on the Naranjo ADR Scale are considered a *definite adverse drug reaction*, scores from 5 to 8 are *probable*, scores of 1 to 4 are *possible*, and scores less than or equal to 0 are *doubtful*. Another report described the development of mania over 13 days in a man with schizoaffective disorder ultimately resulting in his transfer from a chronic care ward to a more acute care ward.[31] The third report described worsening paranoia and delusions over 18 days and the onset of polydipsia in a hospitalized man with schizophrenia in association with varenicline therapy.[33] The second and third case reports also received an ADR score of 2 based on the reported information.

Two case reports[30,32] reported tolerability of varenicline in 2 patients with schizophrenia and tobacco dependence.[30,32] The first case described a male clinic patient with schizophrenia who reduced his tobacco use from 40 cigarettes daily to 5 cigarettes daily after two-and-a-half months of varenicline therapy and maintained this reduced tobacco use for 1 year after 24 weeks of treatment with varenicline.[30] The other report was of a man with schizophrenia who had smoked 30 cigarettes daily for 5 years.[32] By the second week of varenicline therapy, he had abstained from tobacco use and subsequently maintained abstinence for 6 months.[32] Neither patient experienced worsening of any psychiatric symptom.

Case Series

One retrospective case series[34] reported on the clinical course of 19 outpatients with schizophrenia and tobacco dependence who were treated with varenicline. Four patients discontinued use due to associated gastrointestinal disturbances, but no patients discontinued use due to worsening psychiatric symptoms. Thirteen patients abstained from tobacco use at day 21 of varenicline dosing and continued to abstain from smoking at 12 weeks, verified by carbon monoxide measurements. No patients experienced exacerbation of any psychiatric symptoms, although no rating scales were used to measure disorder or symptom severity. Patients treated in this clinic were closely followed and were seen weekly for 2 weeks and then monthly for 24 weeks for monitoring and brief individual counseling.

Prospective Studies

Four[38,41,44,46] of the 7 prospective studies[37,38,41,43–46] were double-blind, randomized, controlled studies. The first randomized controlled study[38] used a balanced crossover design to assess the effect of varenicline on P50 sensory gating in patients with schizophrenia. Six patients were randomized to 1 dose of either varenicline or placebo in week 1. The following week, each patient received the alternate intervention (eg, if a patient received varenicline at week 1, then the patient received placebo at week 2, and vice versa). Serial measurement of P50 evoked potential was done after each week's dose. Three of the 6 patients developed "brief negative psychological effects"[38(p180)] lasting 5 hours after receiving a single dose of varenicline. The study was subsequently cancelled "because of concerning side effects."[38(p179)]

The second double-blind randomized study[41] examined 8 outpatients with schizophrenia or schizoaffective disorder using at least 10 cigarettes per day. Four patients received varenicline, and 4 received placebo. Three of 4 patients receiving varenicline and no patients receiving placebo achieved sustained abstinence (measured by subject report and measurements of expired carbon monoxide) at 12 weeks. There was no difference between groups in the Brief Psychiatric Rating Scale (BPRS) positive symptoms measurement. The

Table 1. Studies of Varenicline in Patients With Schizophrenia and Schizoaffective Disorder Selected for Review

Authors	Article Type and Study Design	Patients and Characteristics	Varenicline Dosing/Method	Adverse Effects	Outcome	Patients Receiving Varenicline, n
Freedman[29]	Case report	42-year-old woman with schizophrenia, treated with thiothixene 10–15 mg/d, smoked 1–2 packs of cigarettes/d	Varenicline 2 mg/d for 5 days	Patient experienced a 5-day psychotic episode characterized by increased activity, aggressive behavior, and isolative behavior and she stopped eating (ADR Probability = 2)	The patient stopped using varenicline, continued thiothixene, and used nicotine replacement for smoking cessation. She experienced no further exacerbations of schizophrenia	1
Fatemi[30]	Case report	40-year-old man with schizophrenia, treated with clozapine 700 mg/d (serum level 432 ng/mL) and citalopram 40 mg/d, smoked 1 pack of cigarettes/d for 20 years and increased use to 2 pack/d 1 year before varenicline use	Varenicline 0.5 mg/d for 3 days, 1 mg/d for 1 week, then 1 mg twice daily (2 mg/d) for 1 year	None	Patient reduced cigarette use to 5 cigarettes/d	1
Liu et al[31]	Case report	43-year-old man with schizoaffective disorder, treated with clothiapine 160 mg/d and lithium 1,200 mg/d (serum level 0.7 mmol/L), smoked 1 pack of cigarettes/d since he was "a teenager"	Varenicline (unknown dose) for 13 days	Over 13 days, patient showed decreased need for sleep, elevated mood, persecutory delusions, and auditory hallucinations (ADR Probability = 2)	Transferred to acute care psychiatric ward, lithium increased to 1500 mg/d (serum level 0.9 mmol/L), clonazepam 2 mg by mouth 4 times/d was initiated, and clothiapine was continued at 160 mg/d. The mania and psychosis resolved after 4 weeks of inpatient treatment	1
Anghelescu[32]	Case report	27-year-old man with schizophrenia and cannabis use (0.5 g/d), treated with long-acting risperidone injection 37.5 mg every 2 weeks, smoked up to 1.5 packs/d for 5 years, with PANSS positive symptom score of 8 points and negative symptom score range of 42–45 points	Varenicline titrated to 2 mg/d over 1 week, then 2 mg/d	None	After 2 weeks, patient abstained from tobacco use for 6 months (confirmed by carbon monoxide measurements), also demonstrated reduction in PANSS negative score from a baseline range of 42–45 points to 22 points	1
Ismail et al[33]	Case report	62-year-old man with schizophrenia, treated with long-acting risperidone injection 25 mg every 2 weeks, smoked 15 cigarettes/d with a 25 pack year history, treated with varenicline after 3 months of acute psychiatric care on a ward	Varenicline 1 mg twice daily for 18 days	He developed increasing paranoia, delusions, irritability, and disorganization after unknown number of days but before developing polydipsia and hyponatremia (serum sodium of 125 mmol/L, urine specific gravity < 1.005) on day 18 of dosing (ADR Probability = 2)	Fluid restriction failed, and the patient received normal saline. Two days later, with normalization of sodium, the paranoia, delusions, and disorganization improved. Varenicline was also discontinued. The antipsychotic dosing was unchanged	1
Evins and Goff[34]	Case series	19 outpatients with schizophrenia and nicotine dependence on stable antipsychotic medications	Varenicline titration (0.5 mg/d for 3 days, 1 mg/d for 4 days, then 2 mg/d), dosed in 13 patients for > 24 wk	Four patients discontinued varenicline due to associated nausea and vomiting In the 13 patients who quit smoking while taking varenicline, no patients demonstrated worsening of psychiatric symptoms	All 19 patients reported reduced craving to smoke. 13 patients stopped smoking within 10–21 days and abstained from smoking for > 12 weeks per self-report and intermittent carbon monoxide measurements	19
Prospective Studies						
Smith et al[37]	Open-label study, prospective, no control	14 male patients with schizophrenia or schizoaffective disorder aged 27–52 years using at least 10 cigarettes/d for "a long time"	14 patients received 0.5–1 mg/d varenicline for 1 week, then 2 mg/d for weeks 2–9 Primary outcomes measurements were exhaled carbon monoxide, serum cotinine levels, and PANSS, RBANS, and Virtual Water Maze Task scores	2 patients (from original 14 patients) dropped out in first 2 weeks secondary to nausea or shaking. 8 inpatients and 4 outpatients remained in the study No significant worsening of psychopathology was found in any patient	Significant increases in list learning, list recall, and language index on RBANS neuropsychological test ($P < .05$) 12 patients demonstrated decreased serum cotinine levels 9 patients reported reduced cravings and number of cigarettes smoked compared to baseline over 9 weeks of treatment with varenicline	14

(continued)

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Table 1 (continued). Studies of Varenicline in Patients With Schizophrenia and Schizoaffective Disorder Selected for Review

Authors	Article Type and Study Design	Patients and Characteristics	Varenicline Dosing/Method	Adverse Effects	Outcome	Patients Receiving Varenicline, n
Prospective Studies						
Waldo et al[38]	Double-blind, placebo-controlled, randomized and balanced crossover design	6 patients with schizophrenia (mean age 48 years ± 5.9), treated with atypical antipsychotics, with unknown smoking status	6 patients were given varenicline 1 mg once or placebo at week 1, then they received placebo or varenicline at week 2, then serial measurements of P50 evoked potential were done after each week's dose	3 of 6 subjects developed "brief negative psychological effects after a single dose" lasting 5 hours	One dose of varenicline 1 mg did not significantly change P50 sensory gating compared to placebo ($P = .59$)	6
Weiner et al[41]	Double-blind, randomized, placebo-controlled pilot study	8 patients with schizophrenia or schizoaffective disorder treated with second-generation antipsychotics using at least 10 cigarettes/d for at least 1 year (and a score of at least 4 on the Fagerstrom Test for Nicotine Dependence)	4 patients received varenicline (2 mg/d) and 4 received placebo over 12 weeks Primary outcome measurements were expired carbon monoxide and subject report of tobacco use	There was a trend toward increase in activation in varenicline group ($P = .06$) No significant exacerbation of psychiatric symptoms in any patient was found	3 of 4 patients receiving varenicline and 0 of 4 patients receiving placebo sustained abstinence at 12 wk ($P = .02$ by mixed model analysis of covariance) No differences were found between groups on BPRS positive symptom measurement or anxiety/depression scores	4
Liu et al[43]	Open-label, non-randomized, control group	20 adult male inpatients with schizophrenia and tobacco dependence (> 10 cigarettes/d) who had been hospitalized for > 3 months at time of study entry, and on stable doses of antipsychotic medications for at least 6 weeks	All patients were instructed to stop smoking, and abstinence was enforced on the ward 20 patients (of 41 patients) who chose to use varenicline were given varenicline for 5 weeks (0.5 mg/d for 3 days, 1 mg/d for 4 days, then 2 mg/d for 4 weeks), and then patients were observed for 7 weeks Numerous symptom measures were done at baseline, then 2, 4, 8, and 12 weeks after abstinence 20 patients received varenicline, and 21 patients chose to not use varenicline or other cessation agents	In the varenicline group, 4 patients were discharged and 1 patient was transferred to another service for care of a urinary tract infection Complaints in varenicline group: nausea (2), vomiting (2), fatigue (1), dry mouth (1), muscle stiffness (1), headache (1) There were no reports of worsening psychopathology	15 patients (75%) in the varenicline group completed the 12-week study Patients who did not receive varenicline had higher HARS and HDRS scores at weeks 2, 4, and 8 postabstinence ($P < .001$, .001, and .012 in HDRS; $P < .001$, <.001, and .005 in HARS, respectively)	20
Hong et al[44]	Double-blind, parallel, randomized, placebo-controlled	69 adult, smoker or nonsmoker outpatients with schizophrenia or schizoaffective disorder	Patients were randomized to receive varenicline 0.5 mg daily for 1 week, then 0.5 mg twice daily for 7 weeks or placebo for 8 weeks. 27 patients receiving placebo and 32 patients receiving varenicline completed the 8-week study	There was no indication that varenicline worsened psychiatric symptoms After 1 week, 3 patients in varenicline group dropped out due to nausea or bowel movement problem No patients randomized to varenicline group dropped out of study between weeks 2–8	This study examined prepulse inhibition, sensory gating, spatial working memory, eye tracking, processing speed and sustained attention Secondary measures included tobacco cessation measures. Carbon monoxide levels were reduced, though not significantly, in varenicline group ($P = .21$) Varenicline group had trend toward reduced psychiatric symptoms measured with BPRS ($F = 3.32$, $P = .07$)	35 (20 smokers)

(continued)

Table 1 (continued). Studies of Varenicline in Patients With Schizophrenia and Schizoaffective Disorder Selected for Review

Authors	Article Type and Study Design	Patients and Characteristics	Varenicline Dosing/Method	Adverse Effects	Outcome	Patients Receiving Varenicline, n
Prospective Studies						
Nino-Gomez et al[45]	Open-label, prospective study, no control	98 adult outpatients with schizophrenia and tobacco dependence (smoked >10 cigarettes/d)	All patients were continued on current antipsychotic medications, and given varenicline for 12 weeks using standard dosing (0.5 mg/d for 3 days, 1 mg/d for 4 days, 2 mg/d for 11 weeks)	10 patients discontinued treatment, 5 reported nausea, 2 reported depressed mood, 1 reported dysphoria, 1 reported substance use and increased psychotic symptoms, and 1 reported anxiety	42 patients (43%) achieved tobacco abstinence verified biochemically Overall, mean ratings on BPRS, SANS, Calgary Depression Rating Scale were not significantly different at 12 weeks compared to baseline scores Mean ratings on BPRS Psychosis subscale improved (10.4 at baseline, 9.6 at 12 weeks; $P < .04$)	98
Shim et al[46]	Randomized, double-blind, placebo-controlled	117 stable, smoker or nonsmoker, adult outpatients with schizophrenia, taking stable doses of antipsychotic medications	All patients were continued on antipsychotic medications, and given varenicline (n = 59) or placebo (n = 58) for 8 weeks (dosed as 0.5 mg/d for 3 days, 1 mg/d for 4 days, 2 mg/d for weeks 2–8) Neuropsychological and clinical assessments were made at weeks 1,2,4, and 8	26 patients dropped out of trial (4 reported nausea, 1 reported anxiety, 1 headache, 1 insomnia, 1 dry mouth, 9 withdrew consent, 5 for protocol violation or other reason) 2 patients receiving varenicline and 2 receiving placebo dropped out due to aggravated psychotic symptoms No patients showed significant depressive symptoms or suicidal ideation	Compared to placebo group, patients in the varenicline group showed significant improvements in Digit Symbol Substitution Test ($P = .013$) and Wisconsin Card Sorting Test of non-perseverative errors ($P = .043$) No significant differences were noted between placebo and varenicline group on PANSS or SANS Tobacco cessation/reduction details were not reported. No smokers in either group stopped cigarette use completely	59 (29 smokers)

Abbreviations: ADR = Naranjo Adverse Drug Reaction Probability Scale, BPRS = Brief Psychiatric Rating Scale, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, RBAN = Repeatable Battery for the Assessment of Neuropsychological Status, SANS = Scale for the Assessment of Negative Symptoms.

patients in the varenicline group had a trend toward increased scores in the activation item in the BRPS, although this difference was not significant ($P = .06$). No patient experienced significant exacerbation of any psychiatric symptoms.

The third double-blind study,[44] which was placebo-controlled, prospectively determined the effect of 8 weeks of treatment with moderate-dose varenicline (1 mg/d) on numerous biomarkers (eg, prepulse inhibition, sensory gating, spatial working memory, eye tracking) in 26 nonsmoking and 43 smoking outpatients with schizophrenia or schizoaffective disorder. The authors reported that varenicline was more likely to bind only to the nicotinic acetylcholine $\alpha_4\beta_2$ subunit (rather than the α_7 subunit and other acetylcholine subunits) at a moderate dose of 1 mg/d. The authors aimed to explore the role of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subunit in mediating biomarkers in schizophrenia, so they used a moderate varenicline dose to isolate this receptor's specific effects. Additionally, they reported that the moderate dose of 1 mg/d was associated with a 50% reduction in nausea, compared to the 2-mg/d dose. Measurements of some of the biomarkers were significantly improved in the patients receiving varenicline (reduced P50 sensory gating, $P = .006$; reduced startle activity, $P = .02$; improved executive functioning, $P = .03$). No patients experienced exacerbation of psychiatric symptoms, and patients who received varenicline had a trend toward reduced psychiatric symptoms ($F = 3.32$, $P = .07$), including psychosis ($F = 3.89$, $P = .053$) as measured by the BPRS. Of the patients who received varenicline, 20 were smokers. Eleven of these 20 patients (55%) reduced the number of cigarettes smoked per day, and 2 of these 11 patients stopped smoking entirely by week 8.

Shim et al[46] completed the fourth double-blind study and investigated the effects of 8 weeks of treatment with adjunctive varenicline on cognitive impairments in 120 stable patients with schizophrenia (60 smokers and 60 nonsmokers) in Korea. Three patients dropped out before any intervention was given, leaving 117 patients overall and 59 patients in the varenicline arm. The investigators completed assessments at baseline and weeks 1, 2, 4, and 8 using the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Hamilton Depression Rating Scale (HDRS), Clinical Global Impressions scale (CGI), and several neuropsychological tests (the Continuous Performance Test, Stroop Color Word Test, Wisconsin Card Sorting Test, Digit Symbol Substitution Test, Digit Span Test, and Visual Span Test) that focused on measuring components of attention. Patients in the varenicline group demonstrated improvement in the week-by-week average scores in the Digit Symbol Substitution

Test ($P = .043$) and Wisconsin Card Sorting Test nonperseverative error ($P = .043$). The authors noted that tobacco cessation and reduction data will be presented in a separate report, although they did mention that "no smokers in either treatment group quit smoking entirely."[46(p663)] Four patients overall dropped out of the study due to worsening psychotic symptoms; 2 patients were in the varenicline group and 2 patients were in the placebo group. No patients experienced worsening of depressive symptoms (measured by the HDRS) or suicidal ideation.

The remaining 3 prospective studies[37,43,45] were open-label, nonrandomized, and not placebo-controlled. The first study[37] examined the effect of 9 weeks of varenicline dosing on cognition and tobacco use in 14 patients with schizophrenia or schizoaffective disorder. Two patients dropped out during the first 2 weeks due to adverse effects of nausea and shaking, but no patients experienced significant worsening of psychopathology measured by the PANSS. Of the remaining 12 patients, 8 were inpatients, and 4 were outpatients. Six of the 12 patients who completed the study had "no detectable nicotine levels at time of sampling at end of study," and overall the patients showed improvement in list learning ($P = .005$), list recall ($P = .025$), and language index ($P = .003$) measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as compared with pretreatment assessments.

In a nonrandomized, prospective study, Liu et al[43] hypothesized that varenicline would attenuate abstinence-induced exacerbations of psychopathology and cognitive dysfunction in male inpatients with schizophrenia living in a long-term care hospital in Taiwan. The authors also evaluated the effects of varenicline on mood, psychotic symptoms, and cognitive functioning. Forty-one male patients were instructed to abstain from tobacco use and were offered varenicline treatment. Twenty patients with schizophrenia chose to receive varenicline, and 21 chose not to receive any tobacco cessation aid including varenicline. Although 8 patients who received varenicline reported common adverse effects (eg, nausea, headache) during the first week of treatment, no patients experienced worsening of psychiatric symptoms over 12 weeks. Furthermore, the patients in the varenicline group had significantly lower Hamilton Anxiety Rating Scale (HARS) and HDRS scores at weeks 2, 4, and 8 after tobacco cessation ($P < .001$, $< .001$, and $< .012$ in HDRS; $P < .001$, $< .001$ and $< .005$ in HARS, respectively).

The final prospective study[45] was a 12-week open-label study examining the effectiveness and safety of varenicline in 98 outpatients with schizophrenia and tobacco dependence. Forty-two patients (43%) achieved abstinence from tobacco at 12 weeks, verified biochemically. Several scales were used to assess psychiatric symptoms and cognitive ability before dosing varenicline and after 12 weeks of treatment. Scores on the BPRS ($P = .49$), SANS ($P = .63$), and Calgary Depression Rating Scale ($P = .63$) measured before and after treatment with varenicline were not significantly different. The posttreatment score on the BPRS psychosis subscale decreased from 10.4 at baseline to 9.6 posttreatment ($P < .04$). Although 10 patients discontinued treatment, only 5 did so due to self-reported worsening of psychiatric symptoms. Two patients reported depressed mood, 1 patient reported dysphoria, 1 patient reported substance use and increased psychotic symptoms, and 1 reported experiencing anxiety.

DISCUSSION

Overall, we found that, in reports published to date, most patients with schizophrenia or schizoaffective disorder who received varenicline, either as treatment for tobacco dependence or to test a different hypothesis (eg, whether varenicline improves attention and other cognitive symptoms) tolerated treatment without experiencing worsening of any psychiatric symptom. It is also notable that no patient was reported to have experienced suicidal ideation or engaged in suicidal behavior, which are symptoms listed in varenicline's black box warning. This finding is in-line with the results of a large cohort study from the United Kingdom.[47] Regarding other symptoms listed in the black box warning, of 260 total patients, 1 patient[29] experienced aggression, and 3 patients experienced depressed mood, dysphoria, or anxiety.[45]

Although 3 initial published case reports[29,31,33] raised concern about the use of varenicline in patients with schizophrenia and schizoaffective disorder, 2 subsequent case reports,[30,32] 1 case series,[34] and 7 prospective studies[37,38,41,43–46] demonstrated the tolerability of varenicline in patients with schizophrenia and schizoaffective disorder. Of the 260 patients with schizophrenia or schizoaffective disorder who received varenicline in these published reports, 13 patients (5%) experienced worsening of any psychiatric symptom. For 3 of these 13 patients, the psychiatric exacerbation was described as a "brief negative psychological effect"[38(p180)] occurring after a single dose and resolving within 5 hours. Excluding these 3 patients, only 10 of 260 patients (3.8%) experienced onset or worsening of psychiatric symptoms. The other 247 patients did not experience worsening of psychiatric symptoms, although some patients were unable to tolerate varenicline therapy due to nausea. For the patients who experienced exacerbation of a psychiatric symptom, we were unable to identify any patient characteristics that predicted symptom worsening.

These reports suggest that clinicians can administer varenicline to stable patients with schizophrenia or schizoaffective disorder to safely treat tobacco use disorders, although it is prudent to monitor patients during this time, including for symptoms of tobacco withdrawal that could resemble worsening psychiatric symptoms. Other reports have also suggested that varenicline can be used in closely monitored patients with psychiatric disorders.[48] However, as Moore et al[27] noted, varenicline may be considered a second-line agent given their findings of increased risk of suicidal behaviors in the general population.

Excluding the single-patient case reports, the Liu et al[43] study, in which abstinence from tobacco was enforced on

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a hospital ward, the Waldo et al[38] study, in which smoking status was unknown, 15 patients from the Hong et al study[44] who received varenicline but were not smokers, and the Shim et al[46] study in which smoking cessation or reduction outcomes were not reported; 155 outpatients with schizophrenia or schizoaffective disorder were smokers and received varenicline for the purpose of reducing cigarette use. Eighty-three of these patients (53.5%) receiving varenicline reduced total daily cigarette use or stopped smoking entirely by endpoints ranging from 8 weeks to 6 months. These findings are encouraging. This rate of reduced tobacco use (53.5%) is also consistent with the results from the largest prospective study[45] (42 of 98 patients [43%]) specifically examining tobacco cessation in patients with schizophrenia treated with 12 weeks of varenicline. In this study, 42 of 98 patients (42.9%) demonstrated greater than or equal to 2 weeks of continuous abstinence during 12 weeks of varenicline use. One randomized controlled trial[7] of varenicline in patients without psychiatric disorders demonstrated that 44% of patients achieved 4 weeks of continuous abstinence compared to 17.7% of patients taking placebo (odds ratio [OR] = 3.85, 95% CI, 2.70–5.50; $P < .001$).

Earlier studies of tobacco cessation treatments available before the introduction of varenicline showed that most patients with chronic mental illness did not abstain from cigarette use. For example, a randomized controlled trial of nicotine replacement plus motivational interviewing in patients with schizophrenia revealed a cessation rate at 3 months of 30%.[49] Randomized, controlled, prospective studies evaluating the use of varenicline in this population are needed to see if these rates, or those seen in earlier studies of varenicline in the general population, can be generalized to those with chronic psychotic illnesses. Some predictive factors for early tobacco cessation in patients with schizophrenia exist for treatment with bupropion and cognitive behavioral therapy[50]; developing such factors for patients treated with varenicline would also be useful in clinical decision-making. However, Dutra et al[42] examined a subset of patients from the study by Nino-Gomez et al,[45] to assess whether the degree of affective flattening and other negative symptoms could predict the response to varenicline treatment plus cognitive behavioral therapy in treating tobacco dependence in 53 patients with schizophrenia. The investigators used the SANS to measure negative symptoms, and found that patients with less affective flattening were significantly more likely to abstain from tobacco use ($r = -0.31$, $P < .026$).

There are several limitations to our review. First, we conducted a review of published studies only. Searching other adverse drug event databases may have increased the number of case reports describing adverse effects associated with varenicline use in patients with schizophrenia or schizoaffective disorder. In 2010, Moore et al[51] reviewed reports to the FDA MedWatch database and found that, of the 26 cases of aggression and violence reportedly associated with varenicline use in adults, 2 patients had a history of psychiatric disorders but no patients in their review had a reported history of schizophrenia or schizoaffective disorder. The more recent review by Moore et al[27] noted increased risk of suicidal behavior and depression in patients treated with varenicline, although the report did not specifically assess patients with schizophrenia or schizoaffective disorder. However, it is possible that some of the 9,575 patients treated with varenicline who experienced a reported adverse event (or some of the 2,925 patients receiving varenicline who experienced suicidal/self-injurious behavior or depression), from this study had schizophrenia or schizoaffective disorder.

Second, we were unable to extract the same data set for each patient receiving varenicline, as we only had access to the information in the published reports. This limited our ability to draw conclusions about clinical factors that might predict an adverse effect of varenicline dosing.

Third, the reports included in our review used different study designs to assess variable outcomes. Four studies[38,41,44,46] used a randomized, placebo-control design, although these combined studies examined only 109 patients, and 51 of the patients may not have had tobacco use disorders. Some studies did not assess the primary outcome of tobacco cessation, complicating definitive conclusions we could make about effectiveness.

At least 3 randomized, controlled trials[52–54] are currently underway to assess the safety and effectiveness of varenicline in treating tobacco dependence in patients with schizophrenia. Other models of treatment delivery (eg, peer groups) might also be studied as an adjunct to varenicline treatment. Ideally, the results of these future studies, combined with the existing literature, would provide an evidence base for safely and effectively treating tobacco dependence in patients with severe and persistent mental illnesses such as schizophrenia and schizoaffective disorder.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), lithium (Lithobid and others), risperidone (Risperdal and others), thiothixene (Navane and others), varenicline (Chantix).

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REFERENCES

1. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res*. 2008;10(12):1691–1715.
2. Schroeder SA. A 51-year-old woman with bipolar disorder who wants to quit smoking. *JAMA*. 2009;301(5):522–531.
3. US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
4. Druss BG, Bornemann TH. Improving health and health care for persons with serious mental illness: the window for US federal policy change. *JAMA*. 2010;303(19):1972–1973.

5. Druss BG. Improving medical care for persons with serious mental illness: challenges and solutions. *J Clin Psychiatry*. 2007;68(suppl 4):40–44.
6. Fiore M, Jaen CR, Baker TB. *Tobacco Use and Dependence: 2008 Update: Clinical Practice Guideline*. Rockville, MD: US Department of Health and Human Services; 2008.
7. Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):47–55.
8. Prochaska JJ. Smoking and mental illness—breaking the link. *N Engl J Med*. 2011;365(3):196–198.
9. Montoya ID, Vocci F. Medications development for the treatment of nicotine dependence in individuals with schizophrenia. *J Dual Diagn*. 2007;3(3-4):113–150.
10. Evins AE, Mays VK, Rigotti NA, et al. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine Tob Res*. 2001;3(4):397–403.
11. Evins AE, Cather C, Rigotti NA, et al. Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. *J Clin Psychiatry*. 2004;65(3):307–311, quiz 452–453.
12. Gelenberg AJ, de Leon J, Evins AE, et al. Smoking cessation in patients with psychiatric disorders. *J Clin Psychiatry*. 2007;68(9):1404–1410.
13. Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med*. 2008;359(19):2018–2024.
14. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):56–63.
15. Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med*. 2006;166(15):1571–1577.
16. Tonstad S, Tønnesen P, Hajek P, et al; Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):64–71.
17. US Food and Drug Administration. *Drug Safety Newsletter.* 2009;2(1):1–4.
18. Laine P, Marttila J, Lindeman S. Hallucinations in the context of varenicline withdrawal. *Am J Psychiatry*. 2009;166(5):619–620.
19. May AC, Rose D. Varenicline withdrawal-induced delirium with psychosis. *Am J Psychiatry*. 2010;167(6):720–721.
20. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. *Am J Psychiatry*. 2007;164(8):1269–1270.
21. Popkin MK. Exacerbation of recurrent depression as a result of treatment with varenicline. *Am J Psychiatry*. 2008;165(6):774–775.
22. Pumariega AJ, Nelson R, Rotenberg L. Varenicline-induced mixed mood and psychotic episode in a patient with a past history of depression. *CNS Spectr*. 2008;13(6):511–514.
23. DiPaula BA, Thomas MD. Worsening psychosis induced by varenicline in a hospitalized psychiatric patient. *Pharmacotherapy*. 2009;29(7): 852–857.
24. Cinemre B, Akdag ST, Metin O, et al. Varenicline-induced psychosis. *CNS Spectr*. 2010;15(7):470–472.
25. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2011; (2):CD006103
26. Harrison-Woolrych M, Ashton J. Psychiatric adverse events associated with varenicline: an intensive postmarketing prospective cohort study in New Zealand. *Drug Saf*. 2011;34(9):763–772.
27. Moore TJ, Furberg CD, Glenmullen J, et al. Suicidal behavior and depression in smoking cessation treatments. *PLoS ONE*. 2011;6(11):e27016.
28. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
29. Freedman R. Exacerbation of schizophrenia by varenicline. *Am J Psychiatry*. 2007;164(8):1269.
30. Fatemi SH. Varenicline efficacy and tolerability in a subject with schizophrenia. *Schizophr Res*. 2008;103(1–3):328–329.
31. Liu ME, Tsai SJ, Yang ST. Varenicline-induced mixed mood and psychotic episode in a patient with schizoaffective disorder. *CNS Spectr*. 2009;14(7):346.
32. Anghelescu I. Successful smoking cessation and improvement of negative symptoms with varenicline in a stable schizophrenia patient. *J Neuropsychiatry Clin Neurosci*. 2009;21(1):102–103.
33. Ismail Z, Syms J, Blumberger D, et al. Varenicline induced polydipsia and hyponatremia in a patient with schizophrenia. *Schizophr Res*. 2010;119(1–3):268.
34. Evins AE, Goff DC. Varenicline treatment for smokers with schizophrenia: a case series. *J Clin Psychiatry*. 2008;69(6):1016.
35. Campbell AR, Anderson KD. Mental health stability in veterans with posttraumatic stress disorder receiving varenicline. *Am J Health Syst Pharm*. 2010;67(21):1832–1837.
36. Stapleton JA, Watson L, Spirling LI, et al. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction*. 2008;103(1):146–154.
37. Smith RC, Lindenmayer JP, Davis JM, et al. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. *Schizophr Res*. 2009;110(1–3):149–155.
38. Waldo MC, Woodward L, Adler LE. Varenicline and P50 auditory gating in medicated schizophrenic patients: a pilot study. *Psychiatry Res*. 2010;175(1–2):179–180.
39. McClure JB, Swan GE, Catz SL, et al. Smoking outcome by psychiatric history after behavioral and varenicline treatment. *J Subst Abuse Treat*. 2010;38(4):394–402.
40. Smith RC, Zhubi A, Maloku E, et al. Varenicline treatment decreases DNMT1 mRNA expression in lymphocytes of schizophrenic patients who are cigarette smokers. *Schizophr Res*. 2010;119(1-3):269–270.
41. Weiner E, Buchholz A, Coffay A, et al. Varenicline for smoking cessation in people with schizophrenia: a double blind randomized pilot study. *Schizophr Res*. 2011;129(1):94–95.
42. Dutra SJ, Stoeckel LE, Carlini SV, et al. Varenicline as a smoking cessation aid in schizophrenia: effects on smoking behavior and reward sensitivity. *Psychopharmacology (Berl)*. 2011;219(1):25–34.
43. Liu ME, Tsai SJ, Jeang SY, et al. Varenicline prevents affective and cognitive exacerbation during smoking abstinence in male patients with schizophrenia. *Psychiatry Res*. 2011;190(1):79–84.
44. Hong LE, Thaker GK, McMahon RP, et al. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 2011;68(12):1195–1206.
45. Nino-Gomez J, Carlini S, Nemani K, et al. Safety and efficacy of varenicline in schizophrenia: preliminary data from 12-week trial. Abstract presented at the 16th Annual Meeting of the Society for Research on Nicotine and Tobacco; Feb 24–Feb 27, 2010; Baltimore, MD.
46. Shim JC, Jung DU, Jung SS, et al. Adjunctive varenicline treatment with antipsychotic medications for cognitive impairments in people with schizophrenia: a randomized double-blind placebo-controlled trial. *Neuropsychopharmacology*. 2012;37(3):660–668.
47. Gunnell D, Irvine D, Wise L, et al. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ*. 2009;339:b3805.
48. Purvis TL, Nelson LA, Mambourg SE. Varenicline use in patients with mental illness: an update of the evidence. *Expert Opin Drug Saf*. 2010;9(3):471–482.
49. Baker A, Richmond R, Haile M, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *Am J Psychiatry*. 2006;163(11):1934–1942.
50. Culhane MA, Schoenfeld DA, Barr RS, et al. Predictors of early abstinence in smokers with schizophrenia. *J Clin Psychiatry*. 2008;69(11):1743–1750.
51. Moore TJ, Glenmullen J, Furberg CD. Thoughts and acts of aggression/violence toward others reported in association with varenicline. *Ann Pharmacother*. 2010;44(9):1389–1394.
52. Safety and tolerability of varenicline in schizophrenia (SATOVA). Clinica Trials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00702793?term=varenicline+AND+schizophrenia&rank=10 Updated September 23rd, 2010. Accessed August 31st, 2011.
53. Varenicline and smoking cessation in schizophrenia (VSCS). Clinical Trials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT01111149?term=varenicline+AND+schizophrenia&rank=2 Updated August 5th, 2011. Accessed August 31st, 2011.
54. A study of varenicline for prevention of relapse to smoking in patients with schizophrenia or bipolar disorder (SCRP). Clinical Trials.gov Web site. http://www.clinicaltrials.gov/ct2/show/NCT00621777?term=varenicline+AND+schizophrenia&rank=6 Updated May 23rd, 2011. Accessed August 31st, 2011.