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Varenicline for tobacco dependence: panacea or plight?

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Introduction: This review examines the postmarketing 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. 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.

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-to-benefit ratio of receiving varenicline to quit smoking must include the increased chances of quitting smoking and avoiding the sizeable risks of smoked-caused disease and death that remain if tobacco addiction is not properly treated.

Keywords: pharmacotherapy, smoking, smoking cessation, tobacco, varenicline

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1. Introduction

The 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 (**Box 1**) compound approved by the 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 α4β2 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 α4β2 selective nicotinic receptor partial agonists like varenicline would be ideally suited to smoking cessation by blocking the action of nicotine and at the same time providing a low level of dopaminergic activation to limit

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Box 1. Drug summary.

Drug name	Varenicline
Phase	Launched
Launched indication	Smoking cessation
Pharmacology description	Neuronal nicotinic receptor partial agonist
Route of administration	Alimentary, po
Chemical structure	
Pivotal trial(s)	Randomized, double-blind, placebo-controlled, parallel-assignment Phase III trial (Inter-ACTIV ; 2008-007948-34; ANRS 144)

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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 with placebo but also when compared with sustained-release bupropion in a head-to-head comparison [5,6]. A third study demonstrated superiority of continuing varenicline (compared with 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 seemed to be mild and limited to mainly nausea and sleep disturbance. The drug is eliminated in the body almost exclusively by the kidneys 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 because of the possibility of serious neuropsychiatric side effects, although data on this are limited to mostly case reports. Use has been decreasing owing to anecdotal reports in the media of serious side effects and consequent bans in certain hospital or employment settings. This review examines the recent story of postmarketing experience with varenicline and reviews all available evidence for current recommendations.

2. Introduction to the compound

Varenicline is a selective nicotinic receptor partial agonist that binds specifically and potently at the $\alpha4\beta2$ receptor, which is one of the main subtypes of nicotinic receptors implicated in nicotine addiction. 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 $\alpha7$, affinity for $\alpha4\beta2$ 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 – 30 h [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 0.5 mg twice daily.

3. Clinical efficacy

Several trials have shown that varenicline is efficacious for smoking cessation. Varenicline increases the chances of quitting smoking nearly threefold compared with placebo and by 50% 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, 95% CI 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 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, two 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 comorbid 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 with the general population [16,17]. Clinical samples of individuals trying to quit smoking reveal sizeable percentages (~ 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 previous depression or substance use and adjusting for other suicide predictors including previous 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.

4. 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 FDA 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

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) [30]	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) [31]	Schizophrenia	Thiothixene	5 days	20 – 40 cpd, no change	Worsening psychosis, psychomotor agitation	Varenicline stopped; symptoms resolved
Kohen (2007) [32]	Bipolar disorder	Valproic acid	1 week	Stopped smoking	Mania	Varenicline stopped; symptoms resolved in 1 week but was also treated with olanzapine
Kutscher (2009) [33]	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) [34]	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) [35]	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) [36]	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) [37]	PTSD, depression, alcohol dependence	Fluoxetine, nortriptyline, quetiapine, prazosin, pramipexole, terazosin, atenolol, spironolactone	19 days	40 cpd to 2 cpd	Visual hallucinations	Varenicline stopped; symptoms resolved in 3 days
Ismail (2010) [38]	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) [39]	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
Pirmoradi (2008) [40]	Major depression, alcohol dependence		7 days	4 – 5 cpd	Severe anxiety, nausea, vertigo, blurred vision and dizziness	Varenicline stopped; symptoms resolved in 3 days

cpd: Cigarettes per day smoked; GAD: Generalized anxiety disorder; h/o: History of; UDS: Urine drug screen.

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 with 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 so far has been 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, 6422 treated with bupropion and 63 265 treated with nicotine-replacement therapy [55]. Over the follow-up period there were 166 episodes of nonfatal 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 with 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 (HR = 0.88, 95% CI 0.77 – 1.00), and varenicline-treated patients were also significantly less likely to die during the follow-up period (HR = 0.26, 95% CI 0.13 – 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 postmarketing reports of drowsiness from varenicline prompting caution while driving/using machinery, somnolence was noted infrequently (< 3%) in clinical trial data [56].

5. 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 nonsmokers, 1 mg varenicline produced significantly greater experience of 'drug high' with an associated greater abuse potential score compared with placebo. There was no difference between 3 mg varenicline and placebo for drug high, drug liking or abuse potential score among nonsmokers and 3 mg was associated with greater levels of unpleasant effects including nausea. Overall, McColl *et al.* [62] concluded that 'varenicline is unlikely to be abused'.

In addition to its partial agonist properties, varenicline works as an antagonist at $\alpha 4\beta 2$ nicotinic acetylcholine receptors to block the rewarding effects of nicotine. Perkins *et al.* [63] evaluated varenicline's effects on acute smoking behavior and reward in smokers willing to try to quit for 1 week. Participants were designated as being high or low in quitting interest and were asked retrospectively to rate cigarette liking for the cigarettes they smoked in the previous 24 h. 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 (vs placebo), while no influence of varenicline was detected among women. When prospectively assessing the cigarettes smoked on the testing day, varenicline (vs 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 nondependent, heavy drinkers receiving 7 days of pretreatment 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 *et al.* [65] found varenicline to reduce ratings of cigarette satisfaction, relief and liking during a scheduled smoking lapse. Comparable effects were found for intravenous nicotine. Sofuoglu *et al.* [66] found that, after overnight abstinence, 12 nontreatment-seeking smokers' ratings of intravenous nicotine strength, high, head rush and stimulation were reduced after a 4-day treatment period of 1 mg/day varenicline.

In more traditional cessation studies, Ebbert *et al.* [67] found that varenicline reduced satisfaction and reward in smokeless

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) [49]	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) [50]	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. 1 patient discontinued due to worse mood	8 stopped smoking (44%), 9 reduced significantly and 1 had no change
Stapleton (2008) [51]	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) [52]	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. 5 self-reported worsening of psychiatric symptoms (depression, agitation, impulsivity)	Smokers with mental illness less likely to quit than those without history
McClure (2010) [20]	n = 542; 271 had previous 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) [53]	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 effect, measured with the PANAS	Significant smoking reduction and more weeks without smoking in varenicline group. No change in cocaine use

ADHD: Attention deficit hyperactivity disorder; DB-PC: Double-blind , placebo controlled; h/o: History of; NRT: Nicotine replacement therapy; PTSD: Post-traumatic stress disorder; SCID: Structured Clinical Interview for DSM for Axis I and II disorders; SPD: Serious psychological distress.

Table 2. Reported neuropsychiatric adverse events during varenicline use use in clinical trials (continued).

	Sample size	Exclusion criteria	Intervention	Trial design	Adverse events	Mood outcomes	Smoking outcomes
Steinberg (2011) [54]	n = 723 smokers assessed with K6 scale of SPD	N/A	Individual or group counseling	n = 168 (23%) treated with open-label vareni-cline for up to 6 months	Not reported	Varenicline not associated with increases in scores of serious psychological distress vs other medications	Smokers with SPD less likely to quit smoking than those without
Gunnell (2009) [55]	80 660 smokers in UK primary care network; included 2244 (3.5%) taking an antidepressant	N/A	Not reported	10 973 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) [56]	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) [57]	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) [48]	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

ADHD: Attention deficit hyperactivity disorder; DB-PC: Double-blind , placebo controlled; h/o: History of; NRT: Nicotine replacement therapy; PTSD: Post-traumatic stress disorder; SCID: Structured Clinical Interview for DSM for Axis I and II disorders; SPD: Serious psychological distress.

tobacco users, and West *et al.* [68] found that varenicline reduced ratings of satisfaction and psychological reward after the first cigarette smoked after a target quit date compared with bupropion or placebo. Overall, these studies provide support for the rationale that varenicline has a dual mechanism of action: i) by directly reducing the severity of nicotine cravings and withdrawal symptoms in abstaining smokers; and ii) by reducing the rewarding effects during a smoking lapse episode in smokers trying to quit.

6. Newer clinical trials

Varenicline has demonstrated good efficacy in achieving abstinence from smoking in numerous clinical trials published up to now [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 comorbidity 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 have become available regarding the use and duration of varenicline, comparison with other treatments, as well as the potential benefit of combining varenicline with other pharmacotherapy.

7. 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 were nausea (40%), abnormal dreams (23%) and insomnia (19%), with fewer leading to discontinuation (nausea, 8%; insomnia, 3%; 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 whereby subjects could choose a quit date between days 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 and 2 mg daily) for weeks 2 to 12. End-of-treatment (week 12) and 52-week 7-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 adverse events led to treatment discontinuation (varenicline 7% and placebo 4.5%) [71].

8. Comparison of varenicline with nicotine replacement therapy

So far, there have been no randomized, placebo-controlled trials directly comparing varenicline with nicotine replacement therapies (NRT). In open-label, nonrandomized 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.

9. 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 7-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 which used nonrandomized 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% 30-day point abstinence rate was reported at 6-month follow-up. Abstinence and adverse event rates were similar to the usual care group who received standard pharmacotherapy regimens [75]. These preliminary studies indicate that combining varenicline with other smoking cessation medicines is safe, but up to now there has been no clear evidence from randomized trials of an increased efficacy resulting from combination versus monotherapy with varenicline.

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10. Varenicline use in smokers with medical comorbidity

10.1 Cardiovascular disease

Tobacco use remains a leading risk factor for the development of cardiovascular disease (CVD). 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 CVD who received varenicline or placebo for 12 weeks [76]. Continuous abstinence rates were higher for varenicline than for placebo during weeks 9 - 12 (47.0 vs 13.9%; OR = 6.11, 95% CI 4.18 – 8.93) and weeks 9 – 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 – 5.0), serious adverse events (6.5 vs 6.0%; 95% CI -3.1 – 4.1) or all-cause mortality (0.6 vs 1.4%; 95% CI -2.3 – 0.6).

Very recent data also support 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.

10.2 Chronic obstructive pulmonary disease

Smoking is the most important risk factor for the development of chronic obstructive pulmonary disease (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 multicenter trial of 504 smokers with mild-to-moderate COPD [78], the week-9 – 12 continuous abstinence rate was significantly higher for varenicline (42.3%) than for 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 adverse events for varenicline. Serious adverse events were infrequent in both treatment groups.

10.3 Hospitalized smokers

No study published so far 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 to 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 used postdischarge 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 rehospitalized 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.

11. Varenicline use in specific populations

11.1 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 [80]. 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 with pooled trials among predominantly Western populations. Among 893 smokers from three 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 adverse events occurred in four varenicline and five placebo participants. Discontinuations due to adverse events 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. Adverse events 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.

11.2 Adult light smokers

Previous varenicline studies have included smokers of 10 or more cigarettes a day only. Owing to factors such as increased cigarette prices and smoke-free air legislation, smokers of fewer cigarettes a day are becoming more common. In an observational study of nearly 37 000 adult smokers of 10 or fewer cigarettes a day from the French cessation services, varenicline was found to double the odds of abstinence at 1-month follow-up [81].

12. 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 (> 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 – 1.87; p < 0.001) and at 26 weeks (45 vs 34%; RR = 1.42, 95% CI 1.08 – 1.79; p = 0.012) [82]. 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.

13. Conclusion

Following the early efficacy trials, subsequent data have shown that varenicline continues to be effective in a broader range of tobacco users with medical, behavioral and diverse demographic characteristics. Now that additional clinical trials in specific populations [76,78,80] 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 so far 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 more than 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. Eleven per cent 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.

14. 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: i) it reduces the severity of nicotine withdrawal symptoms and cravings; and ii) 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 indicate 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 the smoker receives assistance in the form of counseling (individual, group or telephonic) and other social support to persist with their quit attempt.

10) Future research should examine further 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.

Declaration of interest

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. Arch Intern Med 2006;166:1553-9

2. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005;48:3474-7

3. Kuehn BM. FDA speeds smoking cessation drug review. JAMA 2006;295:614

4. Fontanarosa PB, DeAngelis CD. Update on JAMA-EXPRESS Rapid Review and Publication. JAMA 2008;300:2920-1

5. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation. A randomized controlled trial. JAMA 2006;296:47-55

6. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation. A randomized controlled trial. JAMA 2006;296:56-63

7. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006;296:64-71

8. Obach RS, Reed-Hagen AE, Krueger SS, et al. Metabolism and disposition of varenicline, a selective alpha4beta2 acetylcholine receptor partial agonist, in vivo and in vitro. Drug Metab Dispos 2006;34:121-30

9. Eisenberg MJ, Filion KB, Yavin D, et al. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. CMAJ 2008;179:135-44

10. Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC Public Health 2006;6:300

11. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2011;16

•• This important paper reviews the efficacy and tolerability of nicotine receptor partial agonists such as varenicline for smoking cessation from 11 trials of varenicline compared with placebo for smoking cessation; three of these included a bupropion experimental arm. Details of how varenicline at standard dose increases the chances of successful long-term smoking cessation are provided. Benefits for cessation and reduction in the incidence of adverse events with lower-dose regimen are also discussed.

12. Ravva P, Gastonguay MR, French JL, et al. Quantitative assessment of exposure response relationships for the efficacy and tolerability of varenicline for smoking cessation. Clin Pharmacol Ther 2010;87:336-44

13. Hughes JR, Keely JP, Niaura RS, et al. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob Res 2003;5:13-25

14. Dervaux A, Kanit M, Laqueille X. Efficacy of varenicline for smoking cessation. JAMA 2006;296:2555; author reply 2555-6

15. Lasser KE, Boyd JW. Varenicline and smokers with mental illnesses. Lancet 2008;372:1218-19

16. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284:2606-10

17. Hagman BT, Delnevo CD, Hrywna M, Williams JM. Tobacco use among those with serious psychological distress: findings from the National Survey of Drug Use and Health, 2002. Addict Behav 2008;33:582-92

18. Han ES, Foulds J, Steinberg MB, et al. Characteristics and smoking cessation outcomes of patients returning for repeat tobacco dependence treatment. Int J Clin Pract 2006;60:1068-74

19. Piper ME, Smith SS, Schlam TR, et al. Psychiatric disorders in smokers seeking treatment for tobacco dependence: relations with tobacco dependence and cessation. J Consult Clin Psychol 2010;78:13-23

20. McClure JB, Swan GE, Catz SL, et al. Smoking outcome by psychiatric history after behavioral and varenicline treatment. J Subst Abuse Treat 2010;38:394-402

21. Clarke DE, Eaton WW, Petronis KR, et al. Increased risk of suicidal ideation in smokers and former smokers

compared to never smokers: evidence from the baltimore ECA follow-up study. Suicide Life Threat Behav 2010;40:307-18

22. Breslau N, Schultz LR, Johnson EO, et al. Smoking and the risk of suicidal behavior: a prospective study of a community sample. Arch Gen Psychiatry 2005;62:328-34

23. Ostacher MJ, Nierenberg AA, Perlis RH, et al. The relationship between smoking and suicidal behavior, comorbidity, and course of illness in bipolar disorder. J Clin Psychiatry 2006;67:1907-11

24. Oquendo MA, Bongiovi-Garcia ME, Galfalvy H, et al. Sex differences in clinical predictors of suicidal acts after major depression: a prospective study. Am J Psychiatry 2007;164:134-41

25. Moriya F, Hashimoto Y, Furumiya J. Nicotine and cotinine levels in body fluids of smokers who committed suicide. Forensic Sci Int 2007;168(2–3):102-5

26. Berlin I, Henian C, Covey LS. Depressive mood, suicide ideation and anxiety in smokers who do and smokers who do not manage to stop smoking after a target quit day. Addiction 2010;105:2209-16

27. Kuehn BM. Studies linking smoking-cessation drug with suicide risk spark concerns. JAMA 2009;301:1007-8

28. US Food and Drug Administration. Drug Safety and Availability; 2010. Available from: www.fda.gov/Drugs/Drugsafety [Last accessed 1 March 2011]

29. Moore TJ, Glenmullen J, Furberg CD. Thoughts and acts of aggression/violence toward others reported in association with varenicline. Ann Pharmacother 2010;44:1389-94

30. Popkin MK. Exacerbation of recurrent depression as a result of treatment with varenicline. Am J Psychiatry 2008;165:774

31. Freedman R. Exacerbation of schizophrenia by varenicline. Am J Psychiatry 2007;164:1269

32. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. Am J Psychiatry 2007;164:1269-70

33. Kutscher EC, Stanley M, Oehlke K. Chantix-induced mental status changes in a young healthy female. S D Med 2009;62:193-195

34. DiPaula BA, Thomas MD. Worsening psychosis induced by varenicline in a hospitalized psychiatric patient. Pharmacotherapy 2009;29:852-7

35. Lyon GJ. Possible varenicline-induced paranoia and irritability in a patient with major depressive disorder, borderline personality disorder, and methamphetamine abuse in remission. J Clin Psychopharmacol 2008;28:720-1

36. 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;13:511-14

37. Raidoo BM, Kutscher EC. Visual hallucinations associated with varenicline: a case report. J Med Case Reports 2009;3:7560

38. Ismail Z, Syms J, Blumberger D, George TP. Varenicline induced polydipsia and hyponatremia in a patient with schizophrenia. Schizophr Res 2010;119:268

39. Morstad AE, Kutscher EC, Kennedy WK, Carnahan RM. Hypomania with agitation associated with varenicline use in bipolar II disorder. Ann Pharmacother 2008;42:288-9

40. Pirmoradi P, Roshan S, Nadeem SS. Neuropsychiatric disturbance after initiation of varenicline in a patient with a history of alcohol abuse and major depression. Am J Health Syst Pharm 2008;65:1624-6

41. Bird ML, Vesta KS. Varenicline-associated acute renal failure. Ann Pharmacother 2008;42:1908-11

42. Duparc A, Gosset P, Caron J, et al. Acute generalized exanthematous pustulosis caused by varenicline. J Eur Acad Dermatol Venereol 2009;23:1111-12

43. Kristensen PL, Pedersen-Bjergaard U, Thorsteinsson B. Varenicline may trigger severe hypoglycaemia in type 1 diabetes. Diabet Med 2008;25:625-6

44. Smith RC, Lindenmayer JP, Davis JM, et al. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. Schizophr Res 2009;110:149-55

45. Fatemi SH. Varenicline efficacy and tolerability in a subject with schizophrenia. Schizophr Res 2008;103:328-9

46. Evins AE, Goff DC. Varenicline treatment for smokers with schizophrenia: a case series. J Clin Psychiatry 2008;69:1016

47. Anghelescu I. Successful smoking cessation and improvement of negative symptoms with varenicline in a stable schizophrenia patient. J Neuropsychiatry Clin Neurosci 2009;21:102-3

48. 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):94-5

49. McClure JB, Swan GE, Jack L, et al. Mood, side-effects and smoking outcomes among persons with and without probable lifetime depression taking varenicline. J Gen Intern Med 2009;24:563-9

50. Philip NS, Carpenter LL, Tyrka AR, et al. Varenicline augmentation in depresses smokers: an 8-week, open-label study. J Clin Psychiatry 2009;70:1026-31

51. 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;103:146-54

•• This paper evaluates the effectiveness of varenicline with nicotine replacement for smoking cessation and to evaluate the safety and effectiveness of varenicline in people with mental illness. Details include higher short-term cessation success rates and effectiveness among those with mental illness. It also provides details on higher adverse drug symptoms but better tolerability among those taking varenicline. There was no evidence that varenicline exacerbated mental illness.

52. Purvis TL, Mambourg SE, Balvanz TM, et al. Safety and effectiveness of varenicline in a veteran population with a high prevalence of mental illness. Ann Pharmacother 2009;43:862-7

53. Poling J, Rounsaville B, Gonsai K, et al. The safety and efficacy of varenicline in cocaine using smokers maintained on methadone: a pilot study. Am J Addict 2010;19:401-8

54. Steinberg MB, Bover MT, Richardson DL, et al. Abstinence and psychological distress in co-morbid

smokers using various pharmacotherapies. Drug Alcohol Depend 2011;114:77-81

55. 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

•• Important paper summarizing risk of suicide and suicidal behavior for those using varenicline to quit smoking compared with alternative treatments bupropion and nicotine replacement therapy. Authors conclude that despite the twofold increased risk of self-harm with varenicline, there was no evidence of increased risk of depression or suicidal thoughts.

56. Tonstad S, Davies S, Flammer M, et al. Psychiatric adverse events in randomized double-blind, placebo-controleld clinical trials of varenicline. A pooled analysis. Drug Saf 2010;33:289-301

•• This study assesses the incidence and relative risk of psychiatric disorders in 10 randomized, double-blind, placebo-controlled trials of varenicline for smoking cessation. There was no significant increase in overall psychiatric disorders, other than sleep disorders and disturbances, in varenicline-treated subjects in this sample of smokers without current psychiatric disorders.

57. Garza D, Murphy M, Tseng LJ, et al. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. Biol Psychiatry 2011;69(11):1075-82

58. Stapleton J. Do the 10 UK suicides among those taking the smoking cessation drug varenicline suggest a causal link? Addiction 2009;104:864-5

59. Henningfield JE, Shiffman S, Ferguson SG, Gritz ER. Tobacco dependence and withdrawal: science base, challenges and opportunities for pharmacotherapy. Pharmacol Ther 2009;123:1-16

60. Spiller K, Xi Z-X, Li X, et al. Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of a4b2 nicotinic receptors in rats. Neuropharmacology 2009;57:60-6

61. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the a4b2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007;52:985-94

62. McColl SL, Burstein AH, Reeves KR, et al. Human abuse liability of the smoking cessation drug varenicline in smokers and nonsmokers. Clin Pharmacol Ther 2008;83:607-14

63. Perkins KA, Mercincavage M, Fonte CA, et al. Varenicline's effects on acute smoking behavior and reward and their association with subsequent abstinence. Psychopharmacology 2010;210:45-51

64. McKee SA, Harrison ELR, O'Malley SS, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry 2009;66:185-90

65. Patterson F, Jepson C, Strasser AA, et al. Varenicline improves mood and cognition during smoking abstinence. Biol Psychiatry 2009;65:144-49

66. Sofuoglu M, Herman AI, Mooney M, Waters AJ. Varenicline attenuates some of the subjective and physiological effects of intravenous nicotine in humans. Psychopharmacology 2009;207:153-62

67. Ebbert JO, Croghan IT, North F, Schroeder DR. A pilot study to assess smokeless tobacco use reduction with varenicline. Nicotine Tob Res 2010;12:1037-40

68. West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. Psychopharmacology 2008;197:371-7

69. Williams KE, Reeves KR, Billing CB Jr, et al. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Curr Med Res Opin 2007;23:793-801

70. Russ C, Rennard S, Arteaga C, Hughes J. Is setting a quit date a priori essential? A comparison of studies of varenicline using flexible vs. a priori quit date protocols. Poster presented at the Society for Research on Nicotine and Tobacco (SRNT) 17th Annual Meeting, 16 – 19 February 2011, Westin Harbour Castle, Toronto, Canada

71. Niaura R, Hays JT, Jorenby DE, et al. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. Curr Med Res Opin 2008;24:1931-41

72. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008;63:717-24

73. Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Clinical practice guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service, 2008

74. Issa JS, Ogawa TM, Soares de Moura AS, Pereira AC. Effectiveness of varenicline combination therapy in real life setting: PAF database study. Poster presented at the Society for Research on Nicotine and Tobacco (SRNT) 17th Annual Meeting, 16 – 19 February 2011, Westin Harbour Castle, Toronto, Canada

75. Ebbert JO, Burke MV, Hays JT, Hurt RD. Combination treatment with varenicline and nicotine replacement therapy. Nicotine Tob Res 2009;11:572-6

76. Rigotti NA, Pipe AL, Benowitz NL, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation 2010;121:221-9

•• Important prospective trial indicating that varenicline is not only effective for smoking cessation among smokers with CVD, but is also well tolerated and did not increase cardiovascular events or mortality.

77. Willers S. Smoking cessation treatment using varenicline in a patient population with mostly heart and lung diseases. Poster presented at the Society for Research on Nicotine and Tobacco (SRNT) Annual Meeting, 16 – 19 February 2011, Westin Harbour Castle, Toronto, Canada

78. Tashkin DP, Rennard S, Hays JT, et al. Effects of varenicline on smoking cessation in mild-to-moderate COPD: a randomized controlled trial. Chest 2011;139(3):591-9

79. Steinberg MB, Randall J, Greenhaus S, et al. Tobacco dependence treatment intervention for hospitalized smokers: a pilot randomized, controlled trial. Poster presented at the Society for Research on Nicotine and Tobacco (SRNT) Annual Meeting, 16 – 19 February 2011, Westin Harbour Castle, Toronto, Canada

80. Xiao Y, Lv Y, Zhang X, et al.
The pharmacokinetic and tolerability
profile of varenicline in healthy Chinese
volunteers. Int J Clin Pharmacol Ther
2009;47:246-54

81. Baha MY, Le Faou AL.
Smoking cessation interventions offered
to French adult light smokers:
a heterogeneous population with specific
needs. Eur Addict Res 2010;16:162-9

82. Fagerstrom K, Gilljam H, Metcalfe M,
et al. Stopping smokeless tobacco with
varenicline: randomised double blind
placebo controlled trial. BMJ
2010;341:c6549

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