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Involvement of neuronal β_2 subunit-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal: Implications for pharmacotherapies

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SUMMARY

What is known and objective—Tobacco smoking remains a major health problem. Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which can cause addiction and withdrawal symptoms upon cessation of nicotine administration. Pharmacotherapies for nicotine addiction target brain alterations that underlie withdrawal symptoms. This review will delineate the involvement of the β_2 subunit of neuronal nAChRs in nicotine reward and in generating withdrawal symptoms to better understand the efficacy of smoking cessation pharmacotherapies.

Comment—Chronic nicotine desensitizes and upregulates β_2 subunit-containing nAChRs, and the prolonged upregulation of receptors may underlie symptoms of withdrawal. Experimental research has demonstrated that the β_2 subunit of neuronal nAChRs is necessary for generating nicotine reward and withdrawal symptoms.

What is new and conclusion—Smoking cessation pharmacotherapies act on β_2 subunit-containing nAChRs to reduce nicotine reward and withdrawal symptom severity.

Keywords

nicotine reward; nicotine withdrawal; nicotinic acetylcholine receptor; smoking cessation; β_2 subunit

WHAT IS KNOWN AND OBJECTIVE

Introduction

Tobacco use is the leading cause of preventable death and disease in the United States, causing approximately 443 000 premature deaths each year.[1] The health impacts of tobacco use include increased risk of lung and oral cancers, coronary heart disease and stroke.[2] Nicotine addiction is expensive for individuals and the national economy, costing approximately $96.8 billion annually in productivity loss.[3] Approximately 70% of smokers

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

report desiring to quit, but only 42% of smokers actually attempt to quit smoking. Of those who attempt to quit, only 3–5% are successful after 6 months when the quit attempt is unaided by behavioural treatments or pharmacotherapies.[4] Clearly, tobacco smoking remains a major health problem for the United States and other countries.

Nicotine is one of the principal psychoactive and addictive drugs in tobacco products. Similarly to other drugs of abuse, nicotine addiction is characterized by compulsive use, craving, tolerance from continued use and withdrawal upon cessation.[5] The symptoms of nicotine withdrawal include dysphoria, irritability, frustration and difficulty concentrating.[6] Smokers are able to relieve symptoms of withdrawal by relapsing.[7–9] These effects and the health consequences of tobacco smoking point to the importance for a better understanding of the neurobiology of nicotine addiction.[10]

Nicotine alters neurobiological processes by binding to neuronal nicotinic acetylcholine receptors (nAChRs). Similarly to other drugs of abuse, acute nicotine administration causes signalling changes in brain reward substrates, such as increasing the phasic release of mesolimbic dopamine (DA).[11–15] Chronic nicotine leads to desensitization and upregulation of neuronal nAChRs, including heteropentameric β_2 subunit-containing nAChRs.[16–23] During nicotine withdrawal, changes in both brain reward and neuronal nAChR functioning have been observed, which underlie withdrawal symptom development.[21,24–28] It is evident that the β_2 subunit of neuronal nAChRs is pivotal for the generation of reward from nicotine administration[29–35] as well as for the generation of cognitive and affective withdrawal symptoms.[36–41]

Objective

This review will focus on how β_2 subunit-containing nAChRs underlie the symptoms of nicotine withdrawal, as well as how these receptors underlie the rewarding and reinforcing properties of nicotine. Moreover, this review will discuss the utility of pharmacotherapies in reducing withdrawal symptom severity and the rewarding properties of nicotine via acting on β_2 subunit-containing nAChRs. The review will incorporate findings from human and animal studies to elucidate the involvement of the β_2 subunit in nicotine reward and withdrawal.

COMMENT

Nicotine in the brain: effects of chronic use and withdrawal

Neuronal nicotinic acetylcholine receptors—Nicotine and endogenous acetylcholine (ACh) bind to pentameric nicotinic acetylcholine receptors (nAChRs), which are formed from a combination of α and β subunits, to gate the transmembrane flow of cations.[42,43] In the mammalian central nervous system, predominant nAChRs include low-affinity homomeric α_7 and high-affinity heteromeric $\alpha_4\beta_2$ nAChRs. The β_2 subunit can couple with non-α_4 subunits, including α_2, α_3 and α_6 subunits to form functionally distinct nAChRs, but these receptors are much less densely expressed in the central nervous system relative to $\alpha_4\beta_2$* nAChRs (*indicating potential assemblage of β_2 subunits with non-α_4 subunits).[44] In addition to nAChRs forming from different subunit assemblages, stoichiometric study has shown that $\alpha_4\beta_2$ nAChRs can form as either $(\alpha_4)_3(\beta_2)_2$ or $(\alpha_4)_2(\beta_2)_3$, the latter having a

greater affinity for both nicotine and ACh.[45] The high-affinity $\alpha_4\beta_2$* nAChRs are densely expressed in cortex, striatum and hippocampus[46] and are involved in addiction and learning processes.[30,32,34,38,40,47]

Dopamine, reward and the β_2 subunit of neuronal nAChRs—Drugs of abuse can cause alterations in mesocorticolimbic neurotransmitter release, and these release patterns have been associated with the rewarding effects of drug administration.[48] The nucleus accumbens (NAcc) receives a basal (i.e. 'tonic') release of DA from presynaptic dopaminergic cell bodies in the ventral tegmental area (VTA).[49] Rewarding events, such as administration of drugs of abuse, elicit large and transient (i.e. 'phasic') bouts of DA release in the NAcc from VTA cell bodies.[14,15] *In vivo* studies have demonstrated that acute nicotine administration elicits phasic DA release in the NAcc and that this phasic activity continues to be elicited after repeated administrations.[11–13,50–53] Whereas acute nicotine leads to enhanced phasic dopaminergic signalling in the NAcc, withdrawal from chronic nicotine leads to both reduced tonic DA release in the NAcc[28,54] and a concordant reduction in brain reward thresholds.[55] Accordingly, nicotine withdrawal leads to a state of reduced pleasure and reward, which is known as anhedonia.[56] These studies reveal that: (1) acute nicotine elicits phasic DA release in the NAcc even after repeated administrations, (2) nicotine withdrawal leads to a hypodopaminergic state which is associated with anhedonia, and (3) re-administration of nicotine may temporarily resolve this anhedonic state by enhancing dopaminergic signalling in the NAcc.[57]

The dopaminergic activity changes observed in the NAcc following nicotine administration are mediated by presynaptic β_2 subunit-containing nAChRs in the VTA.[29,30] Genetically engineered β_2-knockout ($\beta_2^{-/-}$) mice have allowed for delineating the involvement of the β_2 subunit of neuronal nAChRs in nicotine-induced reward.[58,59] It has been reported that $\beta_2^{-/-}$ mice show significantly reduced phasic DA release in the NAcc upon nicotine administration relative to wild-type control animals and that $\beta_2^{-/-}$ mice show reduced self-administration for nicotine when allowed intravenous[33] or direct intra-VTA[31] self-administration. Targeted lentiviral expression of the β_2 subunit in the VTA of $\beta_2^{-/-}$ mice restored nicotine self-administration[31,33,34] and increased phasic DA release in the NAcc after nicotine administration.[31] Additionally, mice acquire conditioned place preference (CPP) to nicotine,[60] as evidenced by animals spending significantly more time in a nicotine-paired context relative to a saline-paired context. It was demonstrated that $\beta_2^{-/-}$ mice do not acquire nicotine CPP.[32,35] Separate lines of evidence have revealed that other nAChR subunits, such as α_5 and α_6 subunits, can co-assemble with β_2 subunit-containing nAChRs and are involved in the rewarding properties of nicotine and that genetic mutations in the genes coding for these nAChR subunits may confer vulnerability for nicotine addiction.[61,62] Ultimately, the β_2 subunit of neuronal nAChRs is necessary for behavioural and neurochemical properties of nicotine-induced reward.

Receptor upregulation and the β_2 subunit of neuronal nAChRs: Receptor desensitization precedes upregulation—Although several lines of evidence have shown that chronic nicotine can alter receptor function of many nAChRs,[63] including α_7 and $\alpha_3\beta_4$ subtypes, this review will focus on how chronic nicotine alters receptor function of β_2

subunit-containing nAChRs. Several studies have shown that β_2 subunit-containing nAChRs desensitize from chronic nicotine exposure and that these receptors recover from their desensitized states after nicotine is cleared from the system.[16–20,22,23] Moreover, evidence has found that chronic nicotine leads to a dose-dependent increase in number of β_2 subunit-containing nAChRs throughout widespread brain regions and that these receptors persist in an upregulated state after nicotine is cleared from the system.[21,24–27,64–67] Concordantly, $\beta_2^{-/-}$ mice failed to show receptor upregulation following chronic nicotine treatment.[68] To explain the dose-dependent upregulation effect of chronic nicotine on β_2 subunit-containing nAChRs, evidence has found that a positive relationship exists between the recovery time from desensitization and the magnitude of receptor upregulation. Specifically, mutant $\alpha_4\beta_2$ nAChRs in *Xenopus laevis* oocytes that were slow to recover from their desensitized state upregulated in response to low-dose, periodic exposures to nicotine, whereas wild-type channels did not upregulate from low doses of nicotine.[20] This evidence supports the idea that there might be a cause-and-effect relationship between receptor desensitization and upregulation and that the magnitude of nicotine dependence may underlie the degree of receptor upregulation, but this relationship has not been fully uncovered. Combined, these lines of evidence suggest that β_2 subunit-containing nAChRs desensitize from chronic nicotine treatment, which is followed by persistent upregulation, and that these nAChRs return from desensitization upon nicotine clearing the system. Thus, when nicotine is cleared from the system, it might be the case that an increased number of functional β_2 subunit-containing nAChRs are available on cell membranes relative to prenicotine receptor levels. Accordingly, it might be the case that a sensitized nAChR system develops during withdrawal as a result of increased functional β_2 subunit-containing nAChRs.[27,67,69]

The findings from animal research on nicotine-mediated nAChR function have shown to be translational to humans. An early autoradiographic study revealed that smokers had increased nAChR binding sites in multiple brain regions, including the hippocampus, relative to non-smokers.[70] It has since been shown that increases in nAChR binding sites are positively correlated with the magnitude of nicotine dependence[71] and are specific to increased densities of high-affinity β_2 subunit-containing nAC-hRs.[21] Furthermore, smokers who had quit at least 2 months before death were found to have normalized nAChR binding sites that were comparable to levels observed in non-smokers.[71] Initial post-mortem studies provided the first evidence of nAChR upregulation from brains of smokers, and a more extensive understanding of nAChR changes has since been made from imaging the brains of live smokers.

Subtype-selective radioligands have been developed for positron emission topography (PET)[72–75] and single-photon emission computed tomography (SPECT),[76,77] which have allowed for *in vivo* imaging of nAChRs in smokers. One PET study, using the $\alpha_4\beta_2$* nAChR radioligand 2-[^{18}F]fluoro-3-(2(S)azetidinylmethoxy) pyridine (2-F-A-85380), showed that smoking 1–3 cigarettes saturates $\alpha_4\beta_2$* binding sites in widespread brain areas for several hours in smokers.[78] Related studies using iodide 123-labelled 5-iodo-A-85380 ([^{123}I]5-IA; herein referred to as 5IA) SPECT imaging provided evidence that smokers have increased levels of $\alpha_4\beta_2$* nAChRs in thalamic, striatal and cortical brain regions at 1 week but not 24 h into withdrawal relative to non-smokers.[26,79] Notably, it is likely the case that nicotine

metabolites (e.g. cotinine) interfered with radioligand binding at the 24 h post-cessation imaging session, such that high-affinity nAChRs may, indeed, have been upregulated 24 h post-cessation (as evidenced by rodent studies[24,27,80]). Moreover, $\alpha_4\beta_2$* nAChR levels were found to have normalized between 6–12 weeks into abstinence,[26] which extends initial post-mortem findings.[71] Concordantly, Mamede and colleagues[81] used 5IA SPECT imaging to show that the binding potential of $\alpha_4\beta_2$* nAChRs is decreased on average by 33.5% in widespread brain areas, including in frontal and temporal cortices, 4 h after smoking a cigarette relative to non-smokers, which is due to the presence and continued binding of nicotine to neuronal nAChRs. The binding potential of $\alpha_4\beta_2$* nAChRs was significantly increased at 10 days post-cessation by 25.7% on average, providing additional evidence of upregulated receptors during withdrawal. These levels returned to non-smoker levels by 21 days post-cessation. Together, these results suggest that the upregulation of neuronal nAChRs from smoking is an underlying neurobiological correlate of the early symptoms of nicotine withdrawal, but that other circuits may underlie relapse after nAChR levels have normalized.

Nicotine withdrawal symptomatology

Nicotine withdrawal in smokers—An early study by Shiffman and Jarvik[82] showed that physical and psychological withdrawal symptoms were present between 2 days and 14 days post-cessation in abstaining smokers. Hughes[83] showed that 2-day abstainers had increased anxiety, restlessness and difficulty concentrating relative to precessation assessments. Since these early studies, a better understanding of both the time course of withdrawal symptoms and the relationships between withdrawal symptoms, craving and relapse propensity has been reached.

Smokers experiencing nicotine withdrawal report an array of cognitive and affective symptoms as nicotine levels decline in the body.[6] The cognitive symptoms of nicotine withdrawal include concentration difficulty, working memory problems and attentional impairment, and these symptoms have been observed between 0.5 h and 2 days post-cessation.[9,83–95] The affective symptoms of nicotine withdrawal include anxiety, irritability and restlessness, and these symptoms have been observed between 1.5 h and 2 days post-cessation.[83,88,90,92,94] An early report observed that cognitive and affective symptoms in abstaining smokers were resolved by 30 days post-cessation,[83] but the majority of these studies did not assess withdrawal symptoms beyond 2 days post-cessation. Thus, the precise time course of cognitive and affective symptoms during nicotine withdrawal has not been entirely determined. As nicotine plasma levels decline post-cessation, craving for nicotine tends to increase,[94] and craving has been observed in conjunction with cognitive and affective withdrawal symptoms in many of these studies.[82,83,88,91–93] Symptoms of withdrawal and craving for nicotine in smokers abstaining from tobacco products combine to encourage relapse and propagate addiction.

Relapse propensity has been shown to be mediated by the severity of nicotine withdrawal symptoms.[96,97] For example, it has recently been demonstrated that deficits in cognitive functioning during withdrawal are predictive of relapse.[98] In this study, working memory performance during abstinence predicted relapse throughout a 7-day withdrawal period.

Smokers with lower performance tended to relapse more quickly and at greater frequency than smokers with higher performance. Taken together, nicotine withdrawal involves the generation of negative cognitive and affective symptoms, which in turn function to promote relapse, and relapse propensity is mediated by the severity of withdrawal symptoms.[99,100]

Examining nicotine withdrawal in rodents: Cognitive symptoms and the β_2 subunit of neuronal nAChRs—Nicotine withdrawal is characterized by impaired cognitive functioning. Multiple studies have shown that rodents withdrawn from chronic nicotine have impaired learning.[27,40,41,80,101,102] Importantly, impairment was observed in tasks that require hippocampus-dependent learning.[103–106] The β_2 subunit of neuronal nAChRs underlies learning impairment during nicotine withdrawal, as $\beta_2^{-/-}$ mice exhibited no deficits in hippocampus-dependent learning tasks during nicotine withdrawal relative to wild-type control mice.[40,41] Additionally, nicotine withdrawal can be precipitated by the administration of the high-affinity nAChR antagonist dihydro-beta-erythroidine (DHβE),[107] which has high binding affinity to $\alpha_4\beta_2$* nAChRs. Whereas chronic nicotine-treated wild-type control animals had impaired learning when DHβE was administered systemically or directly into the hippocampus, chronic nicotine-treated $\beta_2^{-/-}$ mice did not have impaired learning when DHβE was administered.[38,40] Additionally, antagonizing $\alpha_4\beta_2$* nAChRs increased impulsivity in wildtype mice, suggesting the involvement of β_2 subunit-containing nAChRs in causing impulsivity during nicotine withdrawal.[36,108] Combined, these studies support the role of β_2 subunit-containing nAChRs in generating cognitive impairment during nicotine withdrawal.

Upregulation of β_2 subunit-containing nAChRs underlies learning impairment during nicotine withdrawal. In support, the duration of $\alpha_4\beta_2$* nAChR upregulation in the hippocampus during nicotine withdrawal paralleled the duration of impairments observed in hippocampus-dependent learning.[27] Chronic nicotine administration causes nAChRs to desensitize[16] and upregulate.[60,61] As nicotine clears from the system during withdrawal, receptors return from being desensitized and are maintained in an upregulated state.[19,20,24,27] During this time, endogenous ACh is the only ligand available to bind to the re-sensitized and increased nAChRs. Combined, these receptor-level changes during nicotine withdrawal may produce a hypersensitive nAChR system that could lead to cognitive impairment.

Affective symptoms and the β_2 subunit of neuronal nAChRs—Nicotine withdrawal is also characterized by changes in affect, and the β_2 subunit of neuronal nAChRs is involved in the generation of affective symptoms during nicotine withdrawal. Rodent studies have found that nicotine withdrawal produces anhedonia, which is defined by the American Psychological Association as the reduced ability to obtain pleasure from rewarding stimuli.[109–111] Administration of the high-affinity nAChR antagonist DHβE produced anhedonia in chronic nicotine-treated rodents, which suggests the involvement of β_2 subunit-containing nAChRs in this negative affective state during nicotine withdrawal.[39] Moreover, the β_2 subunit of neuronal nAChRs is involved in anxiogenesis during nicotine withdrawal, as $\beta_2^{-/-}$ mice did not show signs of increased anxiety during nicotine withdrawal relative to wild-type control mice.[37] Taken together, nicotine withdrawal

produces cognitive and affective symptoms that promote relapse and involve changes in β_2 subunit-containing receptor functioning. Pharmacotherapies that target β_2 subunit-containing nAChRs may help alleviate these symptoms.

Pharmacotherapies

Nicotine replacement therapies—The easiest way for smokers to relieve nicotine withdrawal symptoms is to smoke. The rationale behind nicotine replacement therapies (NRTs) is to administer nicotine by means other than smoking. Several forms of NRT that have been approved by the Food and Drug Administration (FDA) are currently available, including gum, transdermal patch, lozenge and intranasal spray.[112,113] A recent meta-analysis of 117 placebo-controlled clinical trials found a 6-month abstinence rate pooled risk ratio for NRT treatments to be 1.60 (95% CI: 1.53 to 1.68) relative to placebo treatment[114]; the authors conclude that all forms of commercially available FDA-approved NRTs are effective aides to smoking cessation.

Although NRTs are largely considered effective, studies have shown mixed results in terms of NRTs' ability to reduce craving and symptoms of nicotine withdrawal.[7,9,115,116–118] For example, an early study by West *et al.*[116] showed that nicotine gum dose dependently reduced certain affective symptoms (e.g. depressed mood) yet failed to reduce cognitive symptoms (e.g. concentration difficulty) in smokers going through overnight withdrawal. A later study found that administration of nicotine nasal spray effectively reduced both cognitive and affective withdrawal symptoms yet did not reduce craving in overnight abstainers and that these effects were sex and dose dependent.[9] Additionally, one study found that performance on a working memory task was significantly improved by the administration of nicotine gum in smokers going through 12 h of abstinence.[7,94] One rodent study found that acute nicotine administration restored cognitive functioning in mice undergoing withdrawal from chronic nicotine.[102] The discrepant findings across NRT clinical literature could be attributed in large part to the type and dosing regimen of treatment used between studies.[119] The studies mentioned here suggest that NRTs can be effective in relieving certain withdrawal symptoms during short-term nicotine withdrawal.

Electronic cigarettes are widely available in the United States. Electronic cigarettes are not approved by the FDA as smoking cessation aides, and concerns have been raised regarding their potentially adverse health effects and abuse liability.[120–122] The intention behind NRTs is to assist in cessation, whereas electronic cigarettes, similarly to smokeless tobacco, are often used as replacements or supplements for tobacco cigarettes.[123] Additionally, clinical trials have provided mixed results for the efficacy of electronic cigarettes to reduce withdrawal symptom severity and aide in cessation, and many of these studies fail to report nicotine abstinence rates (as opposed to tobacco product abstinence rates).[124–127] Moreover, there have been questions raised regarding the impurities in the nicotine delivery device cartridge liquid.[128] Although electronic cigarettes have been discussed by some from a 'harm reduction' perspective,[129,130] there are adverse health effects, particularly on cardiovascular functioning, associated with nicotine administration.[10,131–134] Additionally, studies (reviewed in[135,136]) suggest that activation of nAChRs is mechanistically involved in carcinogenesis and that nicotine may be one of the compounds involved in causing cancer.

Thus, more studies are needed to determine the safety and efficacy of electronic cigarettes for smoking cessation.[137]

Varenicline—Varenicline is a partial agonist of $\alpha_4\beta_2$ nAChRs, a full agonist at the α_7 nAChR and has been approved by the FDA for smoking cessation.[138,139] Clinically, varenicline treatment resulted in 43.9% tobacco product abstinence at 12 weeks following a target quit date and 23.0% abstinence at 52 weeks[140] (see Table 1). For a review and meta-analysis of varenicline's clinical efficacy, see Hays *et al.*[141] and Cahill *et al.*[142], respectively.

Varenicline has been shown to be effective at reducing both craving and the reward associated with smoking in abstaining smokers.[140,143,144] The ability of varenicline to reduce the reward associated with smoking could be due to its activity on the mesolimbic DA system. Specifically, microdialysis study has shown that varenicline significantly reduced the phasic release of DA in the NAcc upon an acute nicotine challenge injection relative to animals that received a nicotine challenge injection but received a saline pretreatment.[138] Although varenicline has the ability by itself to elicit phasic DA release in the NAcc via β_2 subunit-containing nAChRs,[138,145] animal studies have shown that varenicline did not by itself induce conditioned place preference.[146] Moreover, varenicline reduced the reward associated with nicotine[147] and reduced nicotine self-administration.[148] Combined, these studies suggest that varenicline is effective in reducing both craving and the reward associated with nicotine administration during short-term withdrawal but does not by itself carry abuse liability.

Varenicline reduces cognitive and certain affective symptoms during short-term nicotine withdrawal. An initial study in mice found that varenicline ameliorated impairment in hippocampus-dependent learning when animals were withdrawn from chronic nicotine.[149] Moreover, it was found that varenicline reduced the anhedonic state normally experienced by rodents during nicotine withdrawal.[150] However, one animal study showed that varenicline might not be effective in reducing anxiety during short-term nicotine withdrawal.[151] Varenicline treatment reduced negative affect and improved performance in neurocognitive tests of sustained attention and working memory in smokers undergoing short-term withdrawal.[143,152] Taken together, varenicline has been found to be effective in reducing some cognitive and certain affective symptoms during short-term nicotine withdrawal.

Varenicline use has been associated with side effects that discourage treatment and consequently encourage relapse. The most prominent adverse effect associated with varenicline is nausea.[142] At the 1.0 mg/kg BID dose of varenicline, one study reported a 52% incidence rate of nausea.[153] However, it has been observed that titrating dosage of varenicline over the first week of treatment is associated with a reduction in the incidence rate of nausea.[154] Mechanistically, the side effects of varenicline are thought to be due in part to effects on non- $\alpha_4\beta_2$ nAChRs, such as peripheral $\alpha_3\beta_4$* and central α_7 nAChRs.[155–157] Ahmed *et al.*[158] reviewed 25 case reports that detailed neuropsychiatric adverse events, including depressed mood, insomnia, suicidal ideation and aggression, as a result of varenicline treatment. Importantly, 68% of these cases were reported from patients

with a history of mental illness. However, a recent analysis of eight randomized, placebo-controlled clinical trials found that varenicline treatment decreased neuropsychiatric adverse events in patients with no history of mental illness.[159] Thus, the probability of developing neuropsychiatric adverse reactions to varenicline is greater in patients with a history of mental illness, but there appears to be less concern of neuropsychiatric symptom development in treatment-seeking smokers without a history of mental illness.

Bupropion—Bupropion is a DA and norepinephrine (NE) reuptake inhibitor,[160,161] as well as a non-competitive nAChR antagonist with selectivity to β_2 subunit-containing nAChRs.[162] Bupropion is an FDA-approved antidepressant with documented clinical efficacy,[163] and bupropion sustained-released (SR) has been approved for smoking cessation in the United States as of 1997.[164]

An initial clinical trial found that a 7-week daily treatment regimen of bupropion SR in smokers dose dependently increased tobacco product abstinence rates at 3, 6 and 12 months after a target quit date compared to placebo-treated smokers.[165] A study using a 9-week treatment regimen showed that bupropion-treated smokers were, on average, 2.3 times more likely to abstain at 6 and 12 months relative to placebo-treated smokers.[166]

Combination treatment with a nicotine patch showed that smokers co-treated with bupropion SR were three times more likely to continue abstinence at 12 months relative to placebo-treated smokers, but this difference was not significantly different from either bupropion SR or nicotine patch treatment alone.[166] Additional evidence has suggested that combination treatment of bupropion SR and participant-selected NRT is not additionally effective relative to either treatment alone at 6-month follow-up[167] (bupropion SR: 26.7% abstinent, NRT: 24.2% abstinent, combination therapy: 23.4% abstinent). Overall, Stapleton *et al.*[167] conclude that bupropion SR might be best considered a second-line treatment for individuals not responding to NRT or varenicline.

Bupropion has been shown to reduce the cognitive and affective symptoms during nicotine withdrawal.[168] Specifically, working memory ability was significantly improved in bupropion SR-treated vs. placebo-treated overnight abstainers. An earlier study found that high-dose bupropion SR significantly reduced self-reported difficulty concentrating and craving during withdrawal relative to placebo-treated smokers.[169] Predominant adverse reactions to bupropion SR were found at moderate and high doses and included dry mouth and insomnia.[165,166] Preclinical studies have found that bupropion treatment reduced anhedonia during nicotine withdrawal.[170,171] A microdialysis study extended initial findings by showing that bupropion treatment increased DA release in the NAcc.[172] An additional study found that administration of bupropion to nicotine-withdrawn mice reduced hippocampus-dependent learning impairment.[173] An *in vivo* microdialysis study found that acute nicotine administration increased extracellular NE release in the hippocampus,[174] and it has since been suggested that hippocampus-dependent learning impairment during nicotine withdrawal may be due in part to alterations in NE signalling in the hippocampus, as drugs that function primarily to increase NE ameliorate learning impairment.[173,175] The increase in hippocampal NE is one possible mechanism by which bupropion might be therapeutic for treating nicotine addiction. A second mechanism by which bupropion could

aid in cessation and maintain abstinence is by antagonizing β_2 subunit-containing nAChRs,[162] which would function to reduce activity in a potentially hypersensitive nAChR system. It is also possible that the therapeutic action of bupropion involves combined activity on NE- and ACh-mediated neural circuits. Additionally, metabolites of bupropion, such as a hydroxybupropion, have been found to reduce affective and somatic symptoms in nicotine-withdrawn mice,[176] and human studies have further suggested a role of bupropion metabolites in its therapeutic efficacy.[177–179] Delineation of the specific mechanism by which bupropion aids in smoking cessation has not been fully determined, and identification of this mechanism could aid in the development of novel smoking cessation aides.

WHAT IS NEW AND CONCLUSION

New developments

Nicotine vaccine—A nicotine vaccination study was recently published and showed that smokers treated with the vaccine showed significantly reduced neuronal $\alpha_4\beta_2$* nAChR occupancy rates compared to prevaccination receptor occupancy rates after intravenous administration of nicotine.[180] This study was supported by an initial finding in rats, showing that a 2-h pretreatment with a nicotine vaccine reduced the amount of nicotine found in the brain by 35% relative to placebo-treated control animals.[181] The nicotine vaccine works by having the treated individual create antibodies that bind to nicotine upon smoking, which serves to reduce the amount of nicotine able to cross the blood–brain barrier. The study conducted by Esterlis *et al.*[180] also showed that the 20-week vaccination regimen led to a 40% reduction in the amount of cigarettes smoked and significantly reduced craving. The nicotine vaccine is promising in terms of reducing the amount of nicotine available to bind to neuronal nAChRs, which would likely reduce the reward associated with smoking and help to prolong abstinence. Adverse reactions to nicotine vaccines predominantly include injection site tenderness, general discomfort, myalgia and headache.[182,183] Progress is continuing to be made with nicotine vaccine research, but results from clinical trials thus far have provided mixed evidence that nicotine vaccines promote abstinence at greater rates than currently available pharmacotherapies.[184]

Although the focus of this review is on therapeutics acting on β_2 subunit-containing nAChRs, it is noteworthy that other targets exist. For example, nortriptyline is a tricyclic antidepressant that primarily functions to increase extracellular levels of serotonin and has been shown to have long-term smoking cessation efficacy.[185] Additionally, a selective and potent antagonist at $\alpha_3\beta_4$* nAChRs was found to dose dependently reduce nicotine self-administration in rats without affecting natural reward seeking.[186] Moreover, recent developments have shown that antagonists at high-affinity nAChRs containing the α_6 subunit mediate nicotine-evoked mesolimbic DA release and may be effective smoking cessation aides.[187] Although the most effective pharmacotherapies have been found to target β_2 subunit-containing nAChRs, other neuronal circuits that are affected by nicotine have been explored as therapeutic avenues for smoking cessation.

Concluding remarks

One pathway by which nicotine produces reward and addiction is through binding to neuronal β_2 subunit-containing nAChRs. Chronic nicotine desensitizes β_2 subunit-containing nAChRs, and β_2 subunit-containing nAChRs upregulate after chronic nicotine exposure. Upregulation of neuronal β_2 subunit-containing nAChRs persists during withdrawal and is observed in concordance nicotine withdrawal symptoms. Pharmacotherapies, including varenicline and NRTs, are agonists of $\alpha_4\beta_2$* nAChRs, and these compounds reduce cognitive and affective symptoms of withdrawal, reduce the reward associated with smoking and reduce craving. Bupropion is a smoking cessation aide that functions similarly by reducing nAChR system activity but also works by blocking the reuptake of DA and NE.

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References

1. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Current Cigarette Smoking Among Adults – United States. 2011:2012a.
2. Centers for Disease Control and Prevention. Surgeon General's Report – The Health Consequences of Smoking. 2004
3. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses – United States, 2000–2004. 2008
4. Nides M. Update on pharmacologic options for smoking cessation treatment. Am J Sci. 2008; 121:S20–S31.
5. Benowitz NL. Nicotine addiction. Tob Use Cessat. 1999; 26:611–631.
6. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 2007; 9:315–327. [PubMed: 17365764]
7. Ernst M, Matochik JA, Heishman SJ, Van Horn JD, Jons PH, Henningfield JE, London ED. Effect of nicotine on brain activation during performance of a working memory task. Proc Natl Acad Sci. 2001; 98:4728–4733. [PubMed: 11274349]
8. Baker TB, Brandon TH, Chassin L. Motivational influences on cigarette smoking. Annu Rev Psychol. 2004; 55:463–491. [PubMed: 14744223]
9. Myers CS, Taylor R, Moolchan E, Heishman S. Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. Neuropsychopharmacology. 2008; 33:588–598. [PubMed: 17443125]
10. Department of Health and Human Services PHS. A report of the Surgeon General. Washington: Govt. Printing Office; 1988. The health consequences of smoking: nicotine addiction. DHHS (CDC) Publication No. 88-8406
11. Grenhoff J, Aston-Jones G, Svensson TH. Nicotinic effects on the firing pattern of midbrain dopamine neurons. Acta Physiol. 1986; 128:351–358.
12. Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol. 1986; 132:337–338. [PubMed: 3816984]
13. Brazell MP, Mitchell SN, Joseph MH, Gray JA. Acute administration of nicotine increases the *in vivo* extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid and ascorbic acid preferentially in the nucleus accumbens of the rat: comparison with caudate-putamen. Neuropharmacology. 1990; 29:1177–1185. [PubMed: 2293060]

14. Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justic JB Jr. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology. 1995a; 120:10–20. [PubMed: 7480530]
15. Wise RA, Leone P, Rivest R, Leeb K. Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. Synapse. 1995b; 21:140–148. [PubMed: 8584975]
16. Lukas RJ. Effects of chronic nicotinic ligand exposure on functional activity of nicotinic acetylcholine receptors expressed by cells of the PC12 rat pheochromocytoma or the TE671/RD human clonal line. J Neurochem. 1991; 56:1134–1145. [PubMed: 2002334]
17. Hsu Y-N, Amin J, Weiss DS, Wecker L. Sustained nicotine exposure differentially affects α3β2 and α4β2 neuronal nicotinic receptors expressed in Xenopus oocytes. J Neurochem. 1996; 66:667–675. [PubMed: 8592138]
18. Chavez-Noriega LE, Crona JH, Washburn MS, Urrutia A, Elliott KJ, Johnson EC. Pharmacological characterization of recombinant human neuronal nicotinic acetylcholine receptors hα2β2, hα2β4, hα3β2, hα3β4, hα4β2, hα4β4 and hα7 expressed in Xenopus oocytes. J Pharmacol Exp Ther. 1997; 280:346–356. [PubMed: 8996215]
19. Fenster CP, Rains MF, Noerager B, Quick MW, Lester RAJ. Influence of subunit composition on desensitization of neuronal acetylcholine receptors at low concentrations of nicotine. J Neurosci. 1997; 17:5747–5759. [PubMed: 9221773]
20. Fenster CP, Whitworth TL, Sheffield EB, Quick MW, Lester RAJ. Upregulation of surface α4β2 nicotinic receptors is initiated by receptor desensitization after chronic exposure to nicotine. J Neurosci. 1999; 19:4804–4814. [PubMed: 10366615]
21. Perry DC, Dávila-Garcìa MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. J Pharmacol Exp Ther. 1999; 289:1545–1552. [PubMed: 10336551]
22. Wang F, Nelson ME, Kuryatov A, Olale F, Cooper J, Keyser K, Lindstrom J. Chronic nicotine treatment up-regulates human α3β2 but not α3β4 acetylcholine receptors stably transfected in human embryonic kidney cells. J Biol Chem. 1998; 273:28721–28732. [PubMed: 9786868]
23. Bohler S, Gay S, Bertrand S, Corringer PJ, Edelstein SJ, Changeux J-P, Bertrand D. Desensitization of neuronal nicotinic acetylcholine receptors conferred by N-terminal segments of the β2 subunit. Biochemistry. 2001; 40:2066–2074. [PubMed: 11329274]
24. Trauth JA, Seidler FJ, McCook EC, Slotkin TA. Adolescent nicotine exposure causes persistent upregulation of nicotinic cholinergic receptors in rat brain regions. Brain Res. 1999; 851:9–19. [PubMed: 10642823]
25. Salas R, Pieri F, Di Biasi M. Decreased signs of nicotine withdrawal in mice null for the β4 nicotinic acetylcholine receptor subunit. J Neurosci. 2004; 24:10035–10039. [PubMed: 15537871]
26. Cosgrove KP, Batis J, Bois F, et al. β2-nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. Arch Gen Psychiatry. 2009; 66:666–676. [PubMed: 19487632]
27. Gould TJ, Portugal GS, Andre JM, et al. The duration of nicotine withdrawal-associated deficits in contextual fear conditioning parallels changes in hippocampal high affinity nicotinic acetylcholine receptor upregulation. Neuropharmacology. 2012; 62:2118–2125. [PubMed: 22285742]
28. Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol Psychiatry. 2012; 71:184–191. [PubMed: 21872847]
29. Nisell M, Nomikos GG, Svensson TH. Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse. 1994; 16:36–44. [PubMed: 8134899]
30. Picciotto MR, Zoli M, Rimodini R, et al. Acetylcholine receptors containing the β2 subunit are involved in the reinforcing properties of nicotine. Nature. 1998; 391:173–177. [PubMed: 9428762]
31. Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. Nature. 2005; 436:103–107. [PubMed: 16001069]

32. Walters CL, Brown S, Changeux J-P, Martin B, Damaj MI. The β2 but not α7 subunit of the nicotinic acetylcholine receptor is required for nicotine-conditioned place preference in mice. Psychopharmacology. 2006; 184:339–344. [PubMed: 16416156]
33. Pons S, Fattore L, Cossu G, Tolu S, Porcu E, McIntosh JM. Crucial role for α4 and α6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. J Neurosci. 2008; 28:12318–12327. [PubMed: 19020025]
34. Orejarena MJ, Herrera-Solís A, Pons S, Maskos U, Maldonado R, Robledo P. Selective re-expression of β2 nicotinic actylcholine receptor subunits in the ventral tegmental area of the mouse restores intravenous nicotine self-administration. Neuropharmacology. 2012; 63:235–241. [PubMed: 22480616]
35. Tobey KM, Walentiny DM, Wiley JL, et al. Effects of the specific α4β2 nAChR antagonist, 2-fluoro-3-(4-nitrophenyl) deschloroepibatidine, on nicotine reward-related behaviors in rats and mice. Psychopharmacology. 2012; 223:159–168. [PubMed: 22526534]
36. Shoaib M, Bizarro L. Deficits in a sustained attention task following nicotine withdrawal in rats. Psychopharmacology. 2005; 178:211–222. [PubMed: 15338107]
37. Jackson KJ, Martin BR, Changeux J-P, Damaj MI. Differential role of nicotinic acetylcholine receptor subunits in physical and affective nicotine withdrawal signs. J Pharmacol Exp Ther. 2008; 325:302–312. [PubMed: 18184829]
38. Portugal GS, Kenney JW, Gould TJ. β2 containing acetylcholine receptors mediate nicotine withdrawal deficits in learning. Neurobiol Learn Mem. 2008; 89:106–113. [PubMed: 17584502]
39. Stoker AK, Semenova S, Markou A. Affective and somatic aspects of spontaneous and precipitated nicotine withdrawal in C57BL/6J and BALB/cByJ mice. Neuropharmacology. 2008; 54:1223–1232. [PubMed: 18452957]
40. Davis JA, Gould TJ. Hippocampal nAChRs mediate nicotine withdrawal-related learning deficits. Eur Neuropsychopharmacol. 2009; 19:551–561. [PubMed: 19278836]
41. Raybuck JD, Gould TJ. Nicotine withdrawal-induced deficits in trace fear conditioning in C57BL/6 mice—a role for high-affinity beta2 subunit-containing nicotinic acetylcholine receptors. Eur J Neurosci. 2009; 29:377–387. [PubMed: 19200240]
42. Cooper E, Couturier S, Ballivet M. Pentameric structure and subunit stoichiometry of a neuronal acetylcholine receptor. Nature. 1991; 350:235–238. [PubMed: 2005979]
43. Le Novère N, Corringer J-P, Changeux J-P. The diversity of subunit composition in nAChRs: evolutionary origins, physiologic and pharmacologic consequences. J Neurobiol. 2002; 53:447–456. [PubMed: 12436412]
44. Nguyen HN, Rasmussen BA, Perry DC. Subtype-selective up-regulation by chronic nicotine of high-affinity nicotinic receptors in rat brain demonstrated by receptor autoradiography. J Pharmacol Exp Ther. 2003; 307:1090–1097. [PubMed: 14560040]
45. Nelson ME, Kuryatov A, Choi CH, Zhou Y, Lindstrom J. Alternative stoichiometries of α4β2 nicotinic acetylcholine receptors. Mol Pharmacol. 2003; 63:332–341. [PubMed: 12527804]
46. Gotti C, Zoli M, Clementi F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. Trends in Pharmacol Sci. 2006; 27:482–491. [PubMed: 16876883]
47. Gould TJ. Nicotine and hippocampus-dependent learning. Mol Neurobiol. 2006; 34:93–107. [PubMed: 17220532]
48. Di Chiara G, Bassareo V, Fenu S, et al. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology. 2004; 47:227–241. [PubMed: 15464140]
49. Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci. 2003; 6:968–973. [PubMed: 12897785]
50. Livingstone PD, Wonnacott S. Nicotinic acetylcholine receptors and the ascending dopamine pathways. Biochem Pharmacol. 2009; 78:744–755. [PubMed: 19523928]
51. Di Biasi M, Dani JA. Reward, addiction, withdrawal to nicotine. Annu Rev Neurosci. 2011; 34:105–130. [PubMed: 21438686]
52. Damsma G, Day J, Fibiger HC. Lack of tolerance to nicotine-induced dopamine release in the nucleus accumbens. Eur J Pharmacol. 1989; 168:363–368. [PubMed: 2479574]

53. Benwell MEM, Balfour DJK. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol. 1992; 105:849–856. [PubMed: 1504716]
54. Koranda JL, Cone JJ, McGehee DS, Roitman MF, Beeler JA, Zhuang X. Nicotinic receptors regulate the dynamic range of dopamine release in vivo. Journal Neurophysiol. 2013; 111:103–111.
55. Johnson PM, Hollander JA, Kenny PJ. Decreased brain reward function during nicotine withdrawal in C57BL6 mice: evidence from intracranial self-stimulation studies. Pharmacol Biochem Behav. 2008; 90:409–415. [PubMed: 18466962]
56. D'Souza MS, Markou A. Neural substrates of psychostimulant withdrawal-induced anhedonia. Current Topics Behav Neurosci. 200910.1007/7854_2009_20
57. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997; 278:52–58. [PubMed: 9311926]
58. Changeux J-P. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. Nat Rev Neurosci. 2010; 11:389–401. [PubMed: 20485364]
59. Stoker AK, Markou A. Unraveling the neurobiology of nicotine dependence using genetically engineered mice. Curr Opin Neurobiol. 2013; 23:1–7. [PubMed: 23265962]
60. Grabus SD, Martin BR, Brown SE, Damaj MI. Nicotine place preference in the mouse: influences of prior handling, dose and strain and attenuation by nicotinic receptor antagonists. Psychopharmacology. 2006; 184:456–463. [PubMed: 16463055]
61. Bierut LJ. Convergence of genetic findings for nicotine dependence and smoking related disease with chromosome 15q24–25. Trends Pharmacol Sci. 2010; 31:46–51. [PubMed: 19896728]
62. Fowler CD, Tuesta L, Kenny PJ. Role of α5* nicotinic acetylcholine receptors in the effects of acute and chronic nicotine treatment on brain reward function in mice. Psychopharmacology. 2013; 229:503–513.
63. Giniatullin R, Nistri A, Yakel JL. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. Trends Neurosci. 2005; 28:371–378. [PubMed: 15979501]
64. Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. J Pharmacol Exp Ther. 1983; 226:817–825. [PubMed: 6887012]
65. Marks MJ, Stitzel JA, Collins AC. Time course study of the effects of chronic nicotine infusion on drug response and brain receptors. J Pharmacol Exp Ther. 1985; 235:619–628. [PubMed: 4078726]
66. Flores CM, Rogers SW, Pabreza LA, Wolfe BB, Kellar KJ. A subtype of nicotinic cholinergic receptor in rat brain is composed of α4 and β2 subunit and is up-regulated by chronic nicotine treatment. Mol Pharmacol. 1992; 41:31–37. [PubMed: 1732720]
67. Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron. 1996; 16:905–908. [PubMed: 8630247]
68. McCallum SE, Collins AC, Paylor R, Marks MJ. Deletion of the beta 2 nicotinic acetylcholine receptor subunit alters development of tolerance to nicotine and eliminates receptor upregulation. Psychopharmacology. 2006; 184:314–327. [PubMed: 16001112]
69. Wonnacott S. The paradox of nicotinic acetylcholine receptor upregulation by nicotine. Trends Pharmacol Sci. 1990; 11:216–219. [PubMed: 2200178]
70. Benwell MEM, Balfour DJK, Anderson JM. Evidence that tobacco smoking increases the density of (−)-[^{3}H]nicotine binding sites in human brain. J Neurochem. 1988; 50:1243–1247. [PubMed: 3346676]
71. Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, Leonard S. Effect of smoking history on [3H] nicotine binding in human postmortem brain. J Pharmacol Exp Ther. 1997; 282:7–13. [PubMed: 9223534]
72. Koren AO, Horti AG, Mukhin AG, Gündisch D, Kimes AS, Dannals RF, London ED. 2-, 5-, and 6-Halo-3-(2(S)-azetidinylmethoxy)pyridines: synthesis, affinity for nicotinic acetylcholine receptors, and molecular modeling. J Med Chem. 1998; 41:3690–3698. [PubMed: 9733494]
73. Gallezot JD, Bottlaender M, Grégoire MC, et al. In vivo imaging of human cerebral nicotinic acetylcholine receptors with 2-^{18}F-Fluoro-A-85380 and PET. J Nucl Med. 2005; 46:240–247. [PubMed: 15695782]

74. Mukhin AG, Kimes AS, Chefer SI, et al. Greater nicotinic acetylcholine receptor density in smokers than in nonsmokers: a PET study with 2-^{18}F-FA-85380. J Nucl Med. 2008; 49:1628–1635. [PubMed: 18794265]
75. Wong DF, Kuwabara H, Kim J, et al. PET imaging of high-affinity α4β2 nicotinic acetylcholine receptors in humans with ^{18}F-AZAN, a radioligand with optimal brain kinetics. J Nucl Med. 2013; 54:1–7.
76. Kassiou M, Eberl S, Meikle SR, et al. In vivo imaging of nicotinic receptor upregulation following chronic (−)-nicotine treatment in baboon using SPECT. Nucl Med Biol. 2001; 28:165–175. [PubMed: 11295427]
77. Sihver W, Nordberg A, Långström B, Mukhin AG, Koren AO, Kimes AS, London ED. Development of ligands for in vivo imaging of cerebral nicotinic receptors. Behav Brain Res. 2000; 113:143–157. [PubMed: 10942041]
78. Brody AL, Mandelkern MA, London ED, et al. Cigarette smoking saturates brain $\alpha_4\beta_2$ nicotinic acetylcholine receptors. Arch Gen Psychiatry. 2006; 63:907–915. [PubMed: 16894067]
79. Staley JK, Krishnan-Sarin S, Cosgrove KP, et al. Human tobacco smokers in early abstinence have higher levels of β_2* nicotinic acetylcholine receptors than nonsmokers. J Neurosci. 2006; 26:8707–8714. [PubMed: 16928859]
80. Wilkinson DS, Turner JR, Blendy JA, Gould TJ. Genetic background influences the effects of withdrawal from chronic nicotine on learning and high-affinity nicotinic acetylcholine receptor binding in the dorsal and ventral hippocampus. Psychopharmacology. 2013; 225:201–208. [PubMed: 22836371]
81. Mamede M, Ishizu K, Ueda M, Mukai T, Iida Y, Kawashima H. Temporal change in human nicotinic acetylcholine receptor after smoking cessation: 5IA SPECT study. J Nucl Med. 2007; 48:1829–1835. [PubMed: 17942810]
82. Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology. 1976; 50:35–39. [PubMed: 827760]
83. Hughes JR. Tobacco withdrawal in self-quitters. J Consult Clin Psychol. 1992; 60:689–697. [PubMed: 1401384]
84. Snyder FR, Davis FC, Henningfield JE. The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend. 1989; 23:259–266. [PubMed: 2752917]
85. Snyder FR, Henningfield JE. Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. Psychopharmacology. 1989; 97:17–22. [PubMed: 2496420]
86. Parrott AC, Roberts G. Smoking deprivation and cigarette reinstatement: effects upon visual attention. J Psychopharmacol. 1991; 5:404–409. [PubMed: 22282850]
87. Parrott AC, Craig D. Cigarette smoking and nicotine gum (0, 2 and 4 mg): effects upon four visual attention tasks. Biol Psychol. 1992; 25:34–43.
88. Parrott AC, Garnham NJ, Wesnes K, Pincock C. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. Hum Psychopharmacol. 1996; 11:391–400.
89. Blake J, Smith A. Effects of smoking and smoking deprivation on the articulatory loop of working memory. Hum Psychopharmacol. 1997; 12:259–264.
90. Gross J, Lee J, Stitzer ML. Nicotine-containing versus de-nicotinized cigarettes: effects on craving and withdrawal. Pharmacol Biochem Behav. 1997; 57:159–165. [PubMed: 9164567]
91. Xu J, Mendrek A, Cohen MS, et al. Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. Biol Psychiatry. 2005; 58:143–150. [PubMed: 16038685]
92. Hendricks PS, Ditre JW, Drobes DJ, Brandon TH. The early time course of smoking withdrawal effects. Psychopharmacology. 2006; 187:385–396. [PubMed: 16752139]
93. Mendrek A, Monterosso J, Simon SL, Jarvik M, Brody A, Olmstead R. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. Addict Behav. 2006; 31:833–844. [PubMed: 16009504]

94. Brown J, Hajek P, McRobbie H, et al. Cigarette craving and withdrawal symptoms during temporary abstinence and the effect of nicotine gum. Psychopharmacology (Berlin). 2013; 229:209–218. [PubMed: 23636302]

95. Wesnes KA, Edgar CJ, Kezic I, Salih HM, de Boer P. Effects of nicotine withdrawal on cognition in a clinical trial setting. Psychopharmacology (Berlin). 2013; 229:133–140. [PubMed: 23591603]

96. West RJ, Hajek P, Belcher M. Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. Psychol Med. 1989; 19:981–985. [PubMed: 2594893]

97. Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. Exp Clin Psychopharmacol. 1997; 5:137–142. [PubMed: 9234050]

98. Patterson F, Jepson C, Loughead J, et al. Working memory deficits predict short-term smoking resumption following brief abstinence. Drug Alcohol Depend. 2010; 106:61–64. [PubMed: 19733449]

99. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci. 2005; 8:1442–1444. [PubMed: 16251985]

100. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]

101. Davis JA, James JR, Siegel SJ, Gould TJ. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6J mice. J Neurosci. 2005; 25:8708–8713. [PubMed: 16177040]

102. Kenney JW, Adoff MD, Wilkinson DS, Gould TJ. The effects of acute, chronic, and withdrawal from chronic nicotine on novel and spatial object recognition in male C57BL/6J mice. Psychopharmacology. 2011; 217:353–365. [PubMed: 21487656]

103. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci. 1992; 106:274–285. [PubMed: 1590953]

104. Logue SF, Paylor R, Wehner JM. Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. Behav Neurosci. 1997; 111:104–113. [PubMed: 9109628]

105. Fanselow MS, Poulos AM. The neuroscience of mammalian associative learning. Annu Rev Psychol. 2005; 56:207–234. [PubMed: 15709934]

106. Gaskin S, Gamliel A, Tardif M, Cole E, Mumby DG. Incidental (unreinforced) and reinforced spatial learning in rats with ventral and dorsal lesions of the hippocampus. Behav Brain Res. 2009; 202:64–70. [PubMed: 19447282]

107. Damaj MI, Kao W, Martin BR. Characterization of spontaneous and precipitated nicotine withdrawal in the mouse. J Pharmacol Exp Ther. 2003; 307:526–534. [PubMed: 12970387]

108. Semenova S, Stolerman IP, Markou A. Chronic nicotine administration improves attention while nicotine withdrawal induces performance deficits in the 5-choice serial reaction time task in rats. Pharmacol Biochem Behav. 2007; 87:360–368. [PubMed: 17582477]

109. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. Washington, DC: American Psychiatric Publishing; 2013.

110. Markou A, Koob GF. Construct validity of a self-stimulation threshold paradigm: effects of reward and performance manipulations. Physiol Behav. 1992; 51:111–119. [PubMed: 1741436]

111. Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature. 1998; 393:76–79. [PubMed: 9590692]

112. Thompson GH, Hunter DA. Nicotine replacement therapy. Ann Pharmacother. 1998; 32:1067–1075. [PubMed: 9793600]

113. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Coch Datab Syst Rev. 2004; 3:1–106. CD000146.

114. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation (Review). Coch Datab Syst Rev. 2012; 11:1–264.

115. Jarvik ME, Madsen DC, Olmstead RE, Iwamoto-Schaap PN, Elins JL, Benowitz NL. Nicotine blood levels and subjective craving for cigarettes. Pharmacol Biochem Behav. 2000; 66:553–558. [PubMed: 10899369]

116. West RJ, Jarvis MJ, Russell MAH, Carruthers ME, Feyerabend C. Effect of nicotine replacement on the cigarette withdrawal syndrome. Br J Addict. 1984; 79:215–219. [PubMed: 6589006]

117. Fagerström KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology. 1993; 111:271–277. [PubMed: 7870963]

118. Shiffman S, Ferguson SG, Gwaltney CJ, Balabanis MH, Shadel WG. Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. Psychopharmacology. 2006; 184:637–644. [PubMed: 16261317]

119. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. The Lancet. 1994; 343:139–142.

120. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the “e-cigarette”. Am J Public Health. 2010; 100:2340–2342. [PubMed: 21068414]

121. Cobb NK, Abrams DB. E-Cigarette or drug-delivery device? Regulating novel nicotine products. N Engl J Med. 2011; 365:193–195. [PubMed: 21774706]

122. Noel JK, Rees VW, Connolly GN. Electronic cigarettes: a new ‘tobacco’ industry? Tob Control. 2010; 20:81. [PubMed: 20930060]

123. Bell K, Keane H. Nicotine control: E-cigarettes, smoking and addiction. Int J Drug Policy. 2012; 23:242–247. [PubMed: 22365155]

124. Bullen C, McRobbie H, Thornley S, Glover M, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control. 2010; 19:98–103. [PubMed: 20378585]

125. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. The Lancet. 2013:S0140–6736. 61842–61845.

126. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. BMC Public Health. 2011; 11:1–12. [PubMed: 21199570]

127. Polosa R, Morjaria JB, Caponnetto P, et al. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. Intern Emerg Med. 2013:1–10. (in press). 10.1007/s11739-013-0977-z [PubMed: 24293214]

128. Westenberger, BJ. Evaluation of e-cigarettes. (Technical report). Silverspring, MD, USA: US Food and Drug Administration; 2009.

129. Wagener TL, Siegel M, Borrelli B. Electronic cigarettes: achieving a balanced perspective. Addiction. 2012; 107:1545–1548. [PubMed: 22471757]

130. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. Harm Red J. 2013b; 10:1–11.

131. Beeman JA, Hunter WC. Fatal nicotine poisoning: a report of twenty-four cases. Archiv Pathol. 1937; 24:481–485.

132. Totti N III, McCusker KT, Campbell EJ, Griffin GL, Senior RM. Nicotine is chemotactic for neutrophils and enhances neutrophil responsiveness to chemotactic peptides. Science. 1984; 223:169–171. [PubMed: 6318317]

133. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. JACC. 1997; 29:1422–1431. [PubMed: 9180099]

134. Benowitz NL, Hansson A, Jacob P III. Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. Hypertension. 2002; 39:1107–1112. [PubMed: 12052850]

135. Schuller HM. Is cancer triggered by altered signaling of nicotinic acetylcholine receptors? Nat Rev Neurosci. 2009; 9:195–205.

136. Improgo RM, Tapper AR, Gardner PD. Nicotinic acetylcholine receptor-mediated mechanisms in lung cancer. Biochem Pharmacol. 2011; 82:1015–1021. [PubMed: 21640716]

137. Odum LE, O’Dell KA, Schepers JS. Electronic cigarettes: Do they have a role in smoking cessation? J Pharm Pract. 2012; 25:611–614. [PubMed: 22797832]

138. Coe JW, Brooks PR, Vetelino MG, Wirtz MC, Arnold EP, Huang K. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem. 2005; 48:3474–3477. [PubMed: 15887955]
139. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors. Mol Pharmacol. 2006; 70:801–805. [PubMed: 16766716]
140. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:56–63. [PubMed: 16820547]
141. Hays JT, Ebbert JO, Sood A. Efficacy and safety of varenicline for smoking cessation. Am J Med. 2008; 121:S32–S42. [PubMed: 18342165]
142. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation (Review). Coch Datab Syst Rev. 2012; 6:1–119.
143. Patterson F, Jepson C, Strasser AA, et al. Varenicline improves mood and cognition during smoking abstinence. Biol Psychiatry. 2009; 65:144–149. [PubMed: 18842256]
144. McClure EA, Vandrey RG, Johnson MW, Stitzer ML. Effects of varenicline on abstinence and smoking reward following a programmed lapse. Nicotine Tob Res. 2013; 15:139–148. [PubMed: 22573730]
145. Reperant C, Pons S, Dufour E, Rollema H, Gardier AM, Maskos U. Effect of the α4β2* nicotinic acetylcholine receptor partial ago-nist varenicline on dopamine release in β2 knock-out mice with selective re-expression of the β2 subunit in the ventral tegmental area. Neuropharmacology. 2010; 58:346–350. [PubMed: 19887076]
146. Biala G, Staniak N, Budzynska B. Effects of varenicline and mecamylamine on the acquisition, expression, and reinstatement of nicotine-conditioned place preference by drug priming in rats. Narunyn-Schmiedeberg's Arch Pharmacol. 2010; 381:361–370.
147. Spiller K, Xi Z, Li X, Ashby CR Jr, Callahan PM, Tehim A, Gardner EL. Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of α4β2 nicotinic receptors in rats. Neuropharmacology. 2009; 57:60–66. [PubMed: 19393252]
148. Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE. Rationale, pharmacology and clinical efficacy of partial agonists of $\alpha_4\beta_2$ nACh receptors for smoking cessation. Trends Pharmacol Sci. 2007; 28:316–325. [PubMed: 17573127]
149. Raybuck JD, Portugal GS, Lerman C, Gould TJ. Varenicline ameliorates nicotine withdrawal-induced learning deficits in C57BL/6J mice. Behav Neurosci. 2008; 122:1166–1171. [PubMed: 18823172]
150. Igari M, Alexander JC, Ji Y, Qi X, Papke RL, Bruijnzeel AW. Varenicline and cytisine diminish the dysphoric-like state associated with spontaneous nicotine withdrawal in rats. Neuropsychopharmacol. 2013; 39:1–11.
151. Turner JR, Wilkinson DS, Poole RLF, Gould TJ, Carlson GC, Blendy JA. Divergent functional effects of sazetidine-A and varenicline during nicotine withdrawal. Neuropsychopharmacology. 2013; 38:2035–2047. [PubMed: 23624742]
152. Loughead J, Ray R, Wileyto P, et al. Effects of the α4β2 partial agonist varenicline on brain activity and working memory in abstinent smokers. Biol Psychiatry. 2010; 67:715–721. [PubMed: 20207347]
153. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist. Arch Intern Med. 2006; 166:1561–1568. [PubMed: 16908788]
154. Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med. 2006; 166:1571–1577. [PubMed: 16908789]
155. Papke RL, Heinemann SF. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the β2 subunit. Mol Pharmacol. 1994; 45:142–149. [PubMed: 8302273]
156. Papke RL, Porter Papke JK. Comparative pharmacology of rat and human α7 nAChR conducted with net charge analysis. Br J Pharmacol. 2002; 137:49–61. [PubMed: 12183330]

157. Papke RL, Trocmé-Thibierge C, Guendisch D, Al sRubaiy SAA, Bloom SA. Electro-physiological perspectives on the therapeutic use of nicotinic acetylcholine receptor partial agonists. J Pharmacol Exp Ther. 2011; 337:367–379. [PubMed: 21285282]

158. Ahmed AI, Ali AN, Kramers C, Härmark LV, Burger DM, Verhoeven WM. Neuropsychiatric adverse events of varenicline: a systematic review of published reports. J Clin Psychopharmacol. 2013; 33:55–62. [PubMed: 23277249]

159. Foulds J, Russ C, Yu C, et al. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. Nicotine Tob Res. 2013; 15:1849–1857. [PubMed: 23694782]

160. Cooper BR, Hester TJ, Maxwell RA. Behavioral and biochemical effects of the antidepressant bupropion (Wellbutrin): evidence for selective blockade ofdopamine uptake in vivo. J Pharmacol Exp Ther. 1980; 215:127–134. [PubMed: 6778989]

161. Li SX, Perry KW, Wong DT. Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology. 2002; 42:181–190. [PubMed: 11804614]

162. Slemmer JE, Martin BR, Damaj I. Bupropion is a Nicotinic Antagonist. J Pharmacol Exp Ther. 2000; 295:321–327. [PubMed: 10991997]

163. Moreira R. The efficacy and tolerability of bupropion in the treatment of major depressive disorder. Clin Drug Invest. 2011; 31S1:5–17.

164. Richmond R, Zwar N. Review of bupropion for smoking cessation. Drug Alcohol Rev. 2003; 22:203–220. [PubMed: 12850907]

165. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking Cessation. N Engl J Med. 1997; 337:1195–1202. [PubMed: 9337378]

166. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999; 340:685–691. [PubMed: 10053177]

167. Stapleton JA, West R, Hajek P, et al. Randomized trial of NRT, bupropion, and NRT plus bupropion for smoking cessation: effectiveness in clinical practice. Addiction. 2013; 108:2193–2201. [PubMed: 23859696]

168. Perkins KA, Karelitz JL, Jao NC, Gur RC, Lerman C. Effects of bupropion on cognitive performance during initial tobacco abstinence. Drug Alcohol Depend. 2013; 133:283–286. [PubMed: 23726977]

169. Shiffman S, Johnston JA, Khayrallah M, et al. The effect of bupropion on nicotine craving and withdrawal. Psychopharmacology. 2000; 148:33–40. [PubMed: 10663415]

170. Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacology. 2003; 168:347–358. [PubMed: 12698231]

171. Paterson NE, Balfour DJK, Markou A. Chronic bupropion differentially alters the reinforcing, reward-enhancing and conditioned motivational properties of nicotine in rats. Nicotine Tob Res. 2008; 106:995–1008. [PubMed: 18584463]

172. Paterson NE, Balfour DJK, Markou A. Chronic bupropion attenuated the anhedonic component of nicotine withdrawal in rats via inhibition of dopamine reuptake in the nucleus accumbens shell. Eur J Neurosci. 2007; 25:3099–3108. [PubMed: 17561823]

173. Portugal GS, Gould TJ. Bupropion dose-dependently reverses nicotine withdrawal deficits in contextual fear conditioning. Pharmacol Biochem Behav. 2007; 88:179–187. [PubMed: 17868796]

174. Fu Y, Matta SG, Valentine JD, Sharp BM. Desensitization and resensitization of norepinephrine release in the rat hippocampus with repeated nicotine administration. Neurosci Lett. 1998; 241:147–150. [PubMed: 9507942]

175. Davis JA, Gould TJ. Atomoxetine reverses nicotine withdrawal-associated deficits in contextual fear conditioning. Neuropsychopharmacology. 2007b; 32:2011–2019. [PubMed: 17228337]

176. Damaj MI, Grabus SD, Navarro HA, et al. Effects of hydroxymetabolites of bupropion on nicotine dependence behavior in mice. J Pharmacol Exp Ther. 2010; 334:1087–1095. [PubMed: 20576796]

177. Ray R, Tyndale RF, Lerman C. Nicotine dependence pharmacogenetics: role of genetic variation in nicotine-metabolizing enzymes. J Neurogenet. 2009; 233:252–261. [PubMed: 19169923]

178. Zhu AZ, Cox LS, Nollen N, et al. CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion. Clin Pharmacol Ther. 2012; 92:771–777. [PubMed: 23149928]

179. Benowitz NL, Zhu AZ, Tyndale RF, Dempsey D, Jacob P III. Influence of CYP2B6 genetic variants on plasma and urine concentrations of bupropion and metabolites at steady state. Pharmacogenet Genomics. 2013; 233:135–141. [PubMed: 23344581]

180. Esterlis I, Hannestad JO, Perkins E, et al. Effect of a nicotine vaccine on nicotine binding to β_2*-nicotinic acetylcholine receptors in vivo in human tobacco smokers. Am J Psychiatry. 2013; 170:399–407. [PubMed: 23429725]

181. Pravetoni M, Keyler DE, Raleigh MD, et al. Vaccination against nicotine alters the distribution of nicotine delivered via cigarette smoke inhalation to rats. Biochem Pharmacol. 2011; 81:1–17. [PubMed: 20920479]

182. Hatsukami DK, Jorenby DE, Gonzales D, et al. Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. Clin Pharmacol Ther. 2011; 89:392–399. [PubMed: 21270788]

183. Hoogsteder PHJ, Kotz D, van Spiegel PI, et al. The efficacy and safety of a nicotine conjugate vaccine (NicVAX®) or placebo co-administered with varenicline (Champix®) for smoking cessation: study protocol of a phase IIb, double blind, randomized, placebo controlled trial. BMC Public Health. 2012; 12:1–11. [PubMed: 22214479]

184. Raupach T, Hoogsteder PH, Onno van Schayck CP. Nicotine vaccines to assist with smoking cessation: current status of research. Drugs. 2012; 724:e1–16. [PubMed: 22356293]

185. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Coch Datab Syst Rev. 2014; (8):CD000031.

186. Toll L, Zaveri NT, Polgar WE, et al. AT-1001: a high affinity and selective $\alpha_3\beta_4$ nicotinic acetylcholine receptor antagonist blocks nicotine self-administration in rats. Neuropsychopharmacology. 2012; 37:1367–1376. [PubMed: 22278092]

187. Crooks PA, Bardo MT, Dwoskin LP. Nicotinic receptor antagonists as treatments for nicotine abuse. Adv Pharmacol. 2014; 69:513–551. [PubMed: 24484986]

188. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:47–55. [PubMed: 16820546]

189. Tønnesen P, Tonstad S, Hjalmarson A, et al. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. J Intern Med. 2003; 254:184–192. [PubMed: 12859700]

190. Wang C, Xiao D, Chan KPW, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: a placebo-controlled, randomized study. Respirology. 2009; 14:384–392. [PubMed: 19192221]

Table 1

Placebo-controlled clinical trials examining tobacco product abstinence rates from varenicline and bupropion SR treatments

		Continuous abstinence or point prevalence rate (%)					
Drug	**Treatment regimen**	**7 weeks**	**12 weeks**	**24 weeks**	**52 weeks**	**Final *N***	**Report**
Varenicline vs. Bupropion SR vs. Placebo							
Varenicline	10 mg BID for 12 weeks	–	44.0***,‡	29.5***,†	21.9***	352	Gonzales *et al.* 2006[188]
Bupropion SR	150 mg BID for 12 weeks[a]	–	29.5***	20.7***	161***	352	
Placebo		–	17.7	10.5	84	344	
Varenicline	10 mg BID for 12 weeks	–	43.9***,‡	29.7***,†	23.0***,†	344	Jorenby *et al.* 2006[140]
Bupropion SR	150 mg BID for 12 weeks[a]	–	29.8***	20.2**	14.6	342	
Placebo		–	17.6	13.2	10.3	341	
Varenicline	0.3 mg QD for 6 weeks	254*	16.7	9.5	7.9	126	Nides *et al.* 2006[153]
	1.0 mg QD for 6 weeks	31.0**	15.1	9.5	5.6	126	
	10 mg BID for 6 weeks	40.8***	28.8**	20.8**	144**	125	
Bupropion SR	150 mg BID for 7 weeks	28.6**	19.8*	10.3	6.3	126	
Placebo		13.8	10.6	7.3	4.9	123	
Varenicline vs. Placebo							
Varenicline	0.5 mg BID for 12 weeks	36.3***	44.0***	–	18.5***,*b*	123	Oncken *et al.* 2006[154]
	10 mg BID for 12 weeks	39.8***	49.4***	–	22.4***,*b*	146	
Placebo		10.9	11.6	–	3.9*b*	40	
Varenicline	10 mg BID for 12 weeks[a]	–	50.3***	38.2**	–	165	Wang *et al.* 2009[190]
Placebo		–	31.6	25.0	–	168	
Bupropion SR vs. Placebo							
Bupropion SR	100 mg QD for 7 weeks	28.8*	242*	24.2	19.6	153	Hurt *et al.* 1997[165] *b,c*
	150 mg QD for 7 weeks	38.6***	261**	27.5**	22.9*	153	
	300 mg QD for 7 weeks	44.2***	29.5***	26.9*	23.1**	156	
Placebo		19.0	144	15.7	124	153	
Bupropion SR	150 mg BID for 9 weeks[a]	–	–	34.8***	30.3***	169	Jorenby *et al.* 1999[166] *b*
Placebo		–	–	18.8	15.6	82	

		Continuous abstinence or point prevalence rate (%)					
Drug	**Treatment regimen**	**7 weeks**	**12 weeks**	**24 weeks**	**52 weeks**	**Final *N***	**Report**
Bupropion SR	150 mg BID for 7 weeks[a]	46.0***	32.0[e]	25.0***	21.0***	527	Tønnesen *et al.* 2003[189] [d]
Placebo		23.0	18.0	13.0	110	180	

Adapted from[140,153,154, 165,166, 188–190].

*$P \leq .05$ compared to placebo.

**$P \leq .01$ compared to placebo.

***$P \leq .001$ compared to placebo.

†$P \leq .01$ compared to bupropion SR.

‡$P \leq .001$ compared to bupropion SR.

[a]Dose titration within first 7 days of treatment.

[b]Point prevalence rate only at 52 weeks for[154] and at all time points for[165,166].

[c]Time points for continued abstinence rate (CAR) findings are: 6 weeks, 3 months, 6 months and 12 months, respectively.

[d]Time points for CAR findings are: 7 weeks, 12 weeks, 26 weeks and 52 weeks, respectively.

[e]Statistics not performed.