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Discovery and development of varenicline for smoking cessation

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Abstract

Introduction: Tobacco use causes one premature death every six seconds. Current smoking cessation aids include nicotine replacement therapies and bupropion. Although more than 70% of smokers express a desire to quit, fewer than 3% remain abstinent for more than one year, highlighting a critical need for more efficacious smoking cessation treatments.

Areas Covered: The authors discuss the rationale, preclinical and clinical development of varenicline for smoking cessation. They cover the formulation of varenicline as a partial agonist at $\alpha_4\beta_2$ receptors, the primary neural substrate for nicotine reward. Then, they discuss evidence from preclinical studies indicating varenicline's efficacy in blocking nicotine reward, followed by clinical trials demonstrating safety and efficacy in sustaining abstinence in smokers. Finally, they cover post-market surveillance, including contraindications in heavy machine operators, putative cardiovascular risk, and the repealed warning for adverse neuropsychiatric events.

Expert opinion: Varenicline development was based on strong theoretical rationale and preclinical evidence. Clinical studies indicate that varenicline is safe and more effective in sustaining abstinence than placebo, bupropion or nicotine replacement therapies. However, given that continuous abstinence rates across studies remain low (18~30% with varenicline; 4~10% with placebo), novel and more effective medications targeting other nicotinic or glutamate receptors for smoking cessation are required.

Keywords

Acetylcholine receptor; addiction; nicotine; smoking cessation; varenicline

1. Introduction

Tobacco use results in one premature death every six seconds globally [1]. Every year 7 million people die worldwide from tobacco-related health problems, including cardiovascular and respiratory disease. Of these, 6 million deaths are estimated to result directly from tobacco use, while the remaining represent non-smokers exposed to second-

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. One referee declares that they have received honoraria for consulting and for lectures for the manufacturer of varenicline (Pfizer) as well as from other manufacturers of drugs for smoking cessation (GlaxoSmithKline and Novartis).

hand smoke [2]. In the United States alone, 16 million individuals are living with a disease caused by smoking [3], and 35.6 million people are current smokers aged 18 or older (15.1% of the U.S. population; [3]. With an estimated economic cost of 300 billion U.S. dollars per year, smoking is the second most expensive chronic health condition next to cardiovascular disease in the U.S. [3, 4]. Despite the massive individual and public costs of smoking, more than one billion people worldwide continue to use tobacco and nicotine-related products regularly [2].

Tobacco use disorder, as defined by the DSM-V, includes symptoms such as consuming larger quantities of tobacco over time than originally intended, tobacco cravings, unsuccessful attempts to quit or reduce tobacco use, withdrawal symptoms during cessation, and continued tobacco use despite adverse social and health consequences [5]. Although up to 70% of smokers express a desire to quit smoking, 80% of those who try to quit return to smoking within the first month, less than 20% quit for six months, and only 3% remain abstinent for more than one year [6, 7]. With more than 3,200 youth initiating cigarette use each day [7], more people are likely to become addicted to tobacco every year than manage to quit. Taken together, these observations highlight an urgent need for efficacious treatments of tobacco addiction to reduce the individual and public costs of smoking. In this mini-review, we do not intend to give a comprehensive review for the use of varenicline as a tobacco smoking cessation aid, but rather focus on the rationale for varenicline's development as a smoking cessation aid and major findings regarding varenicline use in both preclinical and clinical studies, as well as the current challenges and future research directions in medication discovery for treatment of nicotine addiction.

2. Preclinical development of varenicline for smoking cessation

2.1. Neural mechanisms of tobacco addiction

The primary addictive component in tobacco is nicotine. Nicotine acts by binding to nicotinic acetylcholine receptors (nAchRs) located in the central and peripheral nervous systems [8]. In the brain, nAchRs are pentameric structures composed of a combination of five different subunits, including nine α-subunits (α_2-$\alpha 2_{10}$) and three β-subunits (β_2- β_4), which result in at least 12 unique nAchR subtypes that have been identified thus far [8–10]. There are also non-neuronal nicotinic receptor subunits, including α_1, β_1, γ, δ, and ε, which comprise nAchRs in the peripheral nervous system, most notably at the neuromuscular junction [11]. Neuronal nAChRs are typically composed of either two α and three β subunits (Figure 1), or five α_7 subunits. The $\alpha_4\beta_2$ and α_7 receptor subtypes are the most common in the brain, and are localized both pre- and post-synaptically [8, 9]. Activation of nAChRs by nicotine, or the endogenous ligand acetylcholine, increases neuronal excitability and neurotransmitter release via opening of a gated ion channel and subsequent Ca^{2+} and Na^{+} influx intracellularly (Figure 1) [10, 12, 13].

About one third of $\alpha_4\beta_2$ nAchRs are located on dopamine (DA) cells of the mesolimbic DA system [10, 14]. This mesolimbic DA system is comprised of projections from DA neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and prefrontal cortex (PFC; Figure 1) [15]. Nicotine binding to $\alpha_4\beta_2$ receptors on VTA DA cells stimulates DA release to the NAc [16, 17], an effect which is thought to underlie nicotine's rewarding and

reinforcing effects [16]. Evidence for $\alpha_4\beta_2$ receptor involvement in nicotine addiction derives from both human and animal studies. For example, positron emission tomography (PET) studies in humans indicate that smoking a full nicotine cigarette nearly saturates $\alpha_4\beta_2$ receptor occupancy [18]. In rodents, systemic blockade of the $\alpha_4\beta_2$ receptor by mecamylamine or dihydro-β-erythroidine (DHβE) suppresses nicotine self-administration [19]. Moreover, genetic deletion (knockout) of either the α_4 subunit or the β_2 subunit, but not the α_7 subunit, in mice eliminates intravenous nicotine self-administration [20] as well as nicotine-induced VTA DA neuron firing [21]. In contrast, genetic modifications that *increase* α4 sensitivity to nicotine augment nicotine conditioned place preferences, facilitate tolerance to nicotine's hypothermic effects, and escalate nicotine-induced locomotor sensitization in mice [8, 22]. Finally, selective restoration of either α_4 or β_2 expression in the VTA, but not the neighboring substantia nigra, using lentiviral vectors also restores nicotine self-administration in knockout mouse models [20]. Taken together, these observations strongly implicate VTA $\alpha_4\beta_2$ nAchRs in nicotine addiction, and suggest the $\alpha_4\beta_2$ receptor represents an attractive medicinal target for the treatment of tobacco use disorders.

2.2. Rationale of developing a partial agonist for smoking cessation

Prior to the development of varenicline, available pharmacotherapies for smoking cessation included nicotine replacement therapies (NRTs) such as gum, patches, nasal sprays and inhalers, as well as bupropion, an antidepressant which inhibits DA and norepinephrine reuptake as well as nAchR activity [23]. Modulating nAChRs can be accomplished using full agonists, antagonists, or partial agonists. Full agonists like NRTs mimic nicotine's effects. Since the cessation of nicotine use is the major reason for producing unpleasant withdrawal symptoms, NRTs can help relieve some physical withdrawal by providing supplemental low doses of nicotine, without the other harmful chemicals in tobacco. Antagonists, such as mecamylamine and DHβE, can compete with nicotine to bind to nAChRs and thus block nicotine reward [19]. However, nAchR antagonists produce precipitated withdrawal symptoms including irritability, depression, insomnia, fatigue, headaches, constipation, and weight gain [24, 25]. In contrast, partial agonists bind to nAchRs but do not elicit the maximum response of a full agonist [26], instead depending upon receptor occupancy by other ligands. For example, in the presence of a full agonist like nicotine a partial nAchR agonist will behave as an antagonist, attenuating nicotine's effects at the receptor. However, in the absence of nicotine a partial nAchR agonist will behave as an agonist and mitigate withdrawal symptoms. Partial nAchR agonists therefore have potential to block nicotine reward, minimize craving, and prevent withdrawal, suggesting this mechanism may be an ideal medicinal target for nicotine addiction.

2.3. Cytisine: An initial discovery of a partial agonist for smoking cessation

Cytisine is an alkaloid with a molecular structure similar to nicotine (Figure 2) and has high affinity for the $\alpha_4\beta_2$ nAchR subtype [27]. Cytisine is derived from the plant *Cytisus laburnum*, a deciduous shrub that is native to central and southern Europe. Preclinically, cytisine produces locomotor activation and substitutes for nicotine in self-administration studies, suggesting it may have modest abuse potential [28]. However, cytisine does not induce reinstatement to nicotine-seeking behaviors following extinction and at higher doses blocks

the discriminative effects of nicotine [28], suggesting cytisine is unlikely to induce relapse to nicotine seeking during abstinence.

Cytisine was first discovered in 1818 and was isolated in 1865 (see timeline in Figure 3) [29]. In 1912, cytisine's biological effects were reported to be nearly identical to those of nicotine, and cytisine was proposed as an inexpensive, readily available replacement for tobacco [30]. Consequently, the Cytisus plant was reportedly smoked during World War II by German and Russian soldiers as a tobacco substitute [29]. In 1964, a Bulgarian pharmaceutical company named Sopharma marketed cytisine as a smoking cessation aid under the brand name "Tabex" [29]. Although clinical trials during the 1960's and 1970's reported that cytisine produced quit rates between 21–30% at six-month follow-up, these studies were not conducted systematically. A later placebo-controlled trial published in the *New England Journal of Medicine* reported more modest effects of cytisine on sustained abstinence at 12-month follow up: 8.4% of subjects remained abstinent on cytisine compared to 2.4% on placebo [31]. Similarly, a more recent meta-analysis based on two studies deemed to be of high quality reported a ~three-fold increase (random ratio = 3.29) in the likelihood of maintaining abstinence at six-month follow-up with cytisine use compared to placebo [32]. Cytisine's low efficacy may be due in part to poor absorption and crossing of the blood brain barrier [33]. Although cytisine is superior to NRTs in maintaining abstinence from smoking, it is also associated with more adverse events and side effects, including hospitalizations, mild, moderate and severe adverse events (such as symptoms of cold or flu), nausea and vomiting, and sleep disorders [34]. Today there remains a "call for action" to provide cytisine as a smoking cessation agent in lower income countries, but cytisine is not approved by the European Union or the United States' Food and Drug Administration (FDA) for human use [35]. Taken together, these observations indicate a need for a more efficacious $\alpha_4\beta_2$ receptor partial agonist for the treatment of nicotine addiction and smoking cessation.

2.4. Varenicline: a novel partial agonist for the treatment of nicotine addiction

Varenicline tartrate was originally developed as a smoking cessation agent by Pfizer in 1997 based on the molecular structure of cytisine (Figure 2). There are currently 3 patents protecting varenicline under the brand name Chantix®, which are set to expire in the year 2020 in the U.S. [36]. Varenicline is a highly selective and potent partial agonist at the $\alpha_4\beta_2$ nAchR, with 500-fold selectivity for $\alpha_4\beta_2$ over $\alpha_3\beta_4$, 3500-fold selectivity over α_7, and 20,000-fold selectivity over $\alpha_1\beta\gamma\delta$ [37]. *In vitro* binding assays indicate that varenicline affinity for $\alpha_4\beta_2$ (K_i=0.15 nM) is higher than that of cytisine (K_i=0.23 nM) as well as nicotine (K_i=1.6 nM; see Figure 2) [38–40]. Consistent with a partial agonist profile, patch clamp studies using HEK cells expressing human nAchRs show that varenicline exhibits ~45% of nicotine's maximal efficacy at the $\alpha_4\beta_2$ receptor, with an EC_{50} of 3.1 μM [39]. When co-administered with nicotine, varenicline blocks nicotine-induced DA release in the NAc through activity at the $\alpha_4\beta_2$ and $\alpha_6\beta_2$ receptor subtypes [38, 39, 41].

Preclinical studies indicate that varenicline is superior to cytisine in reducing nicotine addiction-related behaviors (Table 1). In rodents, varenicline attenuates nicotine-induced locomotor sensitization, blocks nicotine conditioned place preferences, reduces nicotine self-administration under fixed- and progressive-ratio schedules, and suppresses nicotine-primed

as well as cue-induced reinstatement of nicotine seeking following intraperitoneal, subcutaneous, or oral routes of administration [39, 42–45]. Varenicline also selectively blocks nicotine's effects on brain stimulation reward in intracranial self-stimulation (ICSS) paradigms through activity at the $\alpha_4\beta_2$, but not the α_7, nAchR [46]. Finally, varenicline attenuates the dysphoria associated with nicotine withdrawal as measured by ICSS thresholds [47]. Taken together, these preclinical findings indicate varenicline may not only attenuate nicotine reward and intake, but could reduce the risk of relapse and mitigate withdrawal symptoms in nicotine-dependent subjects.

Preclinical studies also suggest that varenicline has low abuse liability itself (Table 1). When administered alone, varenicline is 40–60% less efficacious in stimulating DA release in the NAc than nicotine, as shown by *in vitro* slice preparations as well as *in vivo* microdialysis [39]. Although varenicline partially substitutes for nicotine in drug-discrimination studies [48], it is not readily self-administered by drug-naïve animals without prior training to respond for food reinforcement [49], and does not induce reinstatement of nicotine-seeking behaviors [45]. Unlike nicotine, varenicline does not induce locomotor sensitization [43, 50]. Chronic varenicline treatment has anxiolytic effects in rodents as measured in the marble-burying test [51]. Chronic varenicline treatment also upregulates nAchR binding in the cortex, hippocampus, thalamus and striatum in mice [51, 52]. These findings suggest that varenicline has low abuse liability even in the absence of nicotine.

3. Clinical development of varenicline for smoking cessation

3.1. Pharmacokinetics and side effects of varenicline

The strong rationale for targeting the $\alpha_4\beta_2$ nAchR with a partial agonist, coupled with promising findings from preclinical studies described above, lead to the initiation of clinical trials evaluating the safety and efficacy of varenicline in humans. Early studies indicated that varenicline has a longer half-life than cytisine (24 hours vs. 5.8 hours) [53], and a volume of distribution three-fold greater than cytisine [27, 53]. Peak plasma concentrations of varenicline occur approximately 3–4 hours after oral administration, and steady-state levels are observed after 4 days of repeated use [37]. Protein binding of varenicline is less than 12% and metabolism is less than 10%. Varenicline is eliminated renally via the organic cation transporter OCT-2, and because metabolism is limited over 90% of varenicline is excreted unchanged in the urine. Patients with moderate to severe renal impairment are advised to use caution when taking varenicline, but geriatric (aged 65+ years) and pediatric (aged 12–17 years) efficacy and pharmacokinetics of varenicline do not differ from healthy adult populations. There are no reported drug interactions with varenicline, and it does not interact with cytochrome P450 enzymes in human hepatocytes or human renal transport proteins. Varenicline does not have any carcinogenic, genotoxic, or teratogenic effects, although use during pregnancy is advised only if the potential benefit to the fetus justifies putative risks [37].

Nausea is the most common side effect of varenicline and is largely dose-dependent, occurring in approximately 30% of patients taking 1 mg BID (twice daily) in the first week and 16% of patients taking 0.5 mg BID in the first week [37, 54]. Insomnia is the second most-common side effect, reported in 14–37.2% of patients, but is most frequent during the first

month of treatment and subsides with extended administration [54]. Headache, abnormal dreams, sleep disturbances, dizziness, dry mouth, weight gain, and constipation are less common side effects, and are usually temporary and mild to moderate in severity [10, 55]. Varenicline can be used alongside NRTs, but combined therapy does not appear to increase varenicline's efficacy in smoking cessation [56]. In addition, some side effects, such as nausea, headache, vomiting, dizziness, and fatigue are exacerbated with concurrent varenicline and NRT use, and patients may be more likely to discontinue treatment as a result [37].

3.2. Clinical trials evaluating varenicline as a smoking cessation aid

The FDA approved varenicline as a smoking cessation aid on May 11, 2006 (see timeline in Figure 3). By 2008, approximately 3.5 million people in the U.S. and 5 million worldwide were taking varenicline [57]. FDA approval was largely based on six randomized clinical trials conducted in 3,659 subjects in the U.S, which are summarized in Table 2 alongside more recent studies [55, 58–60]. Sample populations in these trials were composed of approximately equal numbers of men and women, aged 43 years old on average. All subjects were chronic cigarette smokers, reporting smoking 21 cigarettes per day on average for the past 25 years. The primary outcome measure was abstinence from smoking, as assessed by self-report in terms of continuous abstinence rate (CAR) or continuous quit rate (CQR), and verified by exhaled carbon monoxide levels of 10 parts per million or less. Secondary outcomes included the urge to smoke, withdrawal symptoms, and the reinforcing effects of nicotine, as measured by the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal Scale [10, 37]. In two seminal 12-week long phase III trials, 0.5 and 1 mg varenicline BID resulted in ~44% abstinence rates from weeks 9–12, a significant improvement over bupropion (~30%) and placebo (~18%) [37, 61]. Varenicline-treated subjects were also more likely to remain abstinent at 28- and 40-week follow-ups [37, 61]. Secondary outcome measures, including the urge to smoke, were likewise improved in varenicline-treated subjects over placebo [37, 61]. Although randomized, double-blind and placebo-controlled, these early trials involved some limitations. For example, the sample population was comprised of healthy volunteers and excluded individuals with medical illnesses or major depression, and may thus not be representative of a typical primary care population [55, 59]. Moreover, all participants received individual counseling sessions for 12 weeks, which may not be available in standard health care settings. Finally, follow-up was not completed in 35–43% of participants, although retention rates were comparable or lower in the placebo groups compared to varenicline or bupropion treatments [55, 59].

Since FDA approval in 2006, a number of reports have continued to demonstrate varenicline's efficacy for smoking cessation over other available pharmacotherapies. For example, in a randomized phase III trial involving 376 participants followed over 52 weeks, varenicline resulted in significantly higher abstinence rates from smoking (55.9%) compared to a transdermal NRT (43.2%), as well as reduced cravings, attenuated withdrawal, and diminished pleasure from smoking [62]. However, it is worth noting that this study involved an open-label design and varenicline treatment was continued 2 weeks longer than NRT, such that some bias may have influenced treatment outcomes and participant drop-out rates after treatment assignment [62]. In another study, varenicline was more efficacious as measured by CAR for 9–12 weeks compared to bupropion and placebo [63], and more than doubled the rate

of smoking cessation at one year with comparable or fewer side effects and adverse events [64, 65]. Varenicline was also favorable to bupropion and placebo in promoting abstinence at six-month follow-up and was associated with fewer depression symptoms and reduced subjective nicotine reward [65]. However, the generalizability of this latter study may be limited to due overlap in the population sample with other phase-III trials [65]. More recently varenicline's efficacy has been demonstrated in light smokers (5–10 cigarettes per day), with 12 weeks of treatment producing abstinence rates of 31% compared to 8% following placebo at six-month follow-up [66].

3.3. Pooled and meta-analyses comparing varenicline outcomes across clinical trials

Large-scale analyses comparing outcomes across trials confirm varenicline's efficacy as a smoking cessation aid [10]. For example, pooled analyses of phase III trials [55, 59] show that cravings (urge to smoke) are reduced following varenicline or bupropion treatment compared to placebo [67]. Both varenicline and bupropion attenuate nicotine withdrawal symptoms such as depression, anxiety, irritability, insomnia, and attentional deficits [67]. Varenicline-treated patients also express reduced smoking satisfaction and pleasurable effects from smoking, as measured by the Modified Cigarette Evaluation Questionnaire [67]. One major limitation of this analyses, however, was that the three treatment groups exhibited differences in abstinence rates that could have influenced outcomes [67]. Nonetheless, a separate pooled analysis of phase III trials further confirmed that abstinence rates are greater for varenicline-treated patients (44%) compared to bupropion (29.7%) and placebo (17.7%) [63l].

A meta-analysis of nine clinical trials, involving over 7,000 participants, indicated that the odds ratio for abstinence on varenicline vs. placebo was 2.33, varenicline vs. bupropion 1.52, and varenicline vs. NRT 1.31 [68]. Similarly, a meta-analysis of 101 trials spanning more than 40,000 participants reported that the odds ratio of abstinence at four-weeks post target quit date for varenicline was 3.16, for bupropion 2.25, and for NRT 2.05, with an odds ratio of varenicline vs. bupropion of 1.86 [69]. A more recent analysis of trials identified in the Cochrane Tobacco Addiction Group, involving a total of ~25,000 participants, reported a pooled risk ratio of 1.39 for varenicline vs. bupropion and 1.25 for varenicline vs. NRT at six-month follow-up [70]. In this report, serious adverse events including infection, cancer, and injury, were increased by 25% in varenicline-treated patients, although these were not expected to be a result of the trial itself [70]. Further, no significant relationship was found between varenicline treatment and depressed mood, agitation, or suicidal behaviors or ideation [70]. Taken together, the results of several clinical trials involving tens of thousands of patients testify to varenicline's safety and efficacy in aiding smoking cessation and maintaining abstinence rates long-term.

3.4. Cognitive effects of varenicline

On a neural systems level, varenicline's efficacy as a smoking cessation aid may derive in part from its positive effects on cognition and processing of smoking-related cues, which are important triggers for relapse. For example, in a functional magnetic resonance imaging (fMRI) study using a region of interest (ROI) analysis, varenicline increased the blood oxygen level dependent (BOLD) signal in the anterior cingulate cortex and dorsolateral PFC

during a working memory task and improved response time in heavily dependent smokers [71]. In smokers who remained abstinent, five weeks of varenicline treatment increased BOLD activation in regions involved in attention, learning and memory, including the insula, putamen, thalamus, and cingulate cortex [72]. Impulsivity and mesocorticolimbic dysfunction were also restored following varenicline treatment in abstinent smokers [73].

In the absence of treatment, smoking-related cues (e.g., videos of individuals discussing smoking, images of lighters and cigarettes, etc.) increase smokers' cravings and BOLD responses in the ventral striatum and orbitofrontal cortex (OFC), two regions in the mesocorticolimbic DA reward pathway [74]. However, three weeks of varenicline treatment attenuated ventral striatal and OFC activation by smoking cues and reduced subjective craving [74]. An event related potential study found that smokers with greater activation to cigarette-related cues over other pleasant stimuli had a 95–98% greater chance of benefit for varenicline over bupropion, and were more likely to remain abstinent at three-month follow-up [75]. Moreover, at six-month follow-up all smokers maintained abstinence on varenicline significantly more than on placebo, an effect driven largely by increased activation to cigarette cues [75]. Together, these findings suggest that attenuation of the salience attributed to smoking and cigarette-related cues may critically underlie varenicline's efficacy as a smoking cessation aid.

4. Post-launch surveillance following varenicline approval

4.1. Neuropsychiatric events and varenicline use

In 2009 the FDA placed a box warning on varenicline for "serious neuropsychiatric events," including depressed mood, suicidal ideation and attempts, hostility, agitation, psychosis, and severe injuries. The warning was based largely on post-marketing surveillance reports analyzed by the Institute for Safe Medication Practices regarding adverse events between May and December of 2007. During this time, 988 serious injuries reported to the FDA were attributed to varenicline, more than any other drug [57]. Of these, 227 were suicidal acts, 397 were psychoses, and 525 were hostility or aggression. Other prominent events associated with varenicline included 173 accidental injuries such as traffic accidents and falls, 148 reports of vision disturbances, 224 heart rhythm disturbances, 86 seizures or abnormal spasms, 338 skin reactions, and 544 cases of diabetes [57]. In November 2007, the FDA issued an early alert about an ongoing safety review of varenicline [76]. Later, in February 2008, a Public Health Advisory was issued calling for pre-screening and continual monitoring of patients taking varenicline for psychiatric illnesses, and discontinuation of treatment if any changes were observed [10, 76]. The box warning was subsequently issued in July 2009. Post-marketing reports described a resolution of symptoms following cessation of varenicline, but in some cases continual monitoring and support were required [37]. In 2015, the warning was updated to include more recent cases in the FDA Adverse Event Reporting System regarding patients who experienced reduced alcohol tolerance and increased drunkenness, aggression and memory loss following alcohol consumption while taking varenicline, as well as a potentially increased risk of seizures [76]. This information was subsequently included in the Warnings and Precautions section of the drug label as well as in the patient Medication Guide.

In 2016, a joint FDA advisory committee voted to remove the box warning on varenicline based on the results of a large clinical trial conducted by Pfizer [76]. This EAGLES trial, which compared varenicline, bupropion, NRT and placebo, included two large cohorts of more than 4000 participants each: one cohort with a psychiatric illness diagnosis (4116 participants), and one without (4028 participants). In patients without a history of psychiatric illness, neither varenicline nor bupropion was associated with a significant increase in moderate-to-severe neuropsychiatric adverse events (the primary outcome measure) compared to placebo (1.5% increase) [77]. More specifically, 1.3% of the varenicline-treated group, 2.2% of the bupropion group, 2.5% of the NRT group, and 2.4% of the placebo group reported neuropsychiatric adverse events [77]. Similarly, in patients with a history of psychiatric illness, varenicline or bupropion did not increase moderate-to-severe neuropsychiatric events by more than 4% [77]. Within the psychiatric cohort, 6.5% of varenicline-treated participants, 6.7% of bupropion-treated participants, 5.2% of NRT-treated participants, and 4.9% of placebo-treated participants reported a moderate-to-severe neuropsychiatric adverse event. Consistent with prior studies, participants receiving varenicline achieved higher abstinence rates compared to all other treatment groups (odds ratio vs. placebo: 3.61; vs. NRT 1.68; and vs. bupropion 1.75). The FDA committee concluded that the neuropsychiatric risks of varenicline are low and may be limited to subjects with a pre-existing illness, such as depression, anxiety, or schizophrenia [76].

While the EAGLES trial demonstrated comparable efficacy of varenicline for smoking cessation regardless of pre-existing psychiatric status, it nonetheless remains possible that individual differences in psychological traits may influence abstinence rates. To address this possibility, a recent study evaluated the influence of trait characteristics including depression, impulsivity, agreeableness, conscientiousness, neuroticism and openness on the efficacy of varenicline for smoking cessation or reduction [78]. Participants achieving continuous abstinence with varenicline scored lower on non-planning and motor impulsivity (as measured by the Barrett Impulsivity Scale) at 12 and 36-week follow-up. Modest relationships between personality traits and smoking cessation were also observed, such that participants scoring high on agreeableness and openness were more likely to maintain continuous abstinence and smoke fewer cigarettes at follow-up when treated with varenicline. In addition, those who had not previously experienced a major depressive episode experienced greater benefit (smoked fewer cigarettes) from varenicline compared to placebo. Lower depressive symptoms at treatment onset (as measured by the Beck Depressive Inventory-II) were also associated with higher continuous abstinence rates at 12-week follow-up. However, no relationships between conscientiousness or neuroticism and varenicline efficacy or smoking reduction were observed. Taken together, these findings suggest that the efficacy of varenicline for smoking cessation may vary depending on individual personality and psychological traits and history of depressive episodes [78]. In the future, personalized medicine and individualized therapeutic strategies will also inevitably rely on advances in genetics, genomics, and proteomics to maximize smoking cessation rates and treat other neuropsychiatric conditions [79].

4.2. Operation of heavy machinery and varenicline use

In addition to post-marketing reports regarding caution for neuropsychiatric events, varenicline is not recommended for people operating vehicles and heavy machinery. As described above, in 2007 prominent adverse events attributed to varenicline included 173 accidents or falls, as well as vision and heart rhythm disturbances. Based on these reports, the Institute for Safe Medication Practices issued safety concerns regarding the use of varenicline by aircraft, train, bus, and other vehicle operators, as well as individuals working with nuclear power reactors, construction cranes, and life-saving medical devices [57]. The Federal Aviation Administration banned varenicline use in pilots in May 2008 [80], and an accidental injury warning remains on the package insert today [37].

4.3. Cardiovascular events and varenicline use

In December 2012, the FDA released the results of a large meta-analysis of 15 clinical trials involving more than 7,000 patients taking varenicline. Varenicline use was associated with increased cardiovascular events, including death, nonfatal heart attack, and nonfatal stroke after 30-days of treatment, compared to patients receiving placebo (13% vs. 6%, respectively, hazard ratio=1.95) [76]. Although the group difference was not statistically significant, the FDA nonetheless cautioned patients and healthcare professionals to weigh the risks and benefits of varenicline treatment for smoking cessation, and to remain vigilant if new or worsening cardiovascular symptoms develop [76]. In rodent models, chronic varenicline exposure caused a reduction in the weight of the heart (0.92 mg following chronic treatment vs. 0.99 mg with acute exposure, $p<0.05$), impaired oxygen saturation and prolonged QT intervals among other negative cardiovascular side effects [81]. However, in a randomized, double-blind placebo-controlled study involving 714 patients with existing cardiovascular disease, no additional adverse cardiovascular events were reported following varenicline treatment compared to placebo, and varenicline was associated with significant improvements in continuous abstinence rates (19.2% of participants on varenicline vs. 7.2% of participants receiving placebo) [109]. Moreover, another recent randomized, placebo-controlled trial involving a subset of participants in the EAGLES study (n=4595)[77] and reported at the 2017 Society for Research on Nicotine and Tobacco indicated that the incidence of cardiovascular adverse events following varenicline, bupropion, or transdermal nicotine patch (an NRT) did not significantly differ from placebo after 12 weeks of treatment or 1-year follow-up [82]. Notably, smoking is associated with cardiovascular disease in itself and cessation can significantly improve long-term outcomes. In randomized trial of 400–700 smokers with cardiovascular disease, varenicline more than doubled abstinence rates and no new safety concerns were noted [76].

5. Summary and Conclusions

Varenicline is the first medication developed to selectively target nicotine activity at the $\alpha_4\beta_2$ nAchR, the primary mechanism of action in nicotine addiction. As a potent partial agonist, varenicline attenuates nicotine-induced DA release and reduces the reinforcing value of nicotine. Because varenicline elicits partial activation of the $\alpha_4\beta_2$ nAchR in the absence of nicotine, it also mitigates withdrawal symptoms during abstinence. In preclinical animal models varenicline blocks nicotine-induced locomotor sensitization, conditioned

place preferences, self-administration, and nicotine-primed or cue-induced reinstatement of nicotine seeking. When administered alone, varenicline has modest reinforcing value and is unlikely to have significant abuse liability.

Clinical trials have demonstrated that varenicline is safe and well-tolerated in diverse patient populations. The most common side effect, nausea, occurs in approximately 30% of patients and is often alleviated with continued use and/or dose titration. Varenicline has consistently been found to be more effective than bupropion and NRTs in sustaining abstinence from smoking, both during initial trials as well as in subsequent post-market surveillance and meta-analyses. Although early post-marketing reports identified potentially adverse neuropsychiatric and cardiovascular events associated with varenicline use, subsequent studies have demonstrated that the probability of these events is low in individuals without a pre-existing disorder. Nonetheless, caution is warranted for varenicline use in individuals who routinely operate heavy machinery.

6. Expert opinion

The development of varenicline was successful largely due to the strong theoretical rationale on which its discovery strategy was based. Varenicline was formulated to target the primary mechanism of nicotine addiction, activity at $\alpha_4\beta_2$ nAchRs in the mesolimbic DA system. Varenicline synthesis was based on existing knowledge of cytisine, an alkaloid derived from a deciduous shrub historically used as a tobacco replacement. As a selective and potent partial agonist at the $\alpha_4\beta_2$ nAchR, varenicline conveys significant advantages over full agonists such as NRTs, which do not eliminate nicotine addiction, and antagonists, which precipitate withdrawal symptoms during abstinence. Moreover, converging evidence in preclinical and clinical studies support the utility of varenicline for smoking cessation.

While varenicline is the most efficacious smoking cessation aid currently available, it is worth noting that a majority of clinical trials evaluating varenicline have been sponsored by its manufacturer, Pfizer. Although these trials are randomized and double-blind, additional studies by independent parties are warranted [10]. Going forward, it will be critical to evaluate the efficacy of varenicline as a cessation aid for nicotine addiction fueled by e-cigarette use, particularly in adolescent and young adult populations in whom e-cigarette consumption is growing rapidly. From 2011 to 2015 alone, e-cigarette use among high school students increased seven-fold [83]. In the 2015 National Youth Tobacco Survey, 27.1% of adolescents in middle school and high school reported using e-cigarettes, representing approximately 7,260,500 teens [83]. While the safety of e-cigarettes remains controversial, the American Lung Association has emphasized concern regarding the effects of e-cigarette use on public health, particularly among youth and adolescents, and urge for additional oversight of e-cigarette production by the Food and Drug Administration [84]. In addition to delivering nicotine, e-cigarette liquid cartridges contain toxic and carcinogenic ingredients (albeit at lower levels than combustible tobacco and cigarettes), and fruity, sweet flavorings appeal to young people and contribute to adolescent consumption [84, 85]. Although large-scale, systematic studies are needed to further determine the long-term health consequences of e-cigarettes, the rise in youth and adolescent use of these nicotine delivery products nonetheless remains a concern. Adolescent drug use more than doubles the likelihood of

developing substance use disorder in adulthood [86, 87], suggesting thousands of young people are at elevated risk for nicotine addiction in the future. Evaluation of the efficacy of varenicline and other smoking cessation aids in this vulnerable population will be urgently needed.

An additional concern regarding varenicline is that chronic treatment upregulates $\alpha_4\beta_2$ nAchR binding much like nicotine, suggesting continued varenicline use may prevent $\alpha_4\beta_2$ levels from returning to baseline in heavy smokers [52]. Alternative mechanisms for the treatment of nicotine addiction may therefore be desirable. In addition to $\alpha_4\beta_2$ activity, varenicline is a potent partial agonist at the $\alpha_6\beta_2$ nAchR subtype (K_i=0.12 nM) [41], and unlike $\alpha_4\beta_2$, chronic varenicline reduces $\alpha_6\beta_2$ binding levels [52]. Accumulating evidence also supports a role for the α_6 subunit in nicotine reward. For example, genetic deletion of α_6 eliminates nicotine self-administration and suppresses nicotine-induced VTA DA neuron firing, while selective re-expression of α_6 in the VTA restores nicotine self-administration [20, 21]. These findings suggest α_6 may represent a viable target for the development of future smoking cessation aids.

In addition to targeting alternative nicotinic receptor subunits, metabotropic glutamate receptor (mGluR) 2/3 agonists and mGluR5 antagonists have recently shown efficacy in attenuating nicotine self-administration preclinically, and may have promise in human studies for smoking cessation [88]. Group 2 mGluRs, including mGluR2 and 3, are located pre-synaptically and on glial cells and are coupled to inhibitory $G_{i/o}$-proteins, such that activation of these receptors inhibits adenyl cyclase signaling and can suppress glutamatergic neuron firing. In contrast, group 1 mGluRs, including mGluR1 and 5, are located post-synaptically, are G_q-coupled, and serve to activate phospholipase C [88]. Nicotine binding to nAChRs located on pre-synaptic glutamatergic neurons in the VTA increases glutamate excitation of DA cells in this region, contributing to nicotine's rewarding and reinforcing effects [16, 88, 89]. Activation of pre-synaptic mGluR2/3 via a pharmacological agonist, or blockade of post-synaptic mGluR5 with an antagonist, would therefore counteract nicotine's effects by suppressing glutamate release and binding at VTA DA neurons as well as in the NAc [90]. Preclinical studies using LY379268, an mGluR2/3 agonist, and MPEP, an mGluR5 antagonist, support this hypothesis. For example, LY379268 reduced nicotine self-administration and nicotine-primed reinstatement of drug seeking in rats and squirrel monkeys [91, 92], and blocked nicotine-induced DA release in the NAc shell when animals were in the presence of a nicotine-associated context and cues [93]. However, LY379268 also increased somatic signs of nicotine withdrawal in rats [92], suggesting this drug may have dysphoric effects that limit its therapeutic efficacy in humans. More recently a specific mGluR2 positive allosteric modulator, AZD8529, has been found to reduce nicotine self-administration and reinstatement in both rats and monkeys [94, 95], although the dysphoric effects of this drug remain to be evaluated. Similar to mGluR2/3 agonists, MPEP (2-methyl-6-(phenylethynyl)-pyridine), a selective mGluR5 antagonist, has been shown to reduce nicotine self-administration, nicotine-primed reinstatement, and nicotine-induced locomotor sensitization in rats and mice [96–99]. In addition, knockout mice with genetic deletion of mGluR5 showed attenuated somatic signs of nicotine withdrawal [100], providing further support for mGluRs as new therapeutic targets for nicotine dependence.

In conclusion, the strong theoretical approach used in varenicline's development can inform new medication discovery strategies for addictions as well as other central nervous system disorders, which have been notoriously difficult to treat [101]. On the contrary, the review cites many studies in animals, non-human primates, and humans to indicate that much of the evidence surrounding varenicline's efficacy as a smoking cessation agent converges across species. Future drug discovery will also inevitably incorporate technological advances in genetics, genomics and proteomics for highly specific, individualized approaches to smoking cessation [79].

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Article Highlights:

- Smoking is the leading cause of preventable death in the United States. While more than 70% of smokers express a desire to quit, fewer than 3% remain abstinent more than one year. There is a critical need for more efficacious smoking cessation aids.
- The primary addictive component in tobacco is nicotine. In the brain, nicotine produces rewarding and psychostimulant effects mainly by binding to $\alpha_4\beta_2$ nicotinic acetylcholine receptors on midbrain dopaminergic neurons, causing an increase in dopamine release in the nucleus accumbens, a key reward processing region.
- Varenicline was developed by Pfizer as a selective partial agonist at the $\alpha_4\beta_2$ receptor based on previous reports that cytisine, a plant-derived alkaloid, was used as a tobacco substitute during World War II.
- Preclinical studies indicate that varenicline suppresses nicotine-induced dopamine release and attenuates nicotine conditioned place preferences, nicotine self-administration, and nicotine- or cue-induced reinstatement of drug-seeking behaviors.
- Clinical studies indicate that varenicline is safe, well-tolerated and more efficacious in sustaining abstinence in smokers compared to placebo as well as to other currently available smoking cessation aids, including bupropion and nicotine replacement therapies.
- Although early post-marketing surveillance suggested that potentially adverse neuropsychiatric and cardiovascular events were associated with varenicline use, subsequent studies indicate that the probability of these events is low. Nonetheless, caution is warranted for varenicline use in individuals who routinely operate heavy machinery.

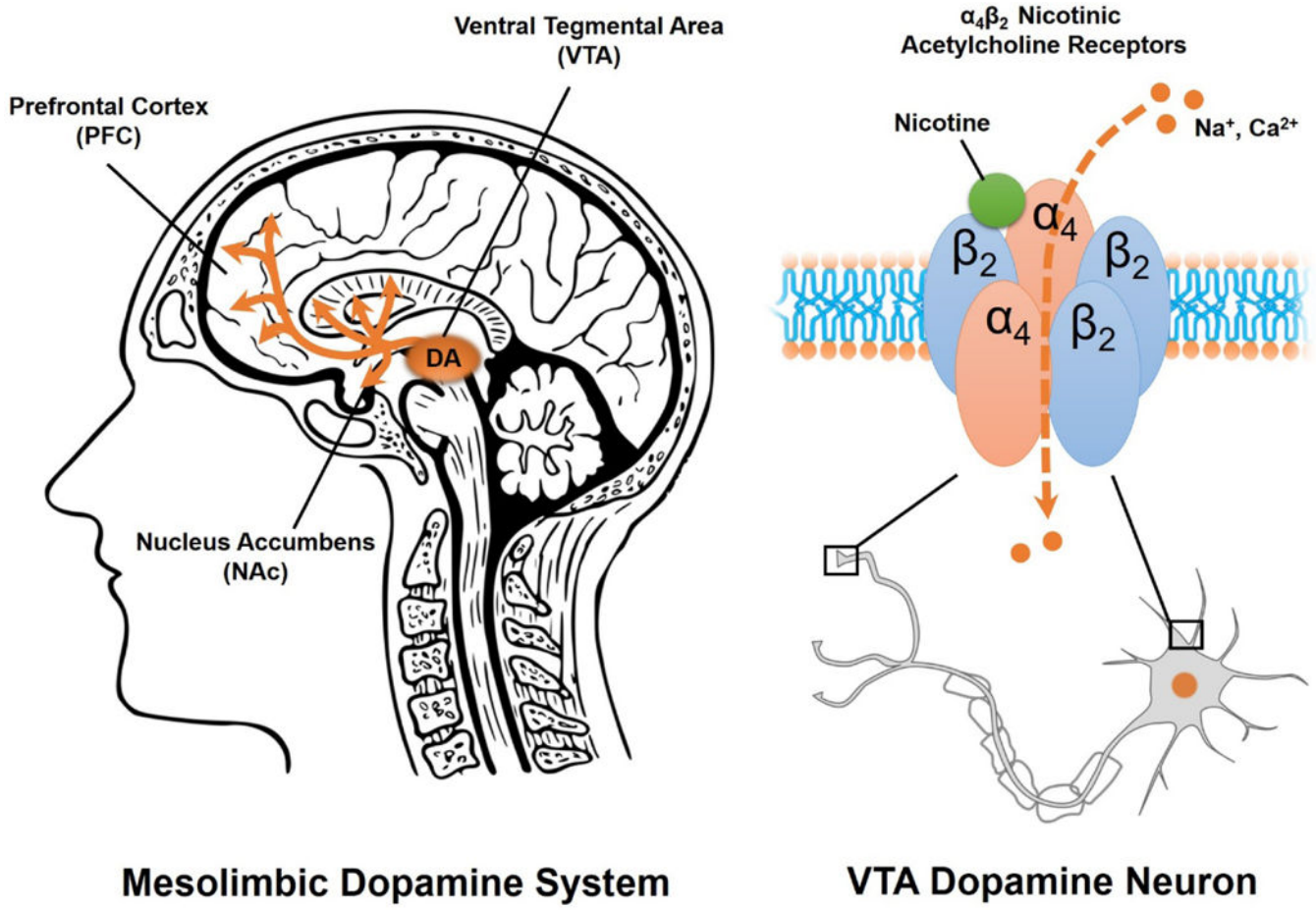
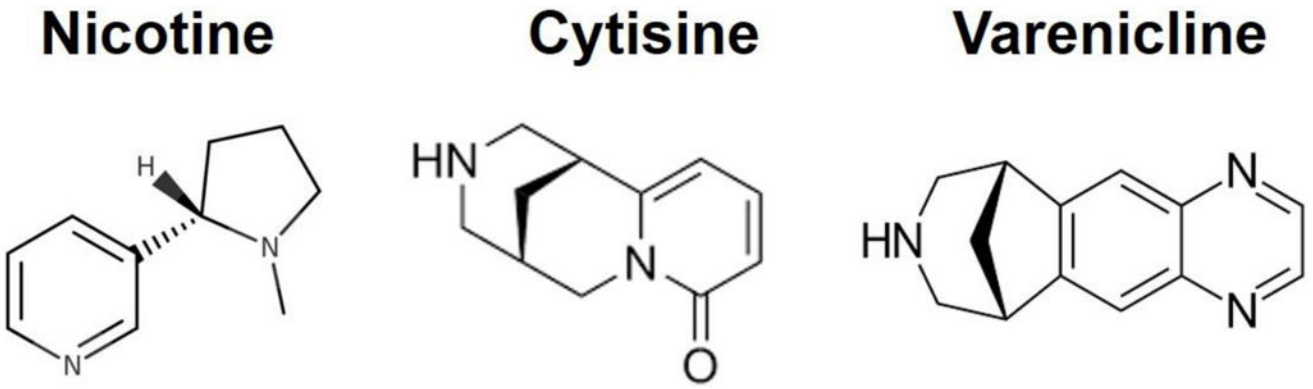


Figure 1.

The mesolimbic dopamine (DA) system (left) is comprised of ventral tegmental area (VTA) projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC). Nicotine stimulates DA release in the mesolimbic system by activating pre- and post-synaptic nicotinic acetycholine receptors (nAchRs) in the VTA (right). Activation of pentameric $\alpha_4\beta_2$ nAchRs in the VTA opens an ion pore, allowing cation (Na^+ and Ca^{2+}) influx and depolarization of the VTA DA neuron.



***In vitro* binding affinity at nAchRs**

	$\alpha_4\beta_2$ (K_i, nM)	α_7 (K_i, nM)	$\alpha_6\beta_2$ (K_i, nM)	$\alpha_3\beta_4$ (K_i, nM)	$\alpha_1\beta_{\gamma\delta}$ (K_i, nM)
Nicotine	1.6[38-40]	6290	0.61[41]	530[38]	6270[38]
Cytisine	0.23[38-40]	4200	N/A	840[38]	250[38]
Varenicline	0.15[38-40]	322	0.12[41]	240[38]	3540[38]

Figure 2.
Chemical structures of nicotine, cytisine, and varenicline (top). Comparison of *in vitro* binding affinities of nicotine, cytisine, and varenicline at nicotinic acetylcholine receptor subtypes (nAchRs; bottom).

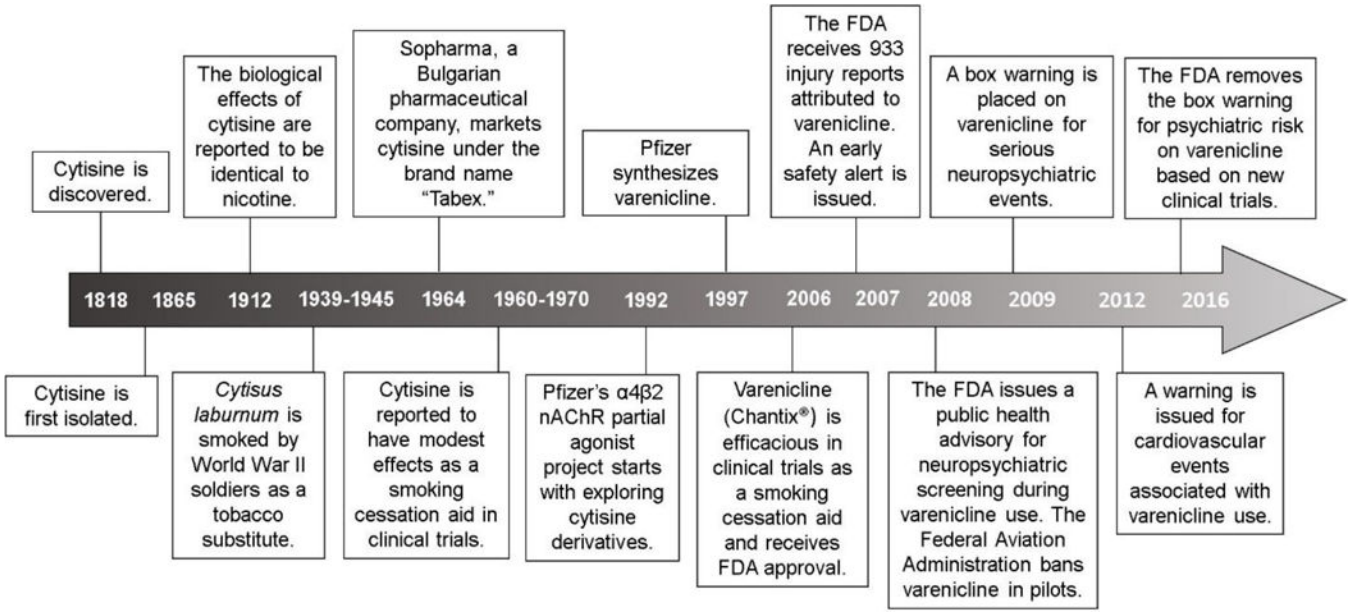


Figure 3.

A summarized history of varenicline discovery and development (see text for details).

Note: Timeline is not presented at scale.

Table 1.

Preclinical studies of nicotine and varenicline on addiction-related behaviors.

Assay	Nicotine Alone	Varenicline Alone	Varenicline Effects on Nicotine
Locomotor Sensitization [43, 50]	↑	No effect	↓
Conditioned Place Preferences [42]	↑	---	↓
Intravenous Self-Administration [81, 102–107]	↑	↑	↓
Brain Stimulation Reward [46, 47]	↑	↑	↓
Reinstatement (Relapse) [39, 44, 45]	↑	No effect	↓
Marble Burying Test (Anxiety) [51]	↓	↓	---
Dopamine Release in the Nucleus Accumbens [38, 39, 41]	↑	↑	↓
$\alpha_4\beta_2$ nAchR binding [51, 52]	↑	↑	---

Table 2.

Clinical Trials Supporting FDA Approval of Varenicline for Smoking Cessation and Post-Approval Trials Conducted on Varenicline Relevant to Post-Market Surveillance Events

	n	Treatment Duration	Purpose		Treatment Regimen	Continuous Abstinence Rate (CAR) Weeks 9–12	Continuous Abstinence Rate (CAR) Weeks 24+
Nides et al. 2006[111]	638	6–7 weeks	Evaluation of efficacy, safety and tolerability of 3 varenicline dosages	Varenicline:	0.3 mg QD 1.0 mg QD 1.0 mg BID	*Not available* (#See table note).	
Oncken at al. 2006[58]	627	12 weeks + 40 week follow-up	Comparison of dosing regimens on tolerability	Varenicline:	0.5 mg BID with/ without 1 week titration	44%	18.5%
				Varenicline:	1 mg BID with/ without 1 week titration	49.4%	22.4%
				Placebo	---	11.6%	3.9%
Niaura et al. 2008[60]	312	12 weeks + 40 week follow-up	Flexible dosing	Varenicline:	0.5 mg BID, voluntarily adjusted up to 1 mg BID *	40.1%	22.3%
				Placebo	---	11.6%	7.7%
Gonzales et al. 2006[59]	1022	12 weeks + 40 week follow-up	Comparison to bupropion sustained release (SR) and placebo	Varenicline:	0.5 mg QD for 3 days, 0.5 mg BID for 4 days, to 1 mg BID	44%	21.9%
				Bupropion SR:	150 mg QD for 3 days, followed by 150 mg BID	29.5%	16.1%
				Placebo	---	17.7%	8.4%
Jorenby et al. 2006[55]	1023	12 weeks + 40 week follow-up	Replication of Gonzales et al.[59]	Varenicline:	0.5 mg QD for 3 days, 0.5 mg BID for 4 days, to 1 mg BID	43.9%	23%
				Bupropion SR:	150 mg QD for 3 days, followed by 150 mg BID	29.8%	14.6%
				Placebo	---	17.6%	10.5%
Cincirpini et al. 2013[65]	294	12 weeks + 24 week follow-up	Addition of more intense behavioral counseling	Varenicline:	0.5 mg QD for 3 days, 0.5 mg BID for 4 days, to 1 mg BID	43%	23%
				Bupropion SR:	150 mg QD for 3 days, followed by 150 mg BID	37.2%	27.9%
				Placebo	---	17%	14.1%
Aubin et al.[62] Ebbert et al. 2016[66]	376 93	12 weeks + 40 week follow-up 12 weeks + 12 week follow-up	Comparison to nicotine replacement therapy (NRT)	Varenicline:	1 mg BID for 12 weeks	55.9%	26.1%

	n	Treatment Duration	Purpose		Treatment Regimen	Continuous Abstinence Rate (CAR) Weeks 9–12	Weeks 24+
Aubin et al.[62] Ramon et al. 2014[56]	376 341	12 weeks + 40 week follow-up 12 weeks	Evaluation in light smokers (5–10 cig/day) Comparison to nicotine replacement therapy (NRT) Evaluation of combined varenicline + NRT	Transdermal NRT:	21 titrated to 12mg/kg/day, 10 weeks	43.2%	20.3%
				Varenicline:		40%	31.1%
				Placebo		8.3%	8.3%
				Varenicline/Transdermal NRT	1 mg BID titrated varenicline + 21 mg daily patch	39.1%	---
				Varenicline + Placebo	1 mg BID titrated varenicline + inactive patch	31.8%	---
Ebbert et al. 2016[66] Tonstad et al. 2006[108]	93 1927	12 weeks + 12 week follow-up 24 weeks + 28 week follow-up	Evaluation in light smokers (5–10 cig/day) Long-term abstinence	Open-label varenicline: 1 mg BID for 12 weeks, followed by blind randomization to varenicline (1mg BID) or placebo for 12 weeks[^]	[^]See table note.		
Rigotti et al. 2014[109]	714	12 weeks + 52 week follow-up	Efficacy in cardiovascular disease[‡]	Varenicline	1 mg BID	47%	19.2%
				Placebo	---	13.9%	7.2%
Anthenelli et al. 2016[77]	8144	12 weeks + 12 week follow-up	Evaluation of neuropsychiatric adverse events	Varenicline:	1 mg BID	33.5% 22.6% 23.4% 12.5% [†]See table note.	21.8% 16.2% 15.7% 9.4%
Rigotti et al. 2014[109]	714	12 weeks + 52 week follow-up	Efficacy in cardiovascular disease[‡]	Bupropion:	150 mg BID	47%	
				NRT:	21 mg/day	13.9%	
Anthenelli et al. 2016[77]	8144	12 weeks + 12 week follow-up	Evaluation of neuropsychiatric adverse events	Placebo	---	33.5% 22.6% 23.4% 12.5% [†]See table note.	21.8% 16.2% 15.7% 9.4%

Table Note. BID: Twice daily. QD: Once daily.

[#]Continuous quit rates were higher for 1.0 mg varenlicine QD (37.3%) and 1.0 mg varenicline BID (48%) compared to placebo (17.1%). Overall varenicline was well tolerated.

[*]69% of subjects titrated to maximum dose.

[^]CAR at weeks 13–24 was higher for varenicline-treated subjects (70.5%) than those switching to placebo (49.6%). Varenicline's efficacy over placebo was maintained at week 52 (43.6% CAR vs. 36.9% CAR, respectively)[108].

[‡] Varenicline and placebo groups with stable cardiovascular disease showed no significant differences in cardiovascular mortality or adverse cardiovascular events[109].

[†] In participants with a history of psychiatric illness 9–12 weeks and 9–24 weeks CARs with varenicline (38%, 25.5%) were higher than that in participants without psychiatric illness (29.2%, 18.3%). Neither varenicline nor bupropion increased moderate-to-severe neuropsychiatric events. At weeks 9–12 follow-up CAR was higher in participants receiving varenicline compared to all other treatment groups (odds ratio vs. placebo: 3.61; vs. NRT 1.68; and vs. bupropion 1.75)[77].