



## Review

## Mechanistic insights into nicotine withdrawal

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## ABSTRACT

Smoking is responsible for over 400,000 premature deaths in the United States every year, making it the leading cause of preventable death. In addition, smoking-related illness leads to billions of dollars in healthcare expenditures and lost productivity annually. The public is increasingly aware that successfully abstaining from smoking at any age can add years to one's life and reduce many of the harmful effects of smoking. Although the majority of smokers desire to quit, only a small fraction of attempts to quit are actually successful. The symptoms associated with nicotine withdrawal are a primary deterrent to cessation and they need to be quelled to avoid early relapse. This review will focus on the neuroadaptations caused by chronic nicotine exposure and discuss how those changes lead to a withdrawal syndrome upon smoking cessation. Besides examining how nicotine usurps the endogenous reward system, we will discuss how the habenula is part of a circuit that plays a critical role in the aversive effects of high nicotine doses and nicotine withdrawal. We will also provide an updated summary of the role of various nicotinic receptor subtypes in the mechanisms of withdrawal. This growing knowledge provides mechanistic insights into current and future smoking cessation therapies.

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**Abbreviations:** AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; 5-CSRTT, five-choice serial reaction time task; CPA, conditioned place aversion; CRF, corticotropin-releasing factor; DA, dopamine; DH $\beta$ E, dihydro- $\beta$ -erythroidine; EPM, elevated plus maze; GABA,  $\gamma$ -aminobutyric acid; 5-HT, 5-hydroxytryptophan; ICSS, intracranial self-stimulation; LDT, laterodorsal tegmentum; MLA, methyllycaconitine; NMDA, N-methyl-D-aspartic acid; NAcc, nucleus accumbens; NE, norepinephrine; PFC, prefrontal cortex; PPT, pedunculopontine tegmentum; VTA, ventral tegmental area.

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## 1. Introduction

In the United States, about 21% of adults currently smoke cigarettes [1]. Cigarette smoking is the leading cause of preventable death, responsible for 443,000 premature deaths every year. The economic impact is staggering, with a cost to the health care system of about \$96 billion and \$97 billion in lost productivity [2]. Smoking decreases one's life expectancy mostly due to tobacco-related vascular, neoplastic, and respiratory disease [3]. Specifically, lung cancer is highly attributable to smoking and is the leading cause of cancer death among men and women [4]. To never smoke is obviously the best strategy to avoid the deleterious consequences of smoking, but for those who have become addicted, quitting brings significant benefits. A smoker who quits at 35 years of age will live about 8 years longer than a continuing smoker [5], and will have a similar life expectancy as a never smoker [3]. Even quitting in old age can add years to one's life [5]. However, in a given year, only 3% of smokers are actually successful in their cessation attempts, even though 70% of smokers express desire to quit [6].

Nicotine, the major addictive component of tobacco, binds to nicotinic acetylcholine receptors (nAChR). nAChRs are ligand gated ion channels activated by the endogenous neurotransmitter acetylcholine (ACh). Neuronal type nAChRs are composed of differing combinations of  $\alpha$  and  $\beta$  subunits, with nine genes encoding  $\alpha$  subunits ( $\alpha 2$ – $\alpha 10$ ) and three encoding  $\beta$  subunits ( $\beta 2$ – $\beta 4$ ) [7–9].  $\alpha 7$  homomers and  $\alpha 4\beta 2$  heteromers represent the two major nAChR subtypes found throughout the brain but other nAChR subunit combinations are expressed in selected brain areas [9–13].

Genetic, developmental, and environmental factors determine whether someone will become addicted to the nicotine contained in tobacco [6,14,15] and will start to smoke compulsively, despite well known health consequences [16,17]. The addiction process involves the activation of various brain circuits, including the dopaminergic (DAergic) reward system and the circuits that underlie motivation, decision making, and habit formation [18]. Many neurotransmitters and neuropeptides are involved in the process, as nAChRs are strategically positioned to modulate the release of virtually every major neurotransmitter [8,19,20]. The neuroadaptations arising from chronic nicotine exposure cause widespread alterations in brain neurotransmission that promote and sustain the use of tobacco [21–24]. Smoking cessation disrupts the equilibrium maintained in the presence of nicotine and leads to the manifestations of withdrawal. The symptoms associated with the nicotine abstinence syndrome contribute to the maintenance of the smoking habit and are a potent deterrent for those who are trying to quit [25–27]. The following sections summarize our current understanding of the mechanisms underlying the behavioral manifestations of nicotine withdrawal and discuss existing and potential strategies for smoking cessation.

## 2. The dopaminergic system, goal-directed behavior, and nicotine's effects

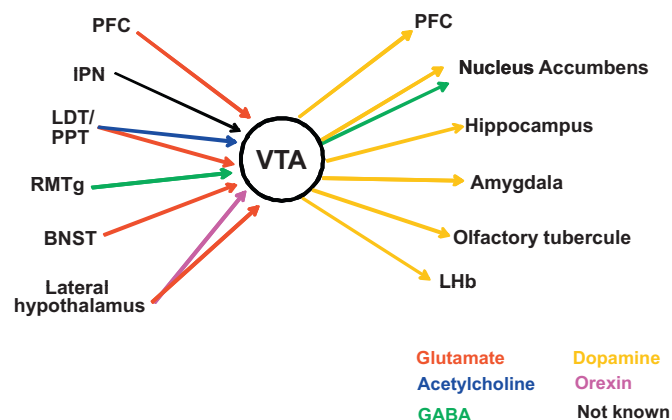
### 2.1. Role of the dopaminergic system

The ventral tegmental area (VTA) and substantia nigra provide the major source of dopamine (DA) in the brain. The role of the

DAergic system (in particular the mesocorticolimbic pathway) in drug addiction derives from DA's ability to modulate many of the limbic and cortical sites involved in goal-directed behavior (Fig. 1) [18,28–31]. Presentation of natural reinforcers, such as food and sex, causes DA neurons to switch from low-frequency tonic activity at rest to phasic bursting. The DA released encodes reward prediction errors and incentive salience and provides a learning signal for the optimization of goal-directed behavior [31,32]. Addictive drugs, including nicotine, hijack the mechanisms of experience-dependent adaptive behavior and lead to abnormally high DA levels [33]. Repeated exposure to the drug results in synaptic adaptations that produce behavioral changes. Although changes in DA levels are the main feature of addictive drugs, it should be kept in mind that other neurotransmitters and neuropeptides participate in nicotine reward, including glutamate, cannabinoids, and opioids [34–37].

### 2.2. Cholinergic influences over midbrain DA neurons and ventral striatum

The cholinergic system exerts a profound effect on DAergic activity as ACh released in the VTA promotes the switch between tonic and phasic activity in DAergic neurons that signals reward and salience [38,39]. Cholinergic inputs to the midbrain DA center originate from the pedunculopontine tegmentum (PPT) and the laterodorsal tegmentum (LDT) in which cholinergic neurons are interspersed with GABAergic and glutamatergic neurons [40–42]. The PPT/LDT are also the source of the excitatory glutamatergic inputs to the DA neurons projecting to the nucleus accumbens (NAcc) [40]. Various nAChR subtypes are expressed on midbrain



**Fig. 1.** Major VTA afferent and efferent projections. VTA DA neurons send projections to NAcc, PFC, the hippocampus, the amygdala and the olfactory tubercle [256]. Through those projections, the DAergic system influences reward-related behavior by affecting reinforcement (NAcc), learning and declarative memory (hippocampus), emotional memory (amygdala), habit formation (ventral and dorsal striatum), and executive functions and working memory (PFC and orbitofrontal cortex). The activity of the VTA is in turn regulated by inputs from the PFC, the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT), the rostromedial tegmental nucleus (RMT), the lateral hypothalamus, the bed nucleus of the stria terminalis (BNST) and the interpeduncular nucleus (IPN) [257–260]. DA neurons also receive inhibitory inputs from intra-VTA GABAergic neurons, NAcc, and ventral pallidum [261,262]. Neurotransmitters are color coded as indicated.

DA, GABA, and glutamatergic neurons, and nAChRs are also expressed on afferent projections including those from cortex, PPT/LDT, and the NAcc [43–45]. nAChRs are also present on DAergic axon terminals [13,46] and GABA interneurons in the NAcc [47]. In the NAcc, cholinergic innervation arises from striatal interneurons [48–50]. Each of these neuronal subpopulations expresses nAChRs of differing subunit compositions and with differing cellular localizations [8,9,51]. By binding to those nAChRs, nicotine can alter DAergic activity by directly activating DA neurons in the VTA and by modulating the release probability of both inhibitory and excitatory neurotransmitters from presynaptic terminals in VTA and NAcc. These actions result in enhanced neuronal firing beyond that normally driven by environmental cues and contribute to the addiction process [52]. Pharmacological experiments, the analysis of nAChR null mice, and lentivirus-based re-expression studies are providing constant refinement to our understanding of the effects of nicotine on the circuits underlying goal-directed behavior (Table 1).

### 2.3. The habenula as a source of anti-reward

Although it was originally postulated that the DA released from the VTA only mediates the hedonic or pleasurable effects of natural reinforcers, it is now clear that changes in DAergic activity can also signal punishment, aversion, or lack of expected reward [53–58]. Reward omission induces phasic inhibition of VTA neurons [56,57] and aversive stimuli excite ventral [58] and inhibit dorsal [55] VTA neurons. Moreover, aversive stimuli increase the firing of NAcc neurons [59]. The fact that inhibition of VTA neurons can signal the motivational value of unexpected and aversive stimuli suggests the existence of neuronal circuits that interact, and partially overlap, to maximize reward and minimize aversive effects. Nicotine follows an inverted U-shaped dose-response curve [18,60], and smokers titrate their nicotine intake to experience the rewarding while avoiding the aversive effects produced by high nicotine doses [61–64]. Our understanding of the circuits and molecular mechanisms governing the processing of aversive stimuli, including the effects of high nicotine doses, is still limited. However, the habenular complex, which receives inputs from the VTA, is emerging as an important component in the process.

**Table 1**  
nAChR influences on neurotransmitter release.

Neurotransmitter released	Brain region	nAChRs involved	References
Dopamine	VTA	$\alpha 4\beta 2^*$ , $\alpha 4^*$ , $\alpha 6^*$ , $\alpha 6\beta 2^*$	[13,263–265]
	NAcc	$\alpha 4\beta 2^*$ ; $\alpha 7$	[12,13,266,267]
	PFC	$\alpha 4\beta 2^*$ ; $\alpha 7$	[268]
Glutamate	VTA	$\alpha 7$	[269,270]
	NAcc	$\beta 2^*$ ?	[271]
	PFC	$\alpha 4\beta 2^*$ ; $\alpha 7$	[268,272]
	Amygdala	$\alpha 4\beta 2^*$ ; $\alpha 7$	[271,273–276]
	IPN	$\alpha 7$	[277]
GABA	VTA	$\alpha 6\beta 2^*$	[278,279]
	NAcc	$\alpha 4\beta 2^*$	[47,280]
	Amygdala	$\alpha 3\beta 4^*$ ; $\alpha 7$	[275,281]
Acetylcholine	MHb		
	IPN	$\alpha 3\beta 4^*$ , $\alpha 3\beta 3\beta 4$	[222]
Norepinephrine	Hippocampus	$\alpha 3\beta 4^*$ , $\beta 4^*$ (rat); $\alpha 6\beta 2\beta 3^*$ (mouse)	[282,283]
	Cortex	$\alpha 3\beta 2^*$ , $\alpha 6^*$	[284]

Neurotransmitters released in response to nicotine, the brain areas where this release is known to occur, and nAChR subtypes known to facilitate this action. VTA, ventral tegmental area; NAcc, nucleus accumbens; PFC, prefrontal cortex; IPN, interpeduncular nucleus; GABA,  $\gamma$ -aminobutyric acid; MHb, medial habenula. The asterisk denotes the potential presence of other nAChR subunits.

The habenula is an epithalamic nucleus involved in the mechanisms of fear, anxiety, depression, and stress [18,30,65,66]. It is divided into the medial nucleus (MHb) and the two divisions of the lateral nucleus (LHb). The LHb receives inputs mainly from the basal ganglia and sends outputs to DAergic neurons and serotonergic neurons, while the MHb receives inputs mainly from the limbic system and sends outputs to the interpeduncular nucleus (IPN) [67]. Studies conducted in recent years have identified the LHb as a source of anti-reward signals that plays an important role in determining the reward-related activity of DA neurons [18,30,68–70]. The firing patterns of glutamatergic LHb neurons mirror those of DA cells: spike activity increases in LHb neurons in the absence of predicted reward and decreases upon delivery of reward [69,70]. Furthermore, electrical stimulation of the LHb inhibits the vast majority of DA neurons [69,71,72]. Such inhibition is not direct, but rather occurs through the stimulation of neurons in the rostromedial tegmental nucleus (RMTg) [73]. The RMTg sends GABAergic inhibitory projections to the VTA and substantia nigra [54,74,75] and provides tonic inhibition of DA cells [30]. Similarly to the LHb, RMTg neurons are phasically activated by aversive stimuli and inhibited by natural rewards like food or reward predictive stimuli [54].

Although it is currently unknown whether the MHb contributes directly to the regulation of monoamine transmission, the literature suggests an involvement of the MHb/IPN axis with brain reward areas. Electrical stimulation of the MHb and the fasciculus retroflexus, the primary efferent pathway of the MHb, produces rewarding effects [76], and most stimulant drugs of abuse cause axonal degeneration in the lateral habenula and the fasciculus retroflexus. In particular, nicotine causes degeneration of neurons in the portion of the fasciculus retroflexus that connects the MHb to the IPN [77,78]. A recent report suggests that  $\alpha 5$ -containing nAChRs in the MHb are key to the control of the amounts of nicotine self-administered as  $\alpha 5^{-/-}$  mice continue to self-administer nicotine at doses that normally elicit strong aversion in wild type animals [79,80]. However, lentiviral-based re-expression of the  $\alpha 5$  subunit in the MHb or the IPN is sufficient to bring nicotine self-administration back to wild type levels [80]. Additionally, blocking cholinergic transmission in either the MHb or IPN is sufficient to precipitate somatic signs of nicotine withdrawal [81]. Taken together, these data suggest a prominent role of the MHb/IPN axis in nicotine dependence because of its involvement in mediating nicotine's aversive effects and somatic symptoms of withdrawal.

### 2.4. Nicotine induced neuroadaptations

Nicotine dependence is accompanied by neuroadaptive changes that occur especially in the circuits underlying emotion and motivation [23,82]. Neuronal nAChR upregulation is an important adaptive change and a major contributor to the addictive properties of nicotine [83–86]. Nicotine desensitizes nAChRs and renders them unresponsive and this phenomenon drives an increase in receptor levels as part of an attempt to maintain circuit-level homeostasis [87–89]. Upregulation of nAChRs is the product of several concurrent mechanisms, including changes in receptor assembly, trafficking, and degradation [18,90]. Isomerization of surface nAChRs to high-affinity nicotinic sites has also been proposed to result from prolonged nicotine exposure [91,92]. Relevant to the understanding of the neuroadaptations produced by nicotine is the fact that nAChR upregulation differs among receptor subtypes, varies among brain regions for the same subtype, and even depends on the contingency of nicotine administration [9,90,93]. Because of this phenomenon, the way in which cholinergic inputs modulate neurotransmitter release is completely altered.

Besides altering cholinergic function, repeated nicotine exposure produces heterologous adaptations. For example, nicotine

increases AMPA/NMDA current ratios (a hallmark of long-term potentiation) at DA neurons [94–96] and other locations involved in drug-associated memory [97–99]. In the NAcc, nicotine leads to an increase in high affinity DA D2 receptors [100]. Such a phenomenon is analogous to that observed upon cocaine exposure, which leads to an increase in G-protein coupled DA D2 receptors and consequent DA supersensitivity in cocaine-treated animals [101]. A similar form of plasticity might occur during nicotine exposure. Nicotine self-administration also decreases expression of the cystine–glutamate exchanger, xCT, in the NAcc and VTA, and decreases the glial glutamate transporter, GLT-1, in the NAcc [102]. Synaptic function might also be altered by changes in the turnover of scaffolding proteins, a phenomenon reflecting nicotine's partial inhibition of proteasomal function [86,103,104].

Another system that is affected by nicotine exposure is the endogenous opioid system [105–107]. The endogenous opioid system influences both negative and positive motivational and affective states [108]. Opioid peptides affect DA function in the VTA and the striatum. In particular, dynorphins decrease and enkephalins increase DA release [109–115]. Conversely, DA controls the synthesis of striatal dynorphin and enkephalin by affecting their mRNA levels [106,116]. Nicotine affects these system-level and cellular interactions by altering synthesis and release of opioid peptides in a time- and peptide-specific fashion [36]. The ensuing plasticity participates in the mechanisms that maintain nicotine consumption but also participate in the nicotine-withdrawal syndrome [7,106]. What we discussed above are examples of the complex changes produced by nicotine. As nAChR activation affects the release of virtually every major neurotransmitter [106,117,118], chronic nicotine exposure is likely to cause global alterations in brain neurotransmission. These complex, within-system and between-system adaptations create a new equilibrium that requires the presence of nicotine to be maintained.

### 3. Nicotine withdrawal: definition, neurobiology, animals models

#### 3.1. Definition of nicotine withdrawal

Withdrawal is a collection of affective and somatic symptoms that emerge a few hours after nicotine abstinence and reflect the imbalance in brain neurochemistry created by the absence of nicotine. Seven nicotine withdrawal symptoms were validated in a recent comprehensive review on the topic [119] and appear in the DSM-IV-TR [120]. The symptoms are irritability/anger/frustration, anxiety, depression/negative affect, concentration problems, impatience, insomnia, and restlessness. Other symptoms (including altered neurohormonal profiles, perturbations of learned behaviors, weight gain, decreased heart rate, constipation, and mouth ulcers) are also likely valid symptoms but require further study [119,121,122]. Many of these symptoms are common to other drugs of abuse, but weight gain and decreased heart rate appear to be more specific to nicotine withdrawal [123]. Nicotine withdrawal symptoms are typically reported to reach a peak within the first week of abstinence and taper off for the next 3–4 weeks [119,124]. However, some reports indicate that symptoms can subside within 10 days [125], while others indicate that withdrawal symptoms may persist past 31 days [126,127].

Nicotine withdrawal symptoms are highly variable between patients and can be quite severe, with increased severity of withdrawal being predictive of increased rates of relapse [25,27,128–130]. Powerful cravings also accompany withdrawal, which may be precipitated by the sight of a cigarette, or a situation/place associated with the act of smoking [131]. The emergence of negative affective symptoms, such as dysphoria, anxiety and irritability and, to a lesser extent, the somatic manifestations of

withdrawal, serve as negative reinforcers that sustain the vicious cycle of addiction [23,121,132–134]. Continued use or relapse is therefore driven not only by the pursuit of hedonically positive effects but also the avoidance of negative states associated with withdrawal.

#### 3.2. Neural basis of withdrawal

Abrupt cessation of nicotine alters the neurochemistry of the addicted brain, thus triggering the affective and somatic signs of withdrawal. Acute withdrawal from all major drugs of abuse, including nicotine, decreases activity of the mesolimbic DAergic system, [135–139] and the consequent decrease in accumbal DA levels is likely the main trigger of the withdrawal syndrome. The hypodopaminergic state associated with withdrawal is produced by both a reduction in DA release and an increase in DA re-uptake [140]. Increased DA re-uptake is due to upregulation of the DA transporter (DAT) [137,141]. Interestingly, the deficits in DA transmission observed in the NAcc during withdrawal are paralleled by an increase in DA output in the prefrontal cortex (PFC) [138]. Such increases in PFC DA release may be important in mediating some of the aversive aspects of nicotine withdrawal. Enhanced DA transmission in the PFC occurs during exposure to stressful and aversive stimuli [142–144], and contributes to anxiety-related behaviors [145,146]. Anxiety and stress exert complex influences on all aspects of nicotine dependence, including the withdrawal syndrome. Due to its perceived calming effects, smoking is often used by smokers as a tool to attenuate stress and anxiety [147–149]. Anxiety is a symptom of withdrawal and it acts as a potent negative reinforcer that promotes smoking [120,124,150–152]. Besides being a product of nicotine withdrawal, stress and anxiety can exacerbate the symptoms of withdrawal, which leads to increased craving and relapse [151,153–156].

The central nucleus of the amygdala (CeA), together with the bed nucleus of the stria terminalis and the posterior shell of the NAcc is part of the “extended amygdala” [157]. This circuit and the HPA axis play crucial roles in the processing of the negative affective states associated with drug withdrawal [23,24,157]. Elevations in corticosterone and corticotropin-releasing factor (CRF) are observed during acute withdrawal from many drugs, including nicotine [21,24]. CRF levels increase by >500% in the CeA after nicotine withdrawal is precipitated with the nAChR antagonist mecamylamine [158]. Injection of a CRF<sub>1</sub> receptor antagonist into the CeA blunts anxiety-like behavior during nicotine withdrawal [158]. These data collectively suggest that smoking cessation rates could be improved by quelling anxiety with drugs that address the dysregulation of the stress response system observed during withdrawal.

As already discussed in Section 2.4, nicotine-induced neuroadaptations occur at many brain sites and affect several neurotransmitter systems. Therefore, nicotine withdrawal is expected to disrupt many of the neurotransmitter and neuropeptide systems that had adapted to the chronic presence of the drug [132]. The opioid system, dynorphin in particular, seems to be engaged in the mechanisms of nicotine withdrawal [106]. Other candidates are the serotonergic and the noradrenergic systems which are known to mediate the manifestations of withdrawal from other drugs of abuse [159–162].

#### 3.3. Animal models of withdrawal

Animal models of nicotine deprivation are invaluable tools for the understanding of the molecular underpinning of nicotine withdrawal symptoms and provide a way to test potential smoking cessation agents. Rodents chronically exposed to nicotine undergo a characteristic withdrawal syndrome which develops spontaneously, after



removing the nicotine source, or can be precipitated by administration of a nAChR antagonist such as mecamylamine [7,11,81,163–166]. Several behavioral tests are available to explore both the somatic and affective dimensions of withdrawal. The distinction between somatic and affective symptoms originated from the notion that the somatic signs reflect mainly peripheral, “bodily” mechanisms in contrast with the affective symptoms which are produced by centrally based mechanisms [167,168]. This distinction is still maintained although there is evidence that, besides a peripheral nAChR component, somatic signs might have a central component that reflects a dysphoric state of heightened irritability [166,169].

The following section briefly describes the tests most commonly used to assess nicotine withdrawal symptoms in rodents. In addition, based on pharmacologic studies and the analysis of nAChR mutant mice, it provides a summary of the most recent advances in the understanding of the nAChR subtypes and the brain areas involved in the nicotine withdrawal syndrome.

### 3.3.1. Somatic signs of withdrawal

The somatic manifestations of nicotine withdrawal in rodents can be detected as an increase in several stereotypic behaviors. Somatic signs of withdrawal include chewing, teeth-chattering, shakes, tremors, writhing, palpebral ptosis, gasps, and yawns [7,163]. The analysis of nAChR mutant mice has helped to identify the brain region and the nAChR subtypes that are responsible for the somatic manifestations of nicotine withdrawal (Table 2). Somatic withdrawal can be precipitated by mecamylamine microinjection into the MHB or the IPN, but not into hippocampus, cortex, or VTA [81]. The MHB/IPN express nAChRs comprising the  $\alpha 2$  (IPN),  $\alpha 5$ , and/or  $\beta 4$  nAChR subunits and absence of any one of those nAChR subunits abolishes the somatic manifestations of nicotine withdrawal [11,81,170].  $\alpha 7$ -Containing nAChRs might contribute to, but are not necessary for, the somatic manifestation of nicotine abstinence [171]. Interestingly, somatic signs of withdrawal are preserved in mice lacking the  $\beta 2$  or the  $\alpha 6$  nAChR subunits [11,172] even though, as described in Section 3.3.2, those subunits are critical for other aspects of withdrawal. These studies demonstrate that the MHB/IPN axis and specific nAChRs expressed within that axis are critical for at least the somatic signs of the nicotine withdrawal syndrome. In combination with the data showing that a circuit comprising the MHB and IPN is involved in controlling the intake of normally aversive doses of nicotine [80], the results suggest that, similarly to the LHB, the MHB may process signals with aversive valence.

### 3.3.2. Affective/cognitive symptoms of withdrawal

Affective symptoms such as anhedonia (inability to find pleasure in previously enjoyable activities), anxiety, and irritability

are some of the most commonly reported manifestations of nicotine withdrawal in humans [119]. Affective signs of withdrawal can also be examined in rodents using behavioral paradigms that test for anhedonia, conditioned place aversion, anxiety, and conditioned fear [7,165–167,173].

**3.3.2.1. Reward/anhedonia.** Intracranial self stimulation is a well established experimental procedure used to measure reward [174,175]. Rodents will repeatedly self stimulate in reward-related areas such as the posterior lateral hypothalamus and the VTA where changes in thresholds for self stimulation can be monitored [167,174,176]. The threshold for intracranial self stimulation decreases with increased function of the brain reward systems and increases when activity in the same centers is reduced. Drugs of abuse, including nicotine, lower reward thresholds [174,177–179]. The effects of nicotine are long lasting and are blocked by nicotinic, but not muscarinic, antagonists [178–181]. Like many of the effects of nicotine, reward threshold also presents a U-shaped dose-response curve: at higher doses of nicotine the reward threshold increases above baseline. This effect is dependent upon the  $\alpha 5$  nAChR subunit in the MHB, since a rat will maintain a decreased reward threshold at higher doses when  $\alpha 5$  is knocked down with lentiviral vector-based shRNA [80].

Withdrawal from drugs of abuse leads to decreased function of the reward system and changes ICSS thresholds [175,182]. Such a phenomenon is thought to represent a negative affective state associated with withdrawal. Rats undergoing spontaneous withdrawal from chronic nicotine treatment show a dramatic increase in reward thresholds [167]. Normally neutral stimuli, such as a light or a tone, will also increase ICSS thresholds if that stimulus is paired with withdrawal from nicotine [183]. This phenomenon indicates that environmental cues associated with abstinence from nicotine may reduce the function of brain reward centers.

**3.3.2.2. Conditioned place aversion.** Conditioned place aversion (CPA) is a paradigm designed to test an animal's drive to avoid contextual cues associated with a negative affect. Animals chronically treated with nicotine are confined in one of two chambers of the CPA apparatus while experiencing nicotine withdrawal symptoms triggered by the injection of a nAChR antagonist. On a different day, the same mice are injected with saline and exposed to the other chamber of the CPA apparatus. During training, associations are made between the negative affective state produced by withdrawal and the withdrawal-paired chamber so that exposure to the apparatus on testing day triggers avoidance of the compartment associated with the withdrawal effects. Both the  $\alpha 4\beta 2$  nAChR antagonist dihydro- $\beta$ -erythroidine (DH $\beta$ E) and mecamylamine produce CPA in nicotine-treated rats, although the doses needed to elicit the behavior may be higher than those required to increase ICSS thresholds [168,184–187]. These differences may signify the existence of different mechanisms for ICSS and CPA, but might also reflect strain-specific differences [185,186]. Pharmacological studies in nAChR null mice indicate that  $\beta 2$ -containing and  $\alpha 6$ -containing nAChRs are necessary for CPA, but neither the  $\alpha 5$ , nor the  $\alpha 7$  subunits affect CPA behavior [170,172,188].

**3.3.2.3. Anxiety-related behaviors.** Nicotine withdrawal can elicit anxiety-like behaviors in mice [189–191]. The most common paradigm used to observe these behaviors is the elevated plus maze (EPM) [192]. When nicotine withdrawal is precipitated in mice or rats, the animals spend significantly less time in the open arms of the EPM than saline-treated mice, a phenomenon that signals increased anxiety [165,193]. In the open field paradigm, mecamylamine-precipitated nicotine withdrawal is accompanied by a dramatic increase in thigmotaxis, i.e. an increase in the time spent in the periphery of the open field [194,195]

**Table 2**  
Effect of nAChR subunits on rodent models of nicotine withdrawal.

Signs	Effect	No effect
Somatic		
	$\alpha 2$ X [81]	$\alpha 6$ [172]
	$\alpha 5$ ↓ or X [81,170]	$\alpha 7$ [170,285]
	$\alpha 7$ ↓ [165,171]	$\beta 2$ [11]
	$\beta 4$ X [11]	
Affective		
Anxiety-related behavior	$\alpha 6$ X dd [172]	$\alpha 5$ [170]
	$\beta 2$ X EPoa [170]	$\alpha 7$ [170]
Attention tasks (5-CSRTT)	–	$\alpha 7$ [205]
Intracranial self stimulation	$\alpha 5$ ↓ [80]	$\alpha 7$ [286]
Conditioned place aversion	$\alpha 6$ X dd [172]	$\alpha 5$ [170]
	$\beta 2$ X [170]	$\alpha 7$ [170]
Trace fear conditioning	$\beta 2$ X [200]	$\alpha 7$ [200]

X, withdrawal phenotype abolished; ↓, withdrawal phenotype diminished; EPoa, effect seen in the elevated plus maze, open arm time only; dd, dose dependent.

Other animal models of anxiety are also altered by nicotine withdrawal. The light–dark box is a testing paradigm in which a mouse is placed in a novel environment that contains a brightly lit compartment and a dark compartment. The mouse will preferentially remain in the dark half of the box. The amount of time spent in the lit half and the time it takes for the mouse to cross into the lit half are measures of anxiety-like behaviors. Mice undergoing spontaneous withdrawal from nicotine will spend less time in the lit compartment relative to nicotine naïve mice [189,191]. The influence of various nAChR subtypes on withdrawal-induced anxiety-like behaviors has not been examined exhaustively. So far, it has been established that the  $\beta 2$  and  $\alpha 6$  nAChR subunits are necessary for increased anxiety during withdrawal [170,172], whereas,  $\alpha 5$  and  $\alpha 7$  may not be required [170].

**3.3.2.4. Fear conditioning.** Trace fear conditioning is a conditioning paradigm in which the conditioned stimulus (CS) is presented and then terminated with a time interval before the unconditioned stimulus (US) is applied [196]. Cued delay fear conditioning, in which the CS co-terminates with the US, is known to be hippocampus independent, whereas trace fear conditioning is dependent on the hippocampal circuitry [196]. Nicotine is known to enhance hippocampus-dependent contextual and cued trace fear conditioning, but not cued delay fear conditioning [197]. This enhancement by nicotine requires  $\beta 2$ -containing but not  $\alpha 7$ -containing nAChRs [198]. Also, systemic administration of NMDA receptor antagonists inhibits acquisition of contextual fear conditioning [199]. This effect is ameliorated by co-administration of systemic nicotine acting at  $\alpha 4\beta 2$ -containing nAChRs, as indicated by antagonism with DH $\beta$ E [199].

As with many effects of acute or chronic drug use, the withdrawal syndrome often results in an opposite effect. Since nicotine enhances trace fear conditioning, one could expect withdrawal to cause a deficit in the same paradigm. Raybuck and Gould [200] demonstrated that spontaneous withdrawal from chronic nicotine leads to deficits in the acquisition of trace fear conditioning. Withdrawal precipitated by DH $\beta$ E, but not methyllycaconitine (MLA), led to a similar deficit, implicating high-affinity receptors such as those containing the  $\alpha 4$ , and the  $\beta 2/\beta 4$  nAChR subunits. Confirming this result,  $\beta 2$ -null mice were not observed to have a deficit in trace fear conditioning upon spontaneous nicotine withdrawal [200].

**3.3.2.5. Five-choice serial reaction time task.** Tobacco deprivation impairs attention and cognitive abilities within 12 h of smoking cessation [201–203]. Models of attention might be useful to test this dimension of the nicotine withdrawal syndrome. The five-choice serial reaction time task (5-CSRTT) is a visual attention task [204] that can reliably detect cognitive aspects of nicotine withdrawal [205,206]. Significant deficits in sustained attention were seen after spontaneous withdrawal from nicotine in male rats [205], as well as during withdrawal precipitated with DH $\beta$ E [205]. The  $\alpha 7$  nAChR antagonist MLA failed to precipitate attention deficits in nicotine-treated rats [205], suggesting that  $\alpha 4\beta 2$ -containing, but not  $\alpha 7$ -containing nAChRs are important for 5-CSRTT.

## 4. Pharmacotherapy of nicotine addiction

### 4.1. Current therapies

To be successful, anti-smoking strategies need to reduce the motivation to smoke and the physiological and psychomotor symptoms experienced during a quit attempt. All current therapeutic strategies, albeit with different mechanisms, address the hypodopaminergic state produced by withdrawal in the VTA.

Other mechanisms of action might also contribute to their ability to promote smoking cessation.

### 4.2. Nicotine replacement therapy

Nicotine replacement therapy (NRT) has been the primary pharmacologic aid for tobacco cessation. As nicotine is the principal addictive component of cigarettes and other tobacco products, supplementing the user with nicotine during abstinence will ease the transition from smoking to complete abstinence by relieving withdrawal and nicotine craving [6,207]. Because nicotine undergoes first pass metabolism in the liver, the bioavailability of nicotine administered *per os* is reduced. To avoid this problem, nicotine replacement products are formulated for absorption through the oral mucosa (chewing gum, lozenges, sublingual tablets, inhaler) or the skin (transdermal patches). Regardless of the route of administration (gum, patch, nasal spray, or inhaler), NRT decreases withdrawal scores by a similar degree [208]. NRT roughly doubles quit rates compared to placebo, but a large percentage of subjects relapses to smoking within 6–12 months [209,210]. For smokers who declare unwillingness or inability to attempt an abrupt quit, the 12-month sustained abstinence success rate is 5.3% with NRT versus approximately 2.6% with placebo. In smokers willing to attempt an abrupt quit with NRT, the success rate is around 16% with NRT versus 10% with placebo [211]. Newer, more targeted pharmacotherapies have led to significant improvements in aiding tobacco cessation rates [212].

### 4.3. Bupropion

Bupropion is an atypical antidepressant and smoking cessation aid that exerts its actions by targeting multiple neurotransmitter systems [213]. Inhibition of catecholamine reuptake is one of bupropion's mechanisms of action [214]. Microdialysis studies indicate that bupropion treatment increases extracellular concentrations of DA and norepinephrine (NE) in the hypothalamus, PFC, and NAcc [215]. The drug may also function by increasing NE levels in the dorsal raphe nucleus, thus leading to increased serotonin (5-HT) levels [216]. Besides reducing NE, DA, and 5-HT reuptake, the drug increases the activity of vesicular monoamine transporters [213]. Bupropion also functions as a non-competitive antagonist at many nAChR subtypes [217]. Bupropion inhibits the function of  $\alpha 3\beta 2$ -,  $\alpha 4\beta 2$ -, and  $\alpha 7$ -nAChRs heterologously expressed in *Xenopus* oocytes [218]. It also non-competitively inhibits carbamylcholine-induced  $^{86}\text{Rb}^+$  efflux from human neuroblastoma cells expressing  $\alpha 3\beta 4$ -containing nAChRs [217].  $\alpha 3\beta 4$ -containing nAChRs are believed to play a major role in nicotine-evoked NE release from the hippocampus [219,220]. In addition, the  $\alpha 3$  and  $\beta 4$  nAChR subunits are expressed at high levels in the MHB/IPN axis [221–223], which, as discussed in Section 2.3, is emerging as a brain circuit involved in the processing of anti-reward stimuli and nicotine withdrawal [11,80,221].

Preclinical studies suggest that bupropion and nicotine might exert similar systems level effects. Both drugs are psychomotor stimulants [224,225] and both increase catecholamine concentrations in midbrain limbic regions [213,226]. In addition, both nicotine and bupropion serve as primary reinforcers in non-human subjects [227] and increase responding for reinforcing non-drug stimuli [228–230]. Therefore, the anti-smoking properties of bupropion may depend on its ability to substitute some of the psychomotor and/or reinforcement-related effects of nicotine [231]. Bupropion improves rates of abstinence to 14–18% of subjects [150,232], which are further augmented to 29% when the drug is combined with NRT [209,233,234].

#### 4.4. Varenicline

Varenicline is the third medication, besides NRT and bupropion, to be approved by the Food and Drug Administration for smoking cessation. It is a derivative of cytisine, a plant alkaloid with selective affinity and partial agonism for  $\alpha 4\beta 2$  nAChRs [235–237]. Varenicline has been touted as being effective through its partial agonism of  $\alpha 4\beta 2$  nAChRs. This effect is thought to decrease withdrawal and cravings [238]. Varenicline can block nicotine-induced decreases in brain stimulation thresholds, suggesting that it makes smoking less enjoyable [239]. Varenicline's effect is removed by pre-treatment with the non-selective nicotinic antagonist mecamylamine, or the  $\alpha 4$ -containing nAChR specific antagonist DH $\beta$ E. On the other hand, the  $\alpha 7$ -specific antagonist, MLA, has no effect on reward thresholds [239]. Besides acting at  $\alpha 4\beta 2$ -containing nAChRs, varenicline has significant effects at other nAChR subtypes. It acts as a partial agonist at  $\alpha 3\beta 4$ -,  $\alpha 2$ -, and  $\alpha 6$ -containing nAChRs, and a full agonist at  $\alpha 7$  nAChRs [237]. Varenicline's interactions with  $\alpha 3\beta 4$ -,  $\alpha 2$ -, or  $\alpha 6$ -containing nAChRs might also contribute to its therapeutic effects given the role of those receptors in both the rewarding and/or aversive effects of nicotine [11,13,80,81].

Two large, randomized, placebo-controlled studies released in 2006 related the efficacy of varenicline to that of bupropion in aided smoking cessation [232,240]. Nearly one quarter (21–23%) of patients taking varenicline for a short period of time (12 weeks) maintained abstinence at 52 weeks of follow-up. This represents a significant improvement over sustained-release bupropion (14–16%) and placebo (8–10%). Further analyzing the mechanisms of this effect, negative affect and craving associated with abstinence were decreased in patients taking varenicline relative to placebo [232]. However, the drug had no significant effect on restlessness, insomnia, or increased appetite. Gonzales et al. [240] found a similar decrease in negative affect, but also found a significant decrease in restlessness in patients taking varenicline. Individuals who relapsed derived less enjoyment from smoking while taking varenicline [240]. A very recent review of the literature suggests that, overall, varenicline works better than bupropion as a smoking cessation aid, although it is not clear how superior it is to NRT in the long term. Two open label, randomized controlled trial were unable to confirm significant improvements with varenicline over NRT in continuous abstinence rates at 52 weeks following short term treatment [212,241,242]. However, it should be noted that the 52 week abstinence rate for NRT was found to be 20.4%, higher than most previously reported rates, while varenicline maintained the usual reported rate (26.1%) [241].

Although bupropion and varenicline were proven safe in clinical trials, safety concerns have arisen based on post-marketing reports that led to the addition of warnings in the prescribing information of the two drugs. Although a causal relationship has not been established, serious adverse events in patients treated with bupropion or varenicline include changes in behavior, depression, self-injurious thoughts, and suicidal behavior [233,243]. Because long-term tobacco use causes morbidity in a high percentage of subjects and ends up killing half of all long-term smokers, the benefits of the two drugs outweigh the risks of serious adverse events in a small percentage of subjects. However, the occurrence of serious side effects and the relatively small, long-term rates of abstinence in smokers serve as an impetus for the development of new, safer therapeutic interventions [238,244].

#### 4.5. Nicotine vaccine

All the previously described pharmacotherapies require compliance to maintain efficacy. Nicotine vaccination offers a promising, more permanent approach to aid the willing addict in cessation attempts. Exposure to nicotine conjugated to immuno-

genic proteins (e.g., cholera toxin b, a virus-like particle, and *Pseudomonas* exotoxin A) leads to production of IgGs, some of which will be targeted against nicotine [238,245]. Anti-nicotine antibodies will bind to nicotine with high affinity and specificity, thus preventing or at least slowing nicotine's entry into the brain [246]. Decreasing the rate of absorption and the actions of an addictive drug on its targets reduce its rewarding effects and may aid in quitting [246,247]. A recent preclinical study demonstrated the efficacy of this approach [248]. After immunization using *Pseudomonas* exoprotein A conjugated to nicotine, rats exposed to cigarette smoke demonstrated a significant increase in serum nicotine levels, indicating prevention of nicotine entry into the brain. With a 10 min nose-only exposure, modeling one cigarette, brain levels of nicotine were reduced by 90% in the vaccinated animals. After a 2 h whole body exposure to smoke, a 35% reduction in brain nicotine was detected [248]. These results confirm other studies using non-inhalation routes of administration [249–251]. Early phase 1/2 clinical trials in humans have demonstrated drug safety, effective immunogenicity, and promising increases in abstinence rates, especially among individuals with higher levels of anti-nicotine IgGs [252–255]. Whether a nicotine vaccine is going to be effective for real-world use remains an open question. The results of ongoing clinical trials are eagerly awaited.

#### 5. Conclusions

Chronic exposure to nicotine produces neuroadaptations in a host of neurotransmitter and neuropeptide systems. Those neuroadaptations are responsible for the psychological and behavioral symptoms associated with nicotine abstinence and make nicotine addiction so hard to break. Driven by preclinical studies in various animal models as well as human studies, the improved understanding of the mechanisms involved in nicotine dependence has led to new treatments. Targeting of the  $\alpha 4\beta 2$  nAChR subtype with varenicline significantly improves abstinence rates, and recent studies provide additional nAChR targets that might help to design more effective pharmacological agents. A multipronged approach that could simultaneously address the dysfunction of the DAergic system, the deficits in executive control over the drug, and the connection between stress/anxiety and nicotine consumption would indeed offer the best relief from the symptoms of withdrawal. Finally, a nicotine vaccine, if effective, could provide a paradigm shift in the treatment of nicotine dependence. The concerted effort of basic scientists and clinicians will be needed to stop the global epidemic of tobacco-related disease and premature mortality.

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