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Review of Varenicline for Tobacco Dependence: Panacea or Plight?

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Abstract

Introduction—This review examines the post-marketing experience with varenicline including case reports, newer clinical trials and secondary analyses of large clinical datasets.

Areas Covered—Varenicline has been shown to be an effective treatment in a broad range of tobacco users with medical, behavioral, and diverse demographic characteristics. The recent studies finding excellent safety and efficacy in groups of smokers with diseases including chronic obstructive pulmonary disease are particularly encouraging and call for increased use of this medication for smoking cessation. Despite case reports of serious neuropsychiatric symptoms in patients taking varenicline, including changes in behavior and mood, causality has not been established. Recent analyses of large datasets from clinical trials have not demonstrated that varenicline is associated with more depression or suicidality than other treatments for smoking cessation.

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Expert opinion—Now that additional clinical trials in specific populations and observational studies on treatment-seeking smokers outside of clinical trials have been published we can be confident that varenicline remains the most efficacious monotherapy for smoking cessation, and that its side-effect profile remains good. The risk benefit ratio of receiving varenicline to quit smoking must be weighed against the sizeable evidence of premature death in smokers and risk of not taking aggressive action to treat tobacco addiction.

Keywords

pharmacotherapy; smoking cessation; smoking; tobacco; varenicline

1. Introduction

The U.S. Food and Drug Administration (FDA) approval of varenicline for smoking cessation in 2006 was greatly anticipated by researchers and clinicians treating tobacco dependence as it was the first new non-nicotine compound approved by FDA for smoking cessation since 1997. The previous compound (bupropion) had been available in various forms since 1985. The story behind the development of varenicline is interesting- its structure is based on cytisine, a little known plant alkaloid that was used in Eastern Europe as a smoking cessation aid for decades. Cytisine has a molecular structure similar to that of nicotine and acetylcholine and is a nicotinic agonist at a4B2 nicotinic receptors. A review of cytisine indicated that despite the existence of placebo-controlled trials demonstrating efficacy, the results remained unnoticed to most of the world and were not cited in the English-language literature until after the emergence of varenicline [1].

The first scientific publication of varenicline appeared in 2005 describing the discovery of a new class of selective nicotinic receptor partial agonists [2]. These early reports suggested that alpha4beta2 (a4B2) selective nicotinic receptor partial agonists like varenicline would be ideally suited for smoking cessation by blocking the action of nicotine and at the same time providing a low level of dopaminergic activation to limit craving and withdrawal symptoms. Varenicline received a “priority review” by the FDA in February 2006, shortening the usual 10-month review period to 6 months because of its demonstrated efficacy in clinical trials and perceived lack of safety issues [3]. Three publications appeared in a July 2006 issue of JAMA under the heading “JAMA-Express”, which is a system of rapid review and publication of major articles that have practice-changing implications or substantial public health importance [4]. Carefully designed studies established its efficacy compared to placebo but also when compared to bupropion SR in a head to head comparison [5-6]. A third study demonstrated superiority of continuing varenicline (compared to placebo) for an additional 12 weeks after successful cessation during a 12 week open-label period of treatment [7]. In addition to strong efficacy data the side effect profile appeared to be mild and limited to mainly nausea and sleep disturbance. The drug is eliminated in the body almost exclusively by the kidney and it is therefore free of nearly all possible interactions with other medications that are metabolized in the hepatic system, making its use relatively straightforward in smokers taking other medications for other conditions.

Now in 2011, the story sounds quite different as compared with the promise in 2006. The FDA has since issued two labeling updates for varenicline including a black box warning due to the possibility of serious neuropsychiatric side effects, although data on this are limited to mostly case reports. Use has been decreased due to anecdotal reports of serious side effects in the media and consequent bans in certain hospital or employment settings. This review will examine the recent story of post-marketing experience with varenicline and will review all available evidence for current recommendations.

2.1 Introduction to the compound

Varenicline is a novel selective nicotinic receptor partial agonist that binds specifically and potently at the a4B2 receptor, which is one of the main subtypes of nicotinic receptors implicated in nicotine addition. As a partial agonist it mimics some of the effects of nicotine, resulting in the release of dopamine in the nucleus accumbens, but it also blocks the effect of the full agonist, nicotine [2]. Although there is also binding at other nicotinic receptor subtypes including a7, affinity for a4B2 is highest [2]. Varenicline is highly absorbed after oral administration, and little is metabolized, making it virtually 100% bioavailable. Varenicline is not significantly protein bound and the compound is excreted primarily unchanged in the urine. Less than 10% is metabolized in the liver and few metabolites are created. The half life is 17 to 30 hours [8]. The approved dosing regimen in adults is 1 mg twice daily for 12 weeks (renewable for another 12 weeks), starting with a 1-week titration. In Canada the drug is also approved at a dose of 0.5mg twice daily.

2.2 Clinical efficacy

Several trials have shown that varenicline is efficacious for smoking cessation. Varenicline increases the chances of quitting smoking nearly threefold as compared with placebo and by 50% as compared with sustained-release bupropion [6, 9-11]. The primary outcome measure in these studies is 4 weeks of continuous abstinence from weeks 9-12 after quitting. Multicenter, placebo-controlled clinical trials demonstrating efficacy of varenicline included more than 5000 men and women smokers (N=5229) who were motivated to stop smoking; most were Caucasian, and they had an average age of 43 years. More than 75% of the smokers reported smoking the first cigarette of the day within the first 30 min of waking up in the morning; the majority smoked at least 11 cigarettes/day, and, of these, >40% smoked at least 20 cigarettes/day [12]. A pooled analysis of varenicline trials found the following adverse events to be reported significantly more often than in the placebo groups: nausea (OR 3.17, 2.35–4.29); flatulence (OR 2.04, 95% CI, 1.16–3.57); and, constipation (OR 2.57, 95% CI, 1.21–5.45; [10]). Nausea is the most prevalent dose-dependent side effect, more commonly seen in women but generally mild and not leading to drug discontinuation [12].

An additional trial evaluated the effect of 24 weeks of therapy with varenicline to delay or prevent smoking relapse after successful cessation [7]. This is an innovative research design that examines the continued effect of treatment after successful cessation. Following 12 weeks of open-label varenicline treatment, those with confirmed abstinence were randomized to continue either varenicline 1 mg twice daily or placebo for an additional 12 weeks. Continuous abstinence rates (CAR) were significantly better in the varenicline-treated subjects than in the placebo group at both the week 24 and week 52. The time to first lapse was significantly longer in the varenicline treated group.

These published clinical trials establishing efficacy of varenicline have many strengths and strictly adhere to guidelines for testing smoking cessation therapies in clinical trials [13]. All participants received 12 weeks of brief individual smoking cessation counseling along with the study drug. Inclusion and exclusion criteria were similar to those used in trials that had demonstrated the efficacy of bupropion allowing for post-hoc comparisons. In addition, 2 studies had identical trial design allowing for direct comparison [5-6].

Some of the criticisms of these early studies were the lack of racial diversity in the samples and the exclusion of smokers with mental illness comorbidity [14-15]. Randomized trials of varenicline excluded patients not only with serious mental illnesses like psychosis and bipolar disorder but also more common conditions including major depression (past year), current or lifetime panic disorder, and drug or alcohol abuse or dependence (past year). It is standard practice in drug development studies to enroll healthy volunteers usually without

complex co morbid issues to establish drug safety and efficacy. This is partly done to protect at risk individuals from exposure to as-yet unproven medicines. However, population studies have indicated that, perhaps increasingly, smokers are overrepresented with comorbid psychiatric or substance use disorders making the definition of a "representative smoker" increasingly complex.

A brief review of smoking and mental illness comorbidity is relevant to an understanding of the risks and benefits of tobacco dependence treatment. Numerous studies have shown increased smoking rates among patients with psychiatric illnesses and substance use disorders compared to the general population [16-17]. Clinical samples of individuals trying to quit smoking reveal sizeable percentages (about 50%) with mental health issues [18-20]. There is a strong link between smoking and major depression and the nicotine withdrawal syndrome can include mood symptoms including depression, anxiety and irritability in addition to insomnia. Smoking has also been linked to suicidal thoughts and behavior in many studies, although the mechanism is unclear [21-25]. A 10-year longitudinal study found that current daily smoking, but not past smoking, was a predictor of suicidal thoughts or attempts, independent of prior depression or substance use and adjusting for other suicide predictors including prior suicidality [22]. An analysis of smokers with a history of major depression indicated that smoking abstinence did not lead to increases in depression, anxiety or suicidal ideation; however, failed quit attempts did [26]. More studies of this emerging area are needed because the effect of successful and unsuccessful smoking cessation on depressed mood, anxiety and suicide-risk outcomes is unclear.

2.3 Safety and Regulatory Affairs

By March of 2009, there was concern that varenicline might cause serious neuropsychiatric adverse events. An analysis of adverse event reports submitted to the FDA between May 2006 and November 2007 found 116 cases of suicidal ideation and 37 cases of suicidal behavior, more than half resulting in death [27]. Half of the patients reporting either suicidal ideation or suicidal behavior had a history of psychiatric problems, 26% had no such history, and 24% had an unknown psychiatric history.

The FDA's preliminary assessment revealed that many of the cases reflect new-onset of depressed mood, suicidal ideation, and changes in emotion and behavior within days to weeks of initiating varenicline treatment. The role of varenicline in these cases is not clear because smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness. At least one highly publicized case of erratic behavior leading to the death of a patient using varenicline may have been linked to alcohol consumption [28]. Moore et al [29] published the results of 78 adverse event reports from the Food and Drug Administration MedWatch database that included possible acts or thoughts of aggression/ violence. Of these, the authors concluded 26 cases met their described criteria for probable or possible association and included 10 assaults, 9 cases of homicidal ideation without a physical act of aggression, and 7 cases of other violent or aggressive thoughts. The authors concluded the temporal relationship evidence was strong, with an early and often immediate onset of abnormal dreams and thoughts, and the adverse effects usually resolved with discontinuation of treatment.

In 2008 the FDA issued an alert that serious neuropsychiatric symptoms have occurred in patients taking varenicline. These symptoms include changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide. While some patients may have experienced these types of symptoms and events as a result of nicotine withdrawal, some patients taking varenicline who experienced serious neuropsychiatric symptoms and events had not yet discontinued smoking. According to their report most

cases of neuropsychiatric symptoms developed during varenicline treatment, but in others, symptoms developed following withdrawal of varenicline therapy.

We identified 10 case reports of smokers with mental illness (schizophrenia, bipolar disorder, post-traumatic stress disorder, depression, substance use or borderline personality) who experienced worsening of symptoms during treatment with varenicline (See Table 1; [30-40]). All were being treated with pharmacotherapy for their condition in addition to varenicline and there is variability in the time course and presentation of adverse symptoms reported. There are also isolated case reports of medical side effects potentially attributable to varenicline, including renal failure, cutaneous drug eruption, and hypoglycemia [41-43]. Far fewer are cases of neuropsychiatric symptoms in individuals with no history of mental illness [33].

There are almost an equal number of published case reports or open label studies of positive effects from varenicline. Twelve smokers with schizophrenia showed significant improvements in cognitive test scores associated with verbal learning and memory, and no increases in psychopathology, depression or suicidal ideation [44]. Other case reports indicate good tolerability and no clinical worsening in smokers with schizophrenia, several of whom were successful in quitting smoking [45-48].

On its website the FDA acknowledges the limitations of case reports including the lack of medical validation, possible influence by the media and other sources, potential for errors in reporting and possible complication of nicotine withdrawal symptoms. For these reasons systematically collected data from prospective or retrospective data sets can be invaluable in assessing true risk associated with use of varenicline. Research data from several studies has now been published; including post-hoc analyses from larger samples of smoking cessation studies as well as pilot safety studies to examine this prospectively. Most of these retrospective analyses have not shown an association between depression or other psychiatric worsening during varenicline treatment and are summarized in Table 2 [20; 48-57]. Stapleton [58] published an analysis of adverse effects in the UK during varenicline treatment that included 10 completed suicides. When compared to the number of individuals taking varenicline and the rate of suicides among smokers in this same period, he estimated that the rate of suicide due to chance alone was 12, making a raised risk from varenicline unlikely. Perhaps the best study to date was an analysis of more than 80,000 smokers treated with a smoking cessation medicine in primary care settings throughout the UK, including 10,973 treated with varenicline, 6,422 treated with bupropion and 63,265 treated with nicotine replacement therapy [55]. Over the follow-up period there were 166 episodes of non-fatal self harm (154 (93%) being cases of self poisoning), two suicides (both in patients prescribed nicotine replacement products, one by means of hanging, the other with a firearm), and 37 episodes of suicidal thoughts. The incidence of self harm, standardized for age and sex, was no different in patients prescribed varenicline compared to bupropion or nicotine replacement products. Patients using varenicline in this study were less likely to be subsequently treated for depression than patients treated with nicotine replacement products (hazard ratio 0.88 (0.77 to 1.00), and varenicline-treated patients were also significantly less likely to die during the follow-up period [hazard ratios 0.26 (0.13 to 0.53)]. There was also no statistical evidence that associations of smoking cessation products with self harm differed by past psychiatric problems. Although there have also been post-marketing reports of drowsiness from varenicline prompting caution while driving/using machinery, somnolence was noted infrequently (less than 3%) in clinical trial data [56].

2.4 Harm Reduction/ Effects on Reward

Although the current primary indication for varenicline is smoking cessation, tobacco treatment medications are being increasingly investigated for usefulness in other areas

including to reduce smoking in those not wanting to quit, to prevent relapse and for "reduce to quit" studies of reduction followed by cessation [59]. These indications might directly support or lead to smoking cessation and/or reduce disease risk in the absence of complete cessation although we could not find any published studies of this. Varenicline's ability to relieve withdrawal symptoms and reduce the reward from smoking makes it an ideal candidate for use as a smoking reduction aid. Multiple research paradigms support varenicline's partial agonist and antagonist properties, in both animal and human studies [60-61]. Despite the rewarding effects of varenicline, because it is a partial agonist, it has a low abuse profile [62]. Interestingly, among 22 non-smokers, 1mg varenicline produced significantly greater experience of "drug high" with an associated greater abuse potential score when compared to placebo. There was no difference between 3mg varenicline and placebo for drug high, drug liking or abuse potential score among non-smokers and 3mg was associated with greater levels of unpleasant effects including nausea. Overall, McColl [62] concluded that "varenicline is unlikely to be abused".

In addition to its partial agonist properties, varenicline works as an antagonist at a4B2 nicotinic acetylcholine receptors to block the rewarding effects of nicotine. Perkins [63] evaluated varenicline's effects on acute smoking behavior and reward in smokers willing to try to quit for one week. Participants were designated as being high or low in quitting interest and were asked to retrospectively rate cigarette liking for the cigarettes they smoked in the previous 24 hours. Retrospective cigarette 'liking' ratings were decreased in men with high but not low interest in quitting smoking and taking varenicline after a 1-week medication run up (versus placebo), while no influence of varenicline was detected among women. When prospectively assessing the cigarettes smoked on the testing day, varenicline (versus placebo) tended to decrease liking more in those with high versus low quit interest and tended to decrease puff volume among women high in quit interest, but not among the other groups. An additional human laboratory study [64] of daily smokers who were non-dependent, heavy drinkers receiving seven days of pre-treatment of varenicline or placebo before receiving a priming dose of alcohol found that although no differences in craving were detected, participants on varenicline smoked less than those on placebo during the three smoke breaks allowed during the study day. Similarly, Patterson [65] found varenicline to reduce ratings of cigarette satisfaction, relief, and liking during a scheduled smoking lapse. Comparable effects were found for intravenous (IV) nicotine. Sofuoglu [66] found that, after overnight abstinence, 12 non-treatment seeking smokers' ratings of IV nicotine strength, high, head rush, and stimulation were reduced after a 4-day treatment period of 1mg/day varenicline.

In more traditional cessation studies, Ebbert [67] found that varenicline reduced satisfaction and reward in smokeless tobacco users, and West [68] found that Varenicline reduced ratings of satisfaction and psychological reward after the first cigarette smoked after a target quit date when compared to bupropion or to placebo. Overall, these studies provide support for the rationale that varenicline has a dual mechanism of action: 1. By directly reducing the severity of nicotine cravings and withdrawal symptoms in abstaining smokers and 2. By reducing the rewarding effects during a smoking lapse episode in smokers trying to quit.

2.5. Newer Clinical Trials

Varenicline has demonstrated good efficacy in achieving abstinence from smoking in numerous clinical trials published to date [11]. However, the early trials were conducted in highly selected smoking populations including predominately white smokers and excluding smokers with significant medical and psychiatric illnesses. However, in clinical practice, many smokers that are treated have significant medical and behavioral co-morbidity and come from diverse racial and ethnic groups. Therefore, it is important to review data on the use of varenicline in smokers with other co-occurring conditions (e.g. cardiovascular

disease, pulmonary disease, hospitalization), and from a broad range of racial and ethnic groups. Finally, since the initial trials, more data are available regarding the use and duration of varenicline, comparison with other treatments, as well as the potential benefit of combining varenicline with other pharmacotherapy.

2.5.1. Varenicline use, dosing, and duration—Building on the original efficacy trials for varenicline, subsequent studies have examined the safety of longer duration of treatment and the use of flexible dosing regimens and flexible quit dates. The standard treatment duration for varenicline in the pivotal trials was 12 weeks with subsequent data indicating a benefit for up to 24 weeks [7]. An extended duration study in 251 smokers found that varenicline can be safely administered for up to 1 year of treatment [69]. The most common adverse events (AEs) were nausea (40%), abnormal dreams (23%), and insomnia (19%), with fewer leading to discontinuation (nausea (8%), insomnia (3%), and abnormal dreams (2%)).

The standard titration protocol for varenicline calls for the target quit date to be set on the 8th day of treatment. A recent study examined the benefit of flexible quit dates for smokers using varenicline where subjects could choose a quit date between day 8 and 35 after starting the medication. Abstinence rates in this trial using a flexible quit date were found to be similar to those of other varenicline trials as were similar side effects [70].

Finally, in contrast to the standard dose of 2 mg daily of varenicline, a study was conducted in 320 smokers who received varenicline or placebo at the standard dose for the first week of treatment and then used a self-regulated flexible dosing regimen (between 0.5 mg and 2 mg daily) for weeks 2 through 12. End of treatment (week 12) and 52-week seven-day point abstinence rates were higher in the varenicline group compared with placebo (46.5 vs. 14.2%; $p<0.001$ and 28.0 vs. 13.5%; $p=0.001$, respectively). These rates were similar to previous trials using standard dosing. Few AEs led to treatment discontinuation (varenicline 7% and placebo 4.5%) [71]

2.5.2 Comparison of varenicline to nicotine replacement therapy—To date, there have been no randomized placebo-controlled trials directly comparing varenicline to nicotine replacement therapies (NRT). In open label, non-randomized studies including 746 smokers, varenicline was found to have higher abstinence rates than nicotine transdermal patch at end of 12-week treatment (56% varenicline vs. 43% for NRT; OR 1.70; 95% CI 1.26-2.28; $p<0.001$) and at 52 weeks (26% varenicline vs. 20% for NRT; OR 1.40, 95% CI 0.99-1.99; $p=0.056$) with higher rates of nausea in varenicline treated subjects (37% vs. 10%; [72]. Comparison studies to NRT are inherently challenging given that non-nicotine medications are typically started before the quit date and are not given in tapering doses at the end of treatment.

2.5.3. Combination therapy of varenicline with other pharmacotherapies—Through its novel mechanism of action, it is possible that combinations of varenicline with other pharmacotherapies could be beneficial in the same way that combining multiple NRTs or combining NRT with bupropion has been proven advantageous [73]. In a pilot study of 38 smokers who received open-label combinations of varenicline and bupropion, the seven-day point-abstinence rate was 58% (95% CI 41%-74%) at 6 months. The most common side effects were sleep disturbance (26%) and nausea (24%). A more recent evaluation of combining varenicline in a “real world” setting demonstrated that smokers using varenicline alone achieved abstinence rates at 52 weeks of 39% while those who used varenicline and bupropion had 55% abstinence [74]. Another study has been published utilizing non-randomized clinical data for 239 smokers treated in a residential treatment program. Among 104 smokers using the combination of varenicline with nicotine replacement medications, a

54% thirty-day-point abstinence rate was reported at 6-months follow-up. Abstinence and adverse event rates were similar to the usual care group who received standard pharmacotherapy regimens [75]. These preliminary studies suggest that combining varenicline with other smoking cessation medicines is safe, but to date there is not clear evidence from randomized trials of an increased efficacy resulting from combination versus monotherapy with varenicline.

2.5.4. Varenicline use in smokers with medical co-morbidity

Cardiovascular disease: Tobacco use remains a leading risk factor for the development of cardiovascular disease. Despite the obvious reasons to stop, a significant proportion of smokers continue to smoke even after an acute cardiovascular illness. Therefore, there is a critical need to assess tobacco treatments in this population of smokers. A clinical trial was recently conducted in 714 smokers with stable cardiovascular disease who received varenicline or placebo for 12 weeks [76]. Continuous abstinence rates were higher for varenicline than for placebo during weeks 9 through 12 (47.0% vs. 13.9%; OR 6.11; 95% CI 4.18-8.93) and weeks 9 through 52 (19.2% vs. 7.2%; OR 3.14; 95% CI 1.93-5.11). Varenicline was well tolerated and did not increase cardiovascular events (7.1% vs. 5.7%; 95% CI -2.3 to 5.0), serious adverse events (6.5% vs. 6.0%; 95% CI -3.1 to 4.1), or all-cause mortality (0.6% vs. 1.4%; 95% CI -2.3 to 0.6). Very recent data also supports the safe use of varenicline in smokers with cardiovascular and pulmonary disease. Willers [77] reported that in 204 patients mostly with heart and lung disease, there was a 38% abstinence rate at 12 months with generally mild side effects including nausea (33%) and some depression (9%), but no serious psychiatric effects.

Chronic Obstructive Pulmonary Disease (COPD): Smoking is the most important risk factor for the development of COPD and accelerates its progression. Despite the health implications, a large proportion of patients with COPD continue to smoke, so finding effective smoking cessation interventions for this population is important. In a multi-center trial of 504 smokers with mild-to-moderate COPD [78], the week 9-12 continuous abstinence rate was significantly higher for varenicline (42.3%) vs. placebo (8.8%; OR 8.40; 95% CI 4.99-14.14; $p<0.0001$) and remained significantly higher than placebo through weeks 9-52 (18.6% vs. 5.6%; OR 4.04; 95% CI, 2.13-7.67; $p<0.0001$).

Nausea, abnormal dreams, upper respiratory tract infection, and insomnia were the most commonly reported AEs for varenicline. Serious AEs were infrequent in both treatment groups.

Hospitalized smokers: No study published to date has evaluated the benefit of initiating varenicline in the hospital setting. A recent randomized, controlled, pilot study [79] has been presented describing 79 smokers admitted to a university-based hospital with various diagnoses from 2007-2009. Overall abstinence at 24 weeks was 27% with no difference between varenicline and placebo treatment groups (23% vs. 31%). Over 40% of all subjects utilized post-discharge behavioral treatment with significantly higher abstinence rates compared with those who did not (53.1% vs. 8.5%, $p<0.01$). Overall adverse events were similar in both treatment groups with the only significant difference being more nausea in the varenicline group (25% vs. 5%; $p<0.01$). Twenty-three subjects were re-hospitalized with no significant differences between treatment groups (13 varenicline vs. 10 placebo). This pilot trial of varenicline in hospitalized smokers demonstrated feasibility of implementation, produced some hypothesis-generating findings, and suggested the benefit of face-to-face treatment following discharge.

2.5.5. Varenicline use in specific populations

Asian smokers: As previously stated, the original varenicline trials were almost entirely performed among white subjects. Therefore, studies in other demographic groups are informative. From a pharmacokinetic standpoint, varenicline 1 mg twice daily was safe and well-tolerated in a cohort of healthy male and female, 18- to 45-year-old Chinese smokers and demonstrated properties that were similar to those observed previously in Western subjects [81]. A pooled analysis was conducted to evaluate the efficacy and safety of varenicline versus placebo for smoking cessation in Asian populations and to compare the data to pooled trials among predominantly Western populations. Among 893 smokers from 3 clinical trials in six Asian countries (Japan, Taiwan, Korea, China, Singapore, and Thailand), the continuous abstinence rate was higher for varenicline than placebo during weeks 9-12 and through 12 weeks of follow-up. The most frequent adverse events in the varenicline group (greater incidence than the placebo group) were: nausea (31.5%), headache (8.5%), dizziness (7.8%), insomnia (7.4%), and upper abdominal pain (5.4%). Serious AEs occurred in four varenicline and five placebo participants. Discontinuations due to AEs occurred in 3.6% of varenicline and 1.6% of placebo participants. Compared with the Western studies, abstinence rates for both varenicline and placebo were numerically higher in the Asian studies, although treatment effects were similar between the two populations. AEs reported in the Asian trials were largely similar to those in the Western populations. There remains a lack of data on outcomes from treatment of people of African origin with varenicline.

Adult light smokers: Prior varenicline studies have included smokers of 10 or more cigarettes per day only. Due to factors such as increased cigarette prices and smoke-free air legislation, smokers of fewer cigarettes per day are becoming more common. In an observational study of nearly 37,000 adult smokers of 10 or fewer cigarettes per day from the French cessation services, varenicline was found to double the odds of abstinence at 1 month follow-up [82].

Varenicline use for smokeless tobacco: In addition to its benefit for treating cigarette smoking, varenicline has also been shown to benefit users of smokeless tobacco. In a study of 20 smokeless tobacco users who were not interested in quitting, varenicline produced a 50% rate of significant (greater than 50%) reduction in smokeless tobacco use and a 10% abstinence at 6 months [67]. In a randomized placebo-controlled trial, among a sample of 431 smokeless tobacco users who were interested in quitting, varenicline use resulted in higher abstinence rates at the end of a 12-week treatment period (59% vs. 39%; RR 1.60; 95% CI 1.32 to 1.87, $P<0.001$) and at 26-weeks (45% vs. 34%; RR 1.42, 1.08 to 1.79, $P=0.012$; [83]). The most common adverse events in the varenicline group compared with the placebo group were nausea (35% vs. 6%), fatigue (10% vs. 7%), headache (10% vs. 9%), and sleep disorder (10% vs. 7%). Few adverse events led to discontinuation of treatment (9% and 4%, respectively), and serious adverse events occurred in two (1%) and three (1%) participants.

3. Conclusion

Following the early efficacy trials, subsequent data have shown that varenicline continues to be effective in a broader rage of tobacco users with medical, behavioral, and diverse demographic characteristics. Now that additional clinical trials in specific populations [76, 78, 81] and observational studies on treatment-seeking smokers outside of clinical trials have been published [51, 54-55] we can remain confident that varenicline remains the most effective monotherapy for smoking cessation, and that its side-effect profile remains good. One potential bias of the current literature is that to date most of the varenicline studies have

been sponsored and managed by the manufacturer. Confirmation by independent trials would remove any remaining doubt and strengthen previous findings.

There are no doubts about varenicline's efficacy, as it is the only pharmacotherapy consistently achieving medium and long term quit rates more than double those obtained with placebo. The recent studies finding excellent safety and efficacy in groups of smokers with smoking-caused diseases (COPD and CVD) are particularly encouraging and call for increased use of this medicine for smoking cessation within these specialties.

However, despite broadly reassuring findings regarding risks of neuropsychiatric side effects from systematic studies, questions still remain as to why more anecdotal reports of such side effects have emerged with varenicline than with other smoking cessation medicines. The Gunnell study [55] is particularly reassuring on this point. This real-world sample of over 80,000 smokers in family practice included 10% who had a history of alcohol misuse, 5% using antipsychotic medication, 13% using anti-anxiety medication and 24% antidepressants. 11% had experienced a previous suicide related event. Overall, this large study found only 18 episodes of self harm out of 10,973 smokers prescribed varenicline, a proportion not significantly different from NRT or bupropion. In addition it found that significantly fewer varenicline-treated patients had a subsequent need for antidepressants. Other smaller studies based on clinical samples with many co-occurring conditions have also produced reassuring results on the safety profile of varenicline relative to other smoking cessation medicines [51, 54]. It is possible that the increased reporting of adverse events with varenicline was largely stimulated by a single, well-publicized case very soon after the initial launch of the medicine. It remains possible that varenicline causes an adverse neuropsychiatric reaction in a very small proportion of smokers, who are perhaps particularly sensitive to some of its effects (e.g. blockade of nicotine receptors). Such a rarely occurring effect may only be detectable in a very large placebo-controlled trial. Another possibility is that varenicline, by virtue of its increased efficacy over previous treatments, enables some smokers who would otherwise not have been able to quit, to abstain long enough to experience certain adverse effects that are really due to abstinence from tobacco. Research should continue to try to answer these questions. In the mean time, clinicians should continue to use varenicline as an effective aid to smoking cessation, but also to heed the black box warning on the labeling and discuss its implications with patients.

4. Expert opinion

1. Varenicline is a safe and effective medicine for helping smokers to quit smoking.
2. Varenicline is the only monotherapy that consistently achieves more than a doubling of medium to long term quit rates.
3. Varenicline has a dual action: (a) it reduces the severity of nicotine withdrawal symptoms and cravings and (b) it reduces the rewarding effects of a lapse cigarette.
4. Smokers using varenicline should be encouraged to continue to use varenicline and to strive for abstinence from tobacco, even if they continue to have occasional lapses.
5. Smokers who feel they continue to be at risk of relapsing back to smoking after the first 12 week course of treatment should be advised to continue on varenicline for another 12 weeks.
6. Varenicline is safe and effective for smoking cessation across a broad spectrum of smokers, including those with co-occurring smoking-caused medical conditions. Data from cohort studies including patients with co-occurring mental health

problems suggest that varenicline, combined with close monitoring, can be used safely and effectively in these patients.

7. The evidence from systematic studies of smokers using varenicline and those quitting without varenicline do not provide evidence supporting the view that varenicline causes neuropsychiatric side effects other than sleep disturbance and vivid dreams.
8. All smokers using varenicline should be informed that a small proportion of people using varenicline have reported hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. They should be advised to stop using varenicline and contact their health professional immediately if they experience any changes in behavior that are not typical of nicotine withdrawal.
9. As with all pharmacotherapies for smoking cessation, the chances of smokers successfully quitting with varenicline are increased if they smoker receive assistance in the form of counseling (individual, group or telephonic), and other social support to persist with their quit attempt.
10. Future research should further examine the safety and efficacy of varenicline in people with mental illness, in racial and ethnic minorities, when combined with other smoking cessation medicines, at increased doses and for extended durations.

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Table 1

Peer-reviewed adverse neuropsychiatric effects reported during varenicline use (case reports)

	Prior Diagnoses	Concomitant Medications	Duration of Varenicline Use	Smoking Outcome	Neuropsychiatric symptoms	Outcome
Popkin (2008)	Major depression, recurrent	Fluoxetine, aspirin, niacin, and metoprolol	6 weeks	Reduced from 20 to 3-4 cpd	Hypersomnia, “unusual” dreams, decreased appetite, irritability, sadness, and guilt.	Varenicline stopped; symptoms resolved in 2 weeks
Freedman (2007)	Schizophrenia	Thiothixene	5 days	20-40 cpd, no change	Worsening psychosis, psychomotor agitation	Varenicline stopped; symptoms resolved
Kohen (2007)	Bipolar disorder	Valproic acid	1 week	Stopped smoking	Mania	Varenicline stopped; symptoms resolved in 1 week but was also treated with olanzapine
Kutscher (2009)	None	Oral contraceptives	10 weeks	Stopped smoking	Paranoia, anxiety and suicidal ideation	Varenicline stopped; symptoms resolved in 3 days but was also treated with zolpidem and clonazepam
DiPaula (2009)	Bipolar disorder, mixed with psychotic features	Lamotrigine, trifluoperazine, diphenhydramine, olanzapine, haloperidol, lorazepam	2 days	20-40 cpd to 0 due to tobacco-free inpatient hospitalization	Worsening psychosis and agitation	Varenicline stopped; mental status returned to baseline
Lyons (2008)	Major depression, GAD, borderline personality disorder, daily marijuana, h/o metamphetamine abuse	Topiramate, duloxetine, modafinil, and clonazepam	Not reported	20 cpd; varenicline helped her quit	Paranoia and irritability	Varenicline stopped; symptoms resolved in 2 weeks; Rechallenge with varenicline caused symptoms to recur
Pumariega (2008)	Depression (Family history of bipolar disorder in brother)	Sertraline	3 months	Not reported	Decreased sleep, racing thoughts, psychomotor activation, irritability, rapid and pressured speech and paranoia	Varenicline stopped; symptoms resolved but was also treated with aripiprazole
Raidoo (2009)	PTSD, Depression, alcohol dependence	Fluoxetine, nortriptyline, quetiapine, prazosin, pramipexole, terazosin, atenolol, spironolactone	19 days	40 cpd to 2cpd	Visual hallucinations	Varenicline stopped; symptoms resolved in 3 days
Ismail (2010)	Schizophrenia	Oral and depot risperidone	18 days	15 cpd to 2 cpd	Polydipsia and hyponatremia, worsening psychosis	Varenicline stopped; symptoms resolved in 5 days
Morstad (2008)	Bipolar II, h/o alcohol and metamphetamine abuse	Bupropion, clonazepam, oxcarbazepine, quetiapine, montelukast, pantoprazole	1 month	40 cpd, decreased smoking	Irritability, reduced sleep, suicidal ideation, feelings of hopelessness, agitation, and racing thoughts	Varenicline stopped; symptoms resolved in 3 days but was also treated with quetiapine UDS positive for cannabis

	Prior Diagnoses	Concomitant Medications	Duration of Varenicline Use	Smoking Outcome	Neuropsychiatric symptoms	Outcome
Pirmoradi (2008)	Major depression, alcohol dependence		7 days	4-5 cpd	Severe anxiety, nausea, vertigo, blurred vision, and dizziness.	Varenicline stopped; symptoms resolved in 3 days

GAD=generalized anxiety disorder; CPD= cigarettes per day smoked; UDS= urine drug screen

Table 2

Reported neuropsychiatric adverse events during varenicline use in clinical trials

	Sample size	Exclusion criteria	Intervention	Trial Design	Adverse events	Mood Outcomes	Smoking Outcomes
McClure (2009)	N=1117 661 had probable lifetime history of depression (DH+) vs. no history (DH-)	Psychosis, bipolar disorder, drug or heavy alcohol use	Telephone and/or web-based counseling	Open label varenicline up to 90 days	DH + more self-reported tension, irritability, difficulty concentrating, nausea, sleep disturbance, and confusion	Indices of mood not different between groups. Depression decreased in both groups over time	No difference in quit smoking rates between groups with and without history of depression
Philip (2009)	N=18 Axis I Depression (unipolar, bipolar or substance induced) and Nicotine Dependence	N/A	Adjunct to depression treatment; No smoking cessation counseling	Open label varenicline for 8 weeks	Sleep disturbance, GI, and irritability	No change in suicide ratings during study. Mean mood scores improved in study. One patient discontinued due to worse mood.	8 stopped smoking (44%), 9 reduced significantly and 1 had no change
Stapleton (2008)	N=111 (depression, bipolar disorder, psychosis, eating disorder)	N/A	Group counseling	Open label varenicline or NRT up to 12 weeks	Nausea and sleep disturbance	No evidence that varenicline exacerbated mental illness	Varenicline equally effective in those with and without mental illness. Short-term cessation rates were higher with varenicline than NRT.
Purvis (2009)	N=50 veterans 24 with mental illness (depression, PTSD, bipolar disorder, anxiety disorder, psychosis, ADHD)	N/A	Telephone counseling	Open label varenicline for up to 12 weeks		No suicidal ideation or attempts in study. Five self- reported worsening of psychiatric symptoms (depression, agitation, impulsivity)	Smokers with mental illness less likely to quit than those without history.
McClure (2010)	N=542 271 had prior psychiatric diagnosis (PH+) from chart review (depression, anxiety, other) vs. no history PH-	Psychosis, bipolar disorder, drug or heavy alcohol use	Telephone and/or web-based counseling	Open label varenicline up to 90 days	No difference in side effects in PH + and PH- smokers	No difference in depression and anxiety in PH+ and PH- smokers	No difference in cessation rates in PH+ vs. PH- smokers
Poling (2010)	N=31 smokers on methadone maintenance also using cocaine	Psychosis, bipolar disorder	Substance abuse CBT counseling	DB-PC varenicline vs. placebo for 12 weeks	None	Varenicline treatment was not associated with increases in negative affect, measured with the PANAS	Significant smoking reduction and more weeks without smoking in varenicline group. No change in cocaine use
Steinberg (2011)	N=723 smokers assessed with K6 scale of SPD	N/A	Individual or group counseling	N=168 (23%) treated with open-label	Not reported	Varenicline not associated with increases in scores of serious	Smokers with SPD less likely to quit smoking than those without

	Sample size	Exclusion criteria	Intervention	Trial Design	Adverse events	Mood Outcomes	Smoking Outcomes
				varenicline for up to 6 months		psychological distress vs. other medications	
Gunnell (2009)	80,660 smokers in UK primary care network Included 2244 (3.5%) taking an antidepressant	N/A	Not reported	10973 received open-label varenicline up to 12 weeks (vs NRT or bupropion)	Not reported	No difference in self-harm between medication treatment groups. No evidence of increased depression in patients taking varenicline with history of depression.	Not reported
Tonstad (2010)	N= 5096 smokers from 10 studies	Past year depression, alcohol or drug dependence or lifetime panic disorder, psychosis, bipolar disorder	Individual counseling	DB-PC varenicline vs. placebo for 6, 12 or 52 weeks	Varenicline associated with more sleep disturbance	No higher rate of psychiatric adverse events in varenicline group. No cases of suicidal ideation or behavior in varenicline-treated subjects.	Not reported
Garza (2011)	N=110	Current/past psychiatric illness by SCID; h/o suicidal thoughts or behavior		DB-PC varenicline vs. placebo for 12 weeks	Nausea, insomnia, somnolence, and abnormal dreams were more frequent in the varenicline group	Comprehensive weekly assessments for neuropsychiatric symptoms. No differences in rating for anxiety, depression, agitation, other symptoms between groups. No reports of suicidality.	
Weiner (2011)	N=9 smokers with schizophrenia or schizoaffective disorder	N/A	Individual counseling	DB-PC varenicline vs. placebo for 12 weeks	Constipation, nausea and insomnia	No worsening of psychotic, depressive or other psychiatric symptoms or suicidal ideation.	Reduced smoking in varenicline group

NRT= nicotine replacement therapy; SPD=serious psychological distress

PTSD= post traumatic stress disorder; ADHD= attention deficit hyperactivity disorder; SCID= Structured Clinical Interview for DSM for Axis I and II disorders