Am J Transl Res 2025;17(4):2396-2410
www.ajtr.org /ISSN:1943-8141/AJTR0155529

Review Article

Nicotine replacement therapy: insights into the mechanisms and potential of nicotine receptor pathway

Nishant Patidar[1], Archana M Navale[1], Nitesh Parsaila[1], Dinesh Sharma[1], Prachi Nahar[1], Sagar Shinde[1], Nilay Solanki[2], Ajay Shelke[1]

[1]Department of Pharmacology, Parul Institute of Pharmacy, Parul University, Limda, Vadodara, Gujarat, India; [2]Department of Pharmacology, Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, Changa, Gujarat, India

Received January 19, 2024; Accepted August 19, 2024; Epub April 15, 2025; Published April 30, 2025

Abstract: Nicotine addiction is a complex phenomenon entwined with intricate mechanisms within the nicotine receptor pathway. This review offers an insightful exploration of this multifaceted landscape, delving into the interplay between nicotinic acetylcholine receptors (nAChRs) and their pivotal role in neurotransmission. The structural and functional aspects of nAChRs, their distribution within the peripheral and central nervous systems, and their involvement in modulating diverse signalling cascades are reviewed. The clinical implications of nicotine addiction and the challenges in smoking cessation are also explored. Nicotine Replacement Therapy (NRT) drugs, designed to alleviate withdrawal symptoms and aid in smoking cessation, are critically evaluated. This article synthesizes current research findings on the efficacy, safety, and limitations of various NRT modalities. Furthermore, emerging pharmacotherapeutic strategies and novel molecules aimed at optimizing NRT outcomes are discussed. The potential of leveraging a deeper understanding of the nicotine receptor pathway to develop more targeted and efficacious NRT interventions is emphasized. The exploration of adjunct therapies and combination approaches to enhance the success rates of smoking cessation is also addressed. Through a synthesis of preclinical and clinical evidence, this article aims to provide a comprehensive resource for researchers, clinicians, and policymakers working towards advancing the field of nicotine addiction treatment. As the global effort to combat tobacco-related health challenges intensifies, a nuanced understanding of the nicotine receptor pathway and its therapeutic implications becomes increasingly imperative.

Keywords: CB1 receptor antagonist, CRF1 receptor pathway, neuropharmacology, reward pathway, bupropion, varenicline

Introduction

Nicotine usage, which increases vulnerability to several infectious diseases and causes deadly health issues like cancer, heart disease, and lung disease, is what keeps people addicted to tobacco. Almost every organ in the body is harmed by smoking.

The hazards of smoking are greatly decreased when one quits, and most smokers want to stop at some point in their lives. Despite this, only around 3% of smokers who attempt to stop do so after six months; most smokers relapse during the first month of sobriety. This illustrates the severity of tobacco addiction in addition to the disorder's chronic nature [1].

Tobacco addiction is mostly caused by the pharmacologic effects of nicotine, even though other parts of cigarette smoke contribute to much of the toxicity associated with smoking. Effective smoking cessation intervention requires an understanding of how nicotine affects smoking behavior and causes addiction. In this article, we explore the neuroscience behind nicotine addiction and withdrawal, delving into its treatment implications.

Neuropharmacology of nicotine

Neuropharmacology of nicotine explores the intricate interactions between nicotine, a primary component of tobacco, and the nervous

https://doi.org/10.62347/MOBZ7773

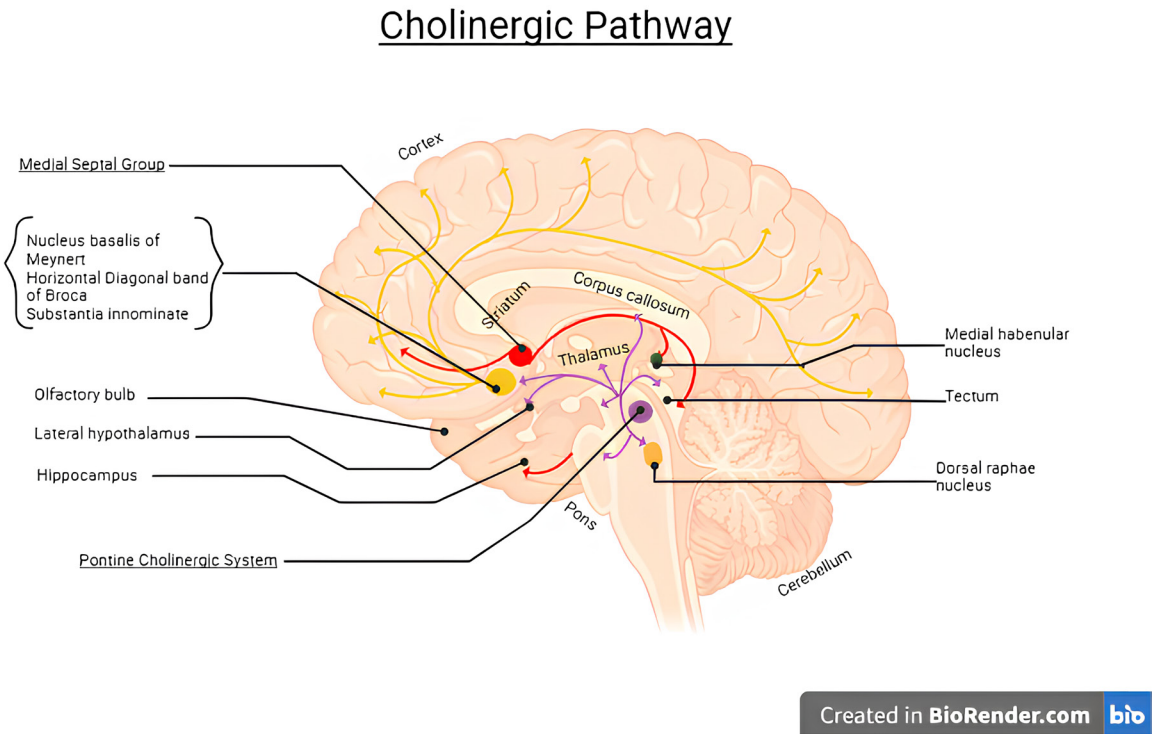

Figure 1. The acetylcholine pathway, also known as the cholinergic pathway, involves the neurotransmitter acetylcholine, which neurons use for communication and neuromodulation. This neurotransmitter is critical for regulating arousal, attention, perception, and motivation. Acetylcholine production begins in the brainstem at the Pedunculopontine nucleus and the laterodorsal tegmental nucleus, which are part of the pontine cholinergic system and are depicted in purple. In the basal forebrain, it is produced in the nucleus basalis of Meynert (highlighted in yellow) and the medial septal group (in red). Key target areas for acetylcholine include the medial habenular nucleus (in green) and the dorsal raphae nucleus (in orange). The pathway also affects parts of the limbic system such as the hippocampus, striatum, and thalamus, which are shown in purple.

system. This field delves into the molecular mechanisms underlying nicotine's effects on neurotransmission, receptor modulation, and its implications for addiction and therapeutic applications.

Pathways associated with nicotine

Nicotine primarily influences the central nervous system (CNS) by activating the nAChRs, initiating a complex neuronal pathway. This pathway involves cholinergic and dopaminergic pathways releasing neurotransmitters, particularly dopamine, playing a crucial role in mediating the rewarding and addictive aspects of nicotine consumption.

Cholinergic pathway

Nicotine readily crosses the blood-brain barrier (BBB) and binds to nAChRs. Activation of presynaptic neuronal nAChRs causes release of neurotransmitter Acetylcholine (Ach). Nicotine exposure over long-term causes initial receptor inactivation followed by subsequent up-regulation of nAChRs. The ventral tegmentum, striatum, nucleus accumbens (Nacc), and midbrain tegmentum are among the brain parts that contain cholinergic receptors. Moreover, it is present in the heart, muscles, adrenal glands, and other bodily tissues [2]. nAChRs are also present in the mesolimbic and nigrostriatal dopaminergic neurons (**Figure 1**). Release of several other neurotransmitters and mediators is associated with stimulation of nAChRs, such as growth hormone, vasopressin, dopamine, norepinephrine, serotonin, and Adrenocorticotropic hormone [3, 4].

The dopamine reward circuit in the mid brain is primarily activated by nicotine. Additionally, its effect on the locus ceruleus stimulates alertness, provocation, anxiety and attentiveness making nicotine addicts even more attentive [5].

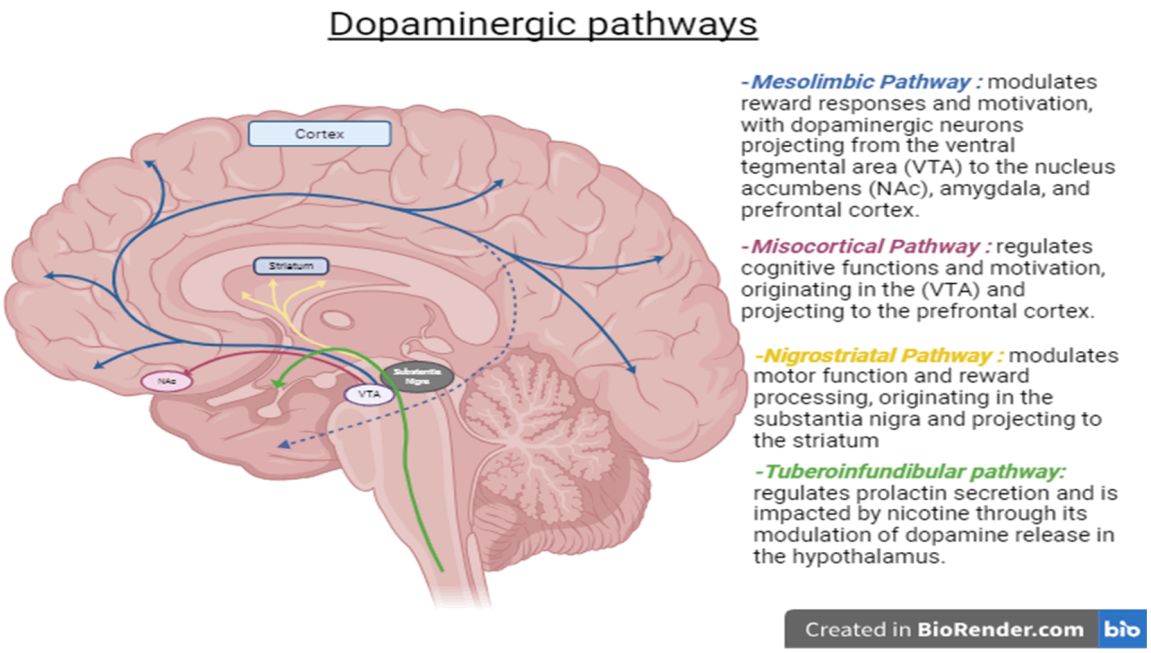

Figure 2. Dopaminergic pathway: neural circuitry underlying reward processing and motor control.

Dopaminergic pathways

The dopaminergic pathway modulated by nicotine encompasses the activation of nAChRs, leading to enhanced dopamine release within mesolimbic and mesocortical circuits. This intricate neurochemical cascade underlies the reinforcing properties of nicotine, elucidating its role in the development and maintenance of addictive behaviors (**Figure 2**).

Mesolimbic pathway: Neuronal projections originating in the ventral tegmental area (VTA) and extending along the medial forebrain bundle to innervate the NAcc, olfactory tubercle, as well as other limbic structures including the hippocampus and amygdala collectively form the mesolimbic dopaminergic system. This intricate neural network plays a pivotal role in regulating motivation, emotion, and motor activity. Notably, the mesolimbic system exhibits remarkable efficacy in modulating the hedonic aspects associated with the consumption of psychoactive substances. Particularly, the NAcc stands as the primary recipient of neuronal projections emanating from the VTA. The ventromedial shell and dorsolateral core are the two most noticeable sub-territories that make up the NAcc. Because the shell gets afferents from the brainstem and subcortical components, it has a greater range of neuroanatomical structures than core. The feed-forward projection allows the core to provide output indicators to the shell. The core region and the shell both become involved in behavior connected to rewards [6, 7].

Mesocortical pathway: The VTA is the starting point for the neurons that make up the mesocortical dopaminergic pathway, which then passes via the entorhinal, cingulate, and prefrontal cortex (PFC). Higher order cognitive processes are regulated by this circuit in the brain. Long-term drug use is also associated with lower dopamine levels in the PFC, which may exacerbate impulsivity and make it harder to resist urges [8, 9].

Nigrostriatal pathway: The nigrostriatal pathway is a dopaminergic system that plays a critical role in muscular tone and motor function. It is made up of neurons from the substantia nigra that reach the striatum mostly through the inner capsule. It also contains dopaminergic cells that are involved in dopamine-related behaviors, such as reward-based responses. This is why nicotine can cause addiction, as it stimulates the production of dopamine, resulting in a feeling of pleasure and satisfaction. The nigrostriatal pathway is a crucial element in

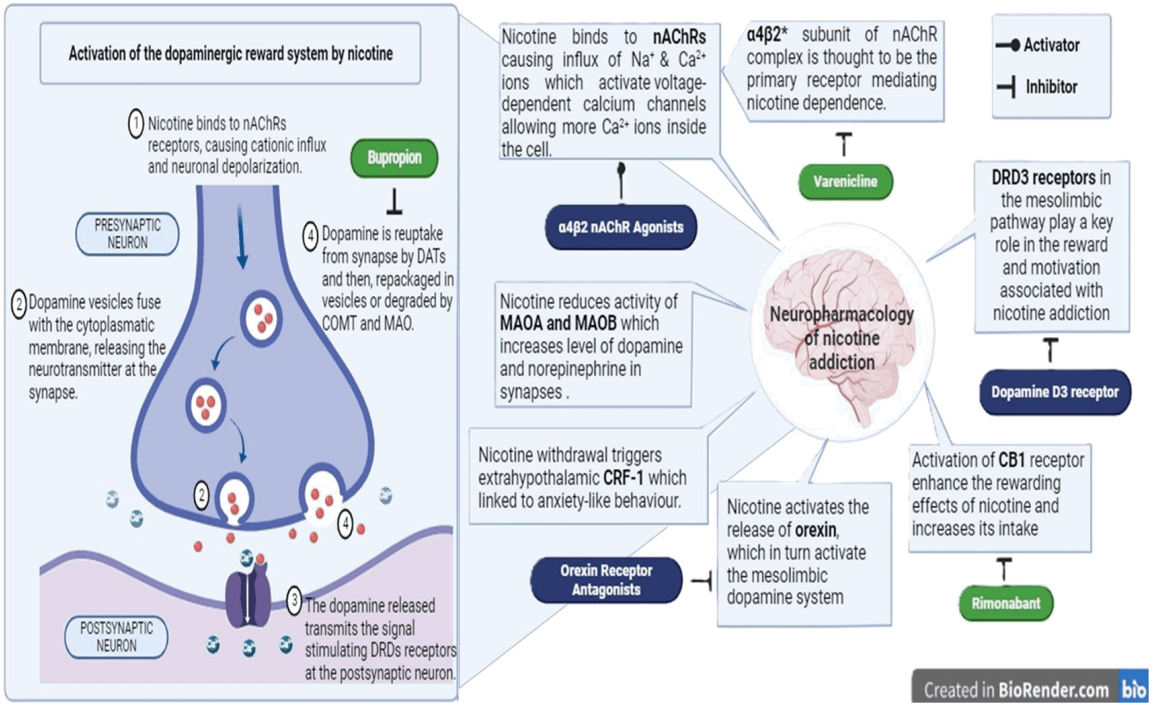

Figure 3. Neuropharmacology of nicotine addiction. nAChRs: Nicotinic acetylcholine receptors; DRDs: Dopamine receptors; DATs: Dopamine transporters; MAO: Monoamine oxidase; COMT: Catechol-O-methyltransferase; NRT: Nicotine Replacement Therapy; CRF-1: Corticotropin-releasing factor-1; CB1: Cannabinoid receptor-1; DRD3: Dopamine D3 Receptor.

nicotine dependency, as it mediates the effects of nicotine on our brain and affects behavior [10, 11].

Therefore, understanding the mechanisms by which nicotine affects this pathway can help us better understand how nicotine dependency develops, allowing us to find more effective treatments for this condition.

Neuropharmacology of nicotine addiction

Nicotine, a tertiary amine with pyridine and pyrrolidine rings, binds stereoselectively to nAChRs in the brain. (S)-nicotine, found in tobacco, strongly binds to nAChRs, while (R)-nicotine, a weak agonist produced during pyrolysis, is present in cigarette smoke. Nicotine present in cigarette smoke is absorbed through the lungs and quickly reaches the brain, by permeating BBB and binds to nAChRs, allowing cations like calcium and sodium to enter and activate further calcium influx through voltage-gated calcium channels (**Figure 3**).

Both the peripheral and central nervous systems include the five subunits that make up the nAChR complex [12, 13]. In the mammalian brain, three β subunits (β2 to β4) and up to nine α subunits (α2 to α10) are present. The most prevalent receptor subtypes in human brains are α4β2, α3β4, and homomeric α7. The α4β2* (asterisk indicates the possibility of other subunits in the receptor) receptor subtype predominates in the human brain and is thought to be the primary receptor mediating nicotine dependence. Knocking out the β2 subunit gene in mice eliminates nicotine's behavioral effects, such that nicotine no longer releases dopamine in the brain or maintains self-administration [14, 15].

Neuroimaging studies reveal that nicotine acutely increases neural activity in the prefrontal cortex, thalamus, and visual system, activating corticobasal ganglia-thalamic circuits [16]. Nicotine stimulates dopamine release in the mesolimbic area, corpus striatum, and frontal cortex, particularly affecting the VTA and the NAcc, which are central to drug-induced reward. Various neurotransmitters, including glutamate, GABA, serotonin, acetylcholine, norepinephrine, and endorphins, also modulate nicotine's diverse effects [17, 18].

Table 1. Neurotransmitter systems involved in nicotine addiction

Neurotransmitter System	Key Brain Regions Involved	Effects	References
Dopamine	Mesolimbic area, VTA, NAcc, corpus striatum, frontal cortex	Stimulates dopamine release, enhancing brain reward function and reinforcing smoking behavior	[14, 16-18]
Glutamate	Prefrontal cortex, NAcc	Increases glutamate, enhancing dopamine release and reinforcing nicotine addiction	[17, 19]
GABA	Various brain regions, including VTA and NAcc	Inhibits GABA function, increasing dopamine release and reinforcing addiction	[17, 19]
Serotonin	Brainstem, prefrontal cortex, NAcc	Affects serotonin release, contributing to mood regulation and reinforcing nicotine's addictive properties	[17]
Acetylcholine	Brain regions with nAChRs, including cortex and hippocampus	Binds to nAChRs, increasing neuronal excitability and neurotransmitter release	[12, 13]
Norepinephrine	Locus coeruleus, prefrontal cortex, limbic system	Increases norepinephrine release, contributing to arousal and stress responses associated with smoking	[17, 19]
Endorphins	Various brain regions, including the NAcc	Stimulates endorphin release, enhancing pleasure and reinforcing smoking behavior	[17]
CRF	Central amygdala, extrahypothalamic regions	Induces anxiety-like behavior and withdrawal symptoms, mitigated by CRF1 receptor blockade	[27]
Endogenous Cannabinoid	NAcc, VTA, other brain regions with CB1 receptors	Influences nicotine's motivational effects but not necessary for physical dependence	[28, 29]
Orexin	Hypothalamus, NAcc, VTA	Affects nicotine self-administration and addiction, with OX1R and OX2R involved in reward processes	[30-42]
Dopamine D3 Receptor	NAcc	Variations in DRD3 gene linked to smoking behavior and susceptibility to drug abuse effects during adolescence	[43-51]

Nicotine increases glutamate, which over time inhibits GABA function, leading to increased dopamine release. Prolonged cigarette smoking inhibits brain monoamine oxidase A and B (MAOA and MAOB), resulting in elevated dopamine and norepinephrine levels, intensifying nicotine's impact and fostering addiction. Studies in rats show MAO inhibition enhances nicotine self-administration, indicating a synergistic effect in reinforcing tobacco dependence [19, 20].

Dopamine release is critical for nicotine's reinforcing effects, as evidenced by experiments where lesioning dopamine neurons prevents nicotine self-administration in rats (**Table 1**). Nicotine administration lowers the threshold for brain reward, while withdrawal raises it, reducing dopamine release and associated reward [21, 22]. This diminished reward function during withdrawal contributes significantly to addiction and cessation difficulty [23].

This neuroadaptive process involves an increase in nAChR binding sites, indicating upregulation due to nicotine-induced receptor desensitization. This desensitization contributes to nicotine tolerance and dependence. In habitual smokers, cravings and withdrawal symptoms occur when desensitized α4β2* nAChRs become responsive during abstinence, such as sleep [24]. Brain imaging shows that regular smoking keeps nAChRs nearly fully saturated, supporting the theory of receptor desensitization [25]. Smokers may maintain plasma nicotine levels to delay withdrawal and are reinforced by conditioned smoking cues like flavor and sensation [26].

Anxiety and the impression of heightened stress are two unpleasant emotional states linked to nicotine withdrawal that may serve as strong triggers for resuming cigarette usage. There is proof that the extrahypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor pathway is involved in the detrimental effects of quitting smoking. CRF is released in the central amygdala during induced nicotine withdrawal in rats, which is linked to anxiety-like behavior (**Table 1**). Pharmacologically inhibiting CRF1 receptors, effectively mitigates the anxiogenic effects associated with nicotine withdrawal. Additionally, the blockade of CRF1 receptors has been demonstrated to impede the escalation in nicotine self-administration observed in rats following the cessation of forced nicotine administration [27].

This pathway also activates during withdrawal from other substances, such as alcohol, cocaine, opioids, and cannabis. Therefore, it appears that both the activation of the CRF system and the hypoactivity of the dopaminergic system play a role in mediating the symptoms of nicotine withdrawal that often result in the desire to smoke again.

The endocannabinoid system, especially CB1R and potentially CB2R and GPR55, plays a crucial role in nicotine's reinforcing effects. CB1R antagonists like rimonabant, AM251, and AM4113 reduce nicotine self-administration and conditioned place preference (CPP) in rodents and non-human primates by blocking nicotine-induced dopamine release in the nucleus accumbens. CB1Rs in the ventral tegmental area, nucleus accumbens, and basolateral amygdala mediate nicotine reward. While CB1R antagonists initially showed promise for smoking cessation, psychiatric side effects led to their suspension [28]. The role of CB2R is controversial, with some studies showing no effect on nicotine reward, while others suggest CB2R agonists like JWH133 and β-Caryophyllene inhibit nicotine self-administration and CPP. The novel cannabinoid receptor GPR55 may also modulate nicotine reward. Overall, the endocannabinoid system represents a potential target for treating nicotine addiction [29].

Orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R) are G-protein coupled receptors [30]. The NAcc has been shown to express both receptors [31]. The orexin system exerts influence over a diverse array of brain processes encompassing sleep/wakefulness, arousal, pain modulation, autonomic function, eating behaviors, metabolism, cognitive functions, responses to both natural and pharmacological rewards, and the dynamics of opioid dependency and withdrawal [32, 33]. Notably, studies have underscored the pivotal role of the orexinergic system in mediating addictive behaviors [34-36], including the addictive response to nicotine. In specific instances, OX1R blockade in the insular cortex or systemic administration of an OX1/2R antagonist has been shown to diminish nicotine self-administration [37]. Prolonged cocaine exposure has been associated with heightened OX2R protein expression in the NAcc [38]. Moreover, OX2R inhibition has demonstrated efficacy in reducing ethanol-induced effects [39], morphine-induced conditioned place preference [40], and heroin self-administration in rats [41]. A recent report has indicated that blocking OX2R in the VTA diminishes nicotine-induced conditioned place preference [42].

Human smoking behavior has been connected to variations in the dopamine D_3 receptor (DRD3) gene [43] The expression pattern of DRD3 is notably confined to NAcc [44, 45], unlike other dopamine receptors with widespread brain distribution [46]. DRD1 and DRD2 demonstrate significant expression in rats during early development, attaining adult levels before puberty [47, 48]. Conversely, DRD3 binding in the NAcc exhibits minimal detectability before adolescence and remains below adult levels throughout the adolescent period [49, 50]. The unique characteristics of DRD3 are intriguing, particularly in light of the heightened susceptibility to the effects of drugs abuse during adolescence [51].

Approved drugs for nicotine replacement therapy

Nicotine replacement therapy (NRT), sanctioned by regulatory bodies, employs pharmaceutical formulations to address tobacco dependency systematically. These interventions, ranging from transdermal patches to oral formulations, intricately regulate nicotine delivery, providing a controlled and evidence-based approach to mitigate withdrawal symptoms and facilitate smoking cessation. **Table 2** gives a comprehensive overview of the existing and experimental approaches for NRT.

Bupropion

Bupropion is an atypical antidepressant with a similar chemical structure to diethylpropion, an appetite suppressant. Bupropion's antidepressant effect is not fully understood, but it inhibits dopamine, noradrenaline, and serotonin reuptake in the CNS [52, 53].

Bupropion is a strong $CYP_{450}2D6$ inhibitor, which lowers the clearance of medicines that are metabolized by this enzyme Bupropion's metabolites, including hydroxybupropion, threohydrobupropion, and erythrobupropion, modulate its actions [54].

Table 2. Comprehensive summary of drugs utilized in nicotine replacement therapy

Drug Name	Target	Mechanism	Use	Side effect
Approved Drugs				
Bupropion	Norepinephrine transporter and the dopamine transporter	Inhibits reuptake of norepinephrine and dopamine	Smoking cessation	Insomnia, dry mouth, nausea, headache
Varenicline	α4β2 nAChR	Partial agonist at α4β2 nAChR, reducing nicotine withdrawal symptoms	Smoking cessation	Nausea, insomnia, abnormal dreams
Rimonabant	CB1 Receptor	Blocks CB1 receptors in the endocannabinoid system	Smoking cessation, Weight loss in obesity	Depression, anxiety, nausea
Drugs under trial				
α4β2 nAChR partial Agonists	α4β2 nAChR	Partial agonist at α4β2 nAChR	Smoking cessation	Respiratory irritation
Nicotine Vaccines	Targets nicotine as antigen	Stimulates the immune system to produce antibodies against nicotine	Smoking cessation	Local reaction at injection site, flu-like symptoms
Dopamine D3 Receptor Antagonists	Dopamine D3 Receptor	Blocks dopamine D3 receptors	Smoking cessation	Insomnia, nausea, headache
Orexin Receptor Antagonists	Orexin receptors	Blocks orexin receptors	Smoking cessation, Insomnia	Headache, dizziness, fatigue

Smoking cigarettes causes nicotine to enter the blood circulation and penetrate the BBB. As a result of this, dopamine is released into the synaptic cleft of the brain's dopaminergic, pleasure-seeking circuits. Dopamine is reabsorbed into the axon terminal vesicles once nicotine intake is reduced. Bupropion is believed to work primarily by preventing this dopamine reuptake, most likely through its impact on the dopamine transporter system.

Bupropion has been demonstrated to enhance striatal vesicular transport, which boosts reuptake from the synaptic cleft, in addition to inhibiting dopamine reuptake in the NAcc. Bupropion may lessen the symptoms of nicotine withdrawal because dopamine reuptake inhibition in the NAcc mitigates the dopamine shortage that occurs during nicotine withdrawal [55, 56].

Varenicline

In 2006, the initial varenicline trials began. Functioning as a partial agonist of the nAChRs, varenicline is a key pharmacotherapeutic agent for smoking cessation when integrated into a comprehensive framework of education and counselling. Demonstrating notable efficacy, it effectively mitigates both short-term and protracted relapse scenarios, positioning itself as the forefront pharmaceutical choice for individuals seeking successful smoking cessation. Studies have shown that varenicline surpasses bupropion and is equally effective as nicotine replacement therapy. Due to its partial agonist properties, varenicline exhibits a lower incidence of withdrawal symptoms compared to other medications [57, 58].

Varenicline's success in aiding smoking cessation is attributed to its high-affinity binding specifically to α4β2 nAChRs. As a partial agonist, it concurrently inhibits nicotine binding to these receptors, facilitating smoking cessation. When bound to α4β2 nAChRs, varenicline activates these receptors less than nicotine does, preventing nicotine from stimulating the mesolimbic dopaminergic system, believed to underlie the reinforcement and reward phenomenon. Varenicline's partial agonism significantly reduces activation of the mesolimbic dopamine pathway linked to nicotine addiction [59, 60].

The most frequent side effects of varenicline include headaches, nausea, sleeplessness, unusually vivid dreams, constipation, irritability, sleepwalking, and disrupted sleep. Lower initial doses and gradual dose increases, as tolerated, can help mitigate nausea. Erythema multiforme, photosensitivity, and Stevens-Johnson syndrome have all been linked to varenicline. Due to the potential for kidney stones and renal failure, renal function needs close monitoring. Patients receiving varenicline should also be closely monitored for any abdominal pancreatitis symptoms, as this medication may raise the risk of pancreatitis [61, 62].

Rimonabant

CB1 endocannabinoid receptors are present on various cell types, including those in the brain, liver, muscles, adipose tissue, heart, and other tissues. The primary clinical impact of these medications is on energy intake and metabolism. Previous studies have shown that marijuana stimulates this pathway, leading to an increase in hunger [63, 64].

Recent research suggests that rimonabant, a selective CB1 receptor antagonist, may aid smoking cessation alongside other therapeutic benefits. CB1 receptors on GABA-related neurons in the CNS regulate dopamine release, with activation of these CB1-mediated GABA neurons reducing dopamine release. CB1 receptor antagonists like rimonabant, therefore, may increase dopamine release, which is considered essential to the nicotine-reward pathway [65].

A study by Cohen C, Perrault G, Griebel G, and Soubrié P demonstrated in rats that rimonabant reduced nicotine-conditioned behavior, measured by decreased nicotine self-administration and dopamine turnover in the NAcc after nicotine stimulation [66, 67] and Balerio GN, Aso E, and Maldonado R found that pretreatment with rimonabant in mice decreased the anxiety-reducing effects of nicotine, confirming the connection between the endocannabinoid system and anxiety-like behaviors caused by smoking [68].

Animal research provides potential explanations for the effects of CB1 receptor inhibition on drug-induced reinforcement/reward and relapse to drug-seeking behavior, although the exact mechanisms remain unknown. For ex-

ample, cannabinoid agonists administered to rodents can elevate the activity of dopaminergic neurons in the VTA, affecting baseline firing rates and action potential bursting frequency [69].

A study by Kodas E, Cohen C, Louis C, and Griebel G discovered that rimonabant suppressed cue-induced nicotine craving in rats by acting on key corticolimbic regions such as the shell of the NAcc, the prelimbic cortex, and the basolateral amygdala. The prefrontal cortex, including the prelimbic cortex, and the basolateral amygdala are essential in the induction of drug-seeking behavior by drug-associated stimuli. Rimonabant injections into these regions may modulate dopaminergic and/or glutamatergic neurotransmission in the shell of the NAcc, offering insight into its effects on cue-induced nicotine seeking [70].

Nicotine replacement therapy modalities under trial

Ongoing investigations into novel NRT modalities aim to expand the scientific understanding and efficacy of smoking cessation interventions. Experimental formulations, including advanced delivery systems and targeted receptor modulators, are currently under trial, offering promising avenues for refining NRT strategies and enhancing their potential for successful tobacco addiction cessation (**Figure 3**).

α4β2 nAChR agonists

As discussed earlier, α4β2 nAChR subtypes present in the NAcc contribute significantly to the reinforcing effects of nicotine [71-74]. A novel class of drugs called partial agonists of the α4β2 nAChRs is currently being researched for a variety of neurological conditions, including dementia, Alzheimer's disease, and attention deficit or hyperactivity disorder in adults [75, 76].

Much emphasis has recently focused on the possibility of the partial agonist at the neuronal acetylcholine receptor subtype α4β2 for smoking cessation. Mecamylamine, a partial agonist, may be a factor in the efficacy of smoking cessation treatments. Treatment with mecamylamine was found to be more effective than existing NRT [77].

Cessation of nicotine use is associated with low dopamine levels in the mesolimbic area of the brain. The same is also linked to withdrawal symptoms and cravings for nicotine. Partial agonists of the α4β2 nAChR induce a slight but sustained increase in dopamine levels in the reward circuit through intrinsic activation. They avert relapse by compensating for the low dopamine levels seen during cessation efforts. Furthermore, the partial agonist property will prevent nicotine from attaching to the α4β2 nAChR, protecting smokers from the dopaminergic activation-induced reward effect during smoking [78].

However, it is entirely justified that the α4β2 nAChR continues to be a major area of study for new treatments for these conditions. The therapeutic potential of orthosteric α4β2 nAChR agonists highlights the opportunity for creating more effective treatments for quitting smoking, as well as for cognitive, neurological disorders, and pathological pain. The α4β2 nAChR are considered promising options because they require lower concentrations of agonists to achieve maximum therapeutic benefits, which is believed to reduce the likelihood of non-specific, or undesirable side effects [79].

Nicotine vaccines

Nicotine vaccinations prompt the immune system to create antibodies that attach to nicotine molecules in the bloodstream, making them too large to cross the blood-brain barrier and produce rewarding effects [80]. Compared to other cessation aids like NRT, bupropion, and varenicline, a nicotine vaccine may offer advantages. It can be administered in just five or six doses, providing effects lasting several months, potentially with fewer side effects. Additionally, it might be more effective in preventing relapse by blocking the rewarding effects of a brief lapse [81]. However, there are potential ways to evade a nicotine vaccination, such as smoking more quickly afterward, using higher nicotine doses, or smoking while using a nicotine patch. The term "vaccine" often brings to mind its preventive use to deter teenage smoking, but there are significant logistical and ethical barriers to implementing such an approach [82, 83]. A conjugate vaccine combines nicotine with a larger carrier protein or virus-like particle. It is administered through a series of injections, for example, one shot per month for three or

four months, gradually producing a serum level of antibodies that lasts for several months. Booster shots are periodically needed to maintain the antibody level. Selecta Biosciences in the USA is currently conducting a Phase I trial on a conjugate combination of nicotine and a synthetic carrier (rather than a biological carrier) [84].

This review study by Scendoni R, Bury E, Ribeiro ILA, Cameriere R, and Cingolani M presents a comparative analysis of several nicotine vaccines currently under clinical trials, aiming to assess their safety, immunogenicity, and efficacy in aiding smoking cessation. The vaccines examined include Niccine, Nic-Qb (NIC002), NicVax (3'-AmNic-rEPA), and TA-NIC, each developed with distinct carrier proteins and formulations. "*Niccine*" (Independent Pharmaceutica AB) uses a tetanus toxoid conjugate but showed no significant effect on smoking cessation or withdrawal symptoms in a Phase II trial, despite increased nicotine antibody levels. "*Nic-Qb*" (Cytos Biotechnology), a virus-like particle vaccine, demonstrated high immunogenicity and safety. Initial results indicated a significant short-term increase in abstinence rates among those with the highest antibody levels, although its long-term efficacy varied and was not uniformly significant across all participants. "*NicVax*" (Nabi Pharmaceuticals, further developed by Glaxo-SmithKline), employs Pseudomonas exoprotein A as its carrier. Multiple studies have shown that higher doses and top antibody responders generally achieve better smoking cessation outcomes, with dose-related immunogenicity observed. However, additional trials, including one with varenicline and behavioral support, did not consistently demonstrate improved abstinence rates compared to placebo. "TA-NIC" (Celtic Pharma) is based on a recombinant cholera toxin-B subunit carrier, similar to the TA-CD vaccine against cocaine. Early phase I/II studies indicated potential efficacy, but more comprehensive research is required to validate these findings fully.

The summarized data highlight that while nicotine vaccines can be safe and immunogenic, their effectiveness in promoting smoking cessation varies, often depending on antibody response levels and vaccine formulations. Further investigations are essential to optimize these vaccines and fully understand their potential in smoking cessation strategies [85].

Dopamine D_3 receptor (DRD3) antagonists

DRD3 is a subtype of dopamine receptor that is primarily expressed in the mesolimbic pathway of the brain, which is involved in reward and motivation. Nicotine stimulates the release of dopamine in this pathway, leading to feelings of pleasure and reward that reinforce smoking behavior. DRD3 antagonists work by blocking the activity of this receptor, thereby reducing the rewarding effects of nicotine and potentially helping smokers quit [86, 87].

The use of DRD3 antagonists as an NRT drug was first identified in preclinical studies using animal models. In one study, rats were trained to self-administer nicotine, and then treated with a DRD3 antagonist called SB-277011A. The researchers found that SB-277011A reduced nicotine self-administration in the rats, suggesting that it may be effective as an NRT drug. Subsequent clinical trials have also shown promising results for DRD3 antagonists as an NRT drug. In one study, smokers were treated with a DRD3 antagonist called GSK598809, and then exposed to smoking cues such as pictures of cigarettes. The researchers found that GSK598809 reduced the smokers' craving for cigarettes and their subjective experience of pleasure from smoking [88].

The mechanism of action of DRD3 antagonists as an NRT drug is thought to involve several pathways. First, by blocking the activity of DRD3 receptors, these drugs reduce the rewarding effects of nicotine and may help to break the cycle of addiction. Second, DRD3 antagonists may also modulate other neurotransmitter systems, such as glutamate and GABA, which are involved in addiction and reward. Finally, DRD3 antagonists may also have anxiolytic and antidepressant effects, which could help to alleviate the negative mood states that often accompany nicotine withdrawal [89].

Orexin receptor antagonists

Orexin receptors are G-protein-coupled receptors that are primarily expressed in the hypothalamus and play a crucial role in regulating wakefulness and appetite. There are two types of orexin receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R). Orexin neurons project to various brain regions, including the

VTA, NAcc and prefrontal cortex, which are involved in reward processing and addiction [90].

Nicotine activates the mesolimbic dopamine system, leading to the release of dopamine in the NAcc, which is responsible for the rewarding effects of nicotine. Orexin neurons in the lateral hypothalamus project to the VTA and NAcc and modulate the activity of dopamine neurons. Orexin receptor antagonists can block the activation of orexin neurons, leading to decreased dopamine release and attenuated nicotine reward. Several studies have investigated the use of orexin receptor antagonists as NRT drugs. One study used SB-334867, a selective OX1R antagonist, to investigate its effect on nicotine self-administration in rats. The results showed that SB-334867 reduced nicotine self-administration and attenuated the reinstatement of nicotine-seeking behavior induced by cues associated with nicotine administration [91].

The study by Azizi F, Fartootzadeh R, Alaei H, and Reisi P showed that blocking either CB1 receptors or OX2 receptors significantly reduced the increased firing rate of VTA-ND neurons triggered by systemic nicotine injection, and in some cases, even reduced the firing rate below baseline levels in rats treated with nicotine. Interestingly, blocking these receptors in control rats treated with saline did not affect neuronal activity. The antagonists were administered locally while nicotine was given systemically, suggesting that nicotine might affect the VTA before its direct action, possibly via other pathways. These findings align with research that examined the effects of blocking CB1R or OX2R within the VTA on nicotine-induced conditioned place preference, and the blockade of OX2R on the stimulating effects of nicotine on neuronal activity in the nucleus accumbens. Overall, these results indicate that the neuronal response in the VTA-ND to nicotine is likely mediated through the endocannabinoid and orexin systems, which can shift nicotine preferences towards either aversion or preference [92].

Another study investigated the effect of orexin receptor antagonists on nicotine-induced dopamine release in the NAcc using microdialysis in rats. The results showed that SB-334867 and TCS-OX2-29, a selective OX2R antagonist, both attenuated nicotine-induced dopamine release in the NAcc. This suggests that both OX1R and OX2R are involved in the modulation of dopamine release in response to nicotine. A clinical trial investigated the effect of suvorexant, an orexin receptor antagonist approved for the treatment of insomnia, on smoking cessation in smokers with insomnia. The results showed that suvorexant increased the abstinence rate and reduced the number of cigarettes smoked per day compared to placebo. This suggests that orexin receptor antagonists may be effective in helping smokers quit smoking, especially those with comorbid insomnia [93].

Conclusion and future prospects

In conclusion, this review provides a comprehensive exploration of the nicotine receptor pathway and its role in addiction, focusing on the intricate mechanisms of nAChRs. The neuropharmacological pathways associated with nicotine, particularly within the cholinergic and dopaminergic systems, are dissected to elucidate the complex interplay influencing neurotransmission. The article emphasizes the clinical implications of nicotine addiction, emphasizing the challenges of smoking cessation and the critical role of NRT drugs.

A critical evaluation of existing NRT modalities, including bupropion and varenicline, is presented, shedding light on their mechanisms of action and comparative efficacy. Understanding the mechanisms of these drugs is crucial for innovating novel approaches and optimizing smoking cessation outcomes. Additionally, emerging pharmacotherapeutic strategies, such as α4β2 nAChR agonists, dopamine D_3 receptor antagonists, and orexin receptor antagonists, are discussed for their potential to optimize smoking cessation outcomes.

The importance of a nuanced understanding of the nicotine receptor pathway is underscored throughout the article, particularly in the context of developing targeted and efficacious NRT interventions. The exploration of adjunct therapies and combination approaches further highlights the multifaceted nature of nicotine addiction treatment.

As the global effort to address tobacco-related health challenges intensifies, this review ser-

ves as a valuable resource for researchers, clinicians, and policymakers. Bridging the gap between basic science and clinical applications, the article contributes critical insights into the development and optimization of NRT drugs. The continual advancement of our understanding of the nicotine receptor pathway holds significant promise for enhancing the success rates of smoking cessation and mitigating the global burden of tobacco-related diseases.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Archana M Navale, Department of Pharmacology, Parul Institute of Pharmacy, Parul University, Limda, Vadodara, Gujarat, India. Tel: +91-9879690685; E-mail: archanachavan_83@yahoo.co.in; archana.navale@paruluniversity.ac.in

References

[1] Office on Smoking and Health. Introduction and Approach to Causal Inference. Atlanta (GA): Centers for Disease Control and Prevention; 2004.
[2] Hopkins TJ, Rupprecht LE, Hayes MR, Blendy JA and Schmidt HD. Galantamine, an acetylcholinesterase inhibitor and positive allosteric modulator of nicotinic acetylcholine receptors, attenuates nicotine taking and seeking in rats. Neuropsychopharmacol 2012; 37: 2310-21.
[3] Addicott MA, Baranger DAA, Kozink RV, Smoski MJ, Dichter GS and McClernon FJ. Smoking withdrawal is associated with increases in brain activation during decision making and reward anticipation: a preliminary study. Psychopharmacol 2011; 219: 563-73.
[4] Zheng P. Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. Prog Neurobiol 2009; 89: 134-152.
[5] Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. Neurosci Biobehav Rev 2010; 35: 129-150.
[6] Lüscher C and Ungless MA. The mechanistic classification of addictive drugs. PLoS Med 2006; 3: e437.
[7] Yamaguchi T, Wang HL, Li X, Ng TH and Morales M. Mesocorticolimbic glutamatergic pathway. J Neurosci 2011; 31: 8476-8490.
[8] Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry 2004; 12: 305-320.
[9] Gorelova N, Mulholland PJ, Chandler LJ and Seamans JK. The glutamatergic component of the mesocortical pathway emanating from different subregions of the ventral midbrain. Cereb Cortex 2012; 22: 327-336.
[10] Rose EJ, Ross TJ and Salmeron BJ. Chronic exposure to nicotine is associated with reduced reward-related activity in the striatum but not the midbrain. Biol Psychiatry 2012; 71: 206-213.
[11] Janhunen S and Ahtee L. Differential nicotinic regulation of the nigrostriatal and mesolimbic dopaminergic pathways: implications for drug development. Neurosci Biobehav Rev 2007; 31: 287-314.
[12] Gotti C, Zoli M and Clementi F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. Trends Pharmacol Sci 2006; 27: 482-491.
[13] Crooks PA and Dwoskin LP. Contribution of CNS nicotine metabolites to the neuropharmacological effects of nicotine and tobacco smoking. Biochem Pharmacol 1997; 54: 743-753.
[14] Picciotto MR, Zoli M and Rimondini R. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 1998; 391: 173-177.
[15] Fowler CD, Arends MA and Kenny PJ. Subtypes of nicotinic acetylcholine receptors in nicotine reward, dependence, and withdrawal: evidence from genetically modified mice. Behav Pharmacol 2008; 19: 461-484.
[16] Brody AL. Functional brain imaging of tobacco use and dependence. J Psychiatr Res 2006; 40: 404-418.
[17] Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci 2005; 8: 1445-1449.
[18] Shannak K, Rajput A, Rozdilsky B, Kish S, Gilbert J and Hornykiewicz O. Noradrenaline, dopamine and serotonin levels and metabolism in the human hypothalamus: observations in Parkinson's disease and normal subjects. Brain Res 1994; 639: 33-41.
[19] Lewis A, Miller JH and Lea RA. Monoamine oxidase and tobacco dependence. Neurotoxicol 2007; 28: 182-195.
[20] Lotfipour S, Arnold MM, Hogenkamp DJ, Gee KW, Belluzzi JD and Leslie FM. The monoamine oxidase (MAO) inhibitor tranylcypromine enhances nicotine self-administration in rats through a mechanism independent of MAO inhibition. Neuropharmacol 2011; 61: 95-104.
[21] Cryan JF, Bruijnzeel AW, Skjei KL and Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacol 2003; 168: 347-58.
[22] Kirch DG, Taylor TR, Creese I, Xu SX and Wyatt RJ. Effect of chronic nicotine treatment and

withdrawal on rat striatal D1 and D2 dopamine receptors. J Pharm Pharmacol 1992; 44: 89-92.
[23] Epping-Jordan MP, Watkins SS, Koob GF and Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 1998; 393: 76-79.
[24] Dani JA and Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron 1996; 16: 905-908.
[25] Brody AL, Mandelkern MA and London ED. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. Arch Gen Psychiatry 2006; 63: 907-915.
[26] Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens. Nicotine Tob Res 2004; 6: 899-912.
[27] George O, Ghozland S and Azar MR. CRF-CRF1 system activation mediates withdrawal-induced increases in nicotine self-administration in nicotine-dependent rats. Proc Natl Acad Sci U S A 2007; 104: 17198-17203.
[28] Saravia R, Ten-Blanco M, Pereda-Pérez I and Berrendero F. New Insights in the Involvement of the Endocannabinoid System and Natural Cannabinoids in Nicotine Dependence. Int J Mol Sci 2021; 22: 13316.
[29] Liu Q,Yu J, Li X, Guo Y, Sun T, Luo L, Ren J, Jiang W, Zhang R, Yang P and Yang Q. Cannabinoid receptor GPR55 activation blocks nicotine use disorder by regulation of AMPAR phosphorylation. Psychopharmacol 2021; 238: 3335-3346.
[30] Sakurai T, Amemiya A and Ishii M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998; 92: 573-585.
[31] Martin G, Fabre V, Siggins GR and de Lecea L. Interaction of the hypocretins with neurotransmitters in the nucleus accumbens. Regul Pept 2002; 104: 111-117.
[32] Date Y, Ueta Y and Yamashita H. Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. Proc Natl Acad Sci U S A 1999; 96: 748-753.
[33] Ahmadi-Soleimani SM, Azizi H, Gompf HS and Semnanian S. Role of orexin type-1 receptors in paragiganto-coerulear modulation of opioid withdrawal and tolerance: a site specific focus. Neuropharmacol 2017; 126: 25-37.
[34] Yazdi F, Jahangirvand M, Pirasteh AH, Moradi M and Haghparast A. Functional interaction between OX2 and CB1 receptors in the ventral tegmental area and the nucleus accumbens in response to place preference induced by chemical stimulation of the lateral hypothalamus. Pharmacol Biochem Behav 2015; 139: 39-46.
[35] Sharf R, Sarhan M and Dileone RJ. Orexin mediates the expression of precipitated morphine withdrawal and concurrent activation of the nucleus accumbens shell. Biol Psychiatry 2008; 64: 175-183.
[36] Narita M, Nagumo Y and Hashimoto S. Direct involvement of orexinergic systems in the activation of the mesolimbic dopamine pathway and related behaviors induced by morphine. J Neurosci 2006; 26: 398-405.
[37] LeSage MG, Perry JL, Kotz CM, Shelley D and Corrigall WA. Nicotine self-administration in the rat: effects of hypocretin antagonists and changes in hypocretin mRNA. Psychopharmacol (Berl) 2010; 209: 203-212.
[38] Zhang GC, Mao LM, Liu XY and Wang JQ. Long-lasting up-regulation of orexin receptor type 2 protein levels in the rat nucleus accumbens after chronic cocaine administration. J Neurochem 2007; 103: 400-407.
[39] Shoblock JR, Welty N and Aluisio L. Selective blockade of the orexin-2 receptor attenuates ethanol self-administration, place preference, and reinstatement. Psychopharmacol (Berl) 2011; 215: 191-203.
[40] Tabaeizadeh M, Motiei-Langroudi R and Mirbaha H. The differential effects of OX1R and OX2R selective antagonists on morphine conditioned place preference in naïve versus morphine-dependent mice. Behav Brain Res 2013; 237: 41-48.
[41] Schmeichel BE, Barbier E and Misra KK. Hypocretin receptor 2 antagonism dose-dependently reduces escalated heroin self-administration in rats. Neuropsychopharmacol 2015; 40: 1123-1129.
[42] Azizi F, Fartootzadeh R, Alaei H and Reisi P. Effects of concurrent blockade of OX2 and CB1 receptors in the ventral tegmental area on nicotine-induced place preference in rats. Neurosci Lett 2018; 684: 121-126.
[43] Novak G, LeBlanc M and Zai C. Association of polymorphisms in the BDNF, DRD1 and DRD3 genes with tobacco smoking in schizophrenia. Ann Hum Genet 2010; 74: 291-298.
[44] Bouthenet ML, Souil E, Martres MP, Sokoloff P, Giros B and Schwartz JC. Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D2 receptor mRNA. Brain Res 1991; 564: 203-219.
[45] Le Moine C and Bloch B. Expression of the D3 dopamine receptor in peptidergic neurons of the nucleus accumbens: comparison with the D1 and D2 dopamine receptors. Neurosci 1996; 73: 131-143.

[46] Sokoloff P, Giros B, Martres MP, Bouthenet ML and Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 1990; 347: 146-151.
[47] Mansour A, Meador-Woodruff JH, Bunzow JR, Civelli O, Akil H and Watson SJ. Localization of dopamine D2 receptor mRNA and D1 and D2 receptor binding in the rat brain and pituitary: an in situ hybridization-receptor autoradiographic analysis. J Neurosci 1990; 10: 2587-2600.
[48] Sales N, Martres MP, Bouthenet ML and Schwartz JC. Ontogeny of dopaminergic D-2 receptors in the rat nervous system: characterization and detailed autoradiographic mapping with [125I]iodosulpride. Neurosci 1989; 28: 673-700.
[49] Schambra UB, Duncan GE, Breese GR, Fornaretto MG, Caron MG and Fremeau RT Jr. Ontogeny of D1A and D2 dopamine receptor subtypes in rat brain using in situ hybridization and receptor binding. Neurosci1994; 62: 65-85.
[50] Stanwood GD, McElligot S, Lu L and McGonigle P. Ontogeny of dopamine D3 receptors in the nucleus accumbens of the rat. Neurosci Lett 1997; 223: 13-16.
[51] Gurevich EV, Himes JW and Joyce JN. Developmental regulation of expression of the D3 dopamine receptor in rat nucleus accumbens and islands of Calleja. J Pharmacol Exp Ther 1999; 289: 587-598.
[52] Smith RF. Animal models of periadolescent substance abuse. Neurotoxicol Teratol 2003; 25: 291-301.
[53] Roddy E. Bupropion and other non-nicotine pharmacotherapies. BMJ 2004; 328: 509-511.
[54] Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB and Learned-Coughlin S. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. Prim Care Companion J Clin Psychiatry 2004; 6: 159-166.
[55] Walsky RL, Astuccio AV and Obach RS. Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. J Clin Pharmacol 2006; 46: 1426-1438.
[56] Kalkhoran S, Benowitz NL and Rigotti NA. Prevention and treatment of tobacco use: JACC health promotion series. J Am Coll Cardiol 2018; 72: 1030-1045.
[57] Mooney ME and Sofuoglu M. Bupropion for the treatment of nicotine withdrawal and craving. Expert Rev Neurother 2006; 6: 965-981.
[58] McCarthy DE and Versella MV. Quitting failure and success with and without using medication: latent classes of abstinence and adherence to nicotine monotherapy, combination therapy, and varenicline. Nicotine Tob Res 2019; 21: 1488-1495.
[59] Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. Int J Clin Pract 2006; 60: 571-576.
[60] Rollema H and Hurst RS. The contribution of agonist and antagonist activities of α4β2* nAChR ligands to smoking cessation efficacy: a quantitative analysis of literature data. Psychopharmacol (Berl) 2018; 235: 2479-2505.
[61] Gelfand EV and Cannon CP. Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. J Am Coll Cardiol 2006; 47: 1919-1926.
[62] Cohen C, Perrault G, Griebel G and Soubrié P. Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). Neuropsychopharmacol 2005; 30: 145-155.
[63] Drovandi AD, Chen CC and Glass BD. Adverse effects cause varenicline discontinuation: a meta-analysis. Curr Drug Saf 2016; 11: 78-85.
[64] Balerio GN, Aso E and Maldonado R. Role of the cannabinoid system in the effects induced by nicotine on anxiety-like behaviour in mice. Psychopharmacol (Berl) 2006; 184: 504-513.
[65] Xie S, Furjanic MA and Ferrara JJ. The endocannabinoid system and rimonabant: a new drug with a novel mechanism of action involving cannabinoid CB1 receptor antagonism--or inverse agonism--as potential obesity treatment and other therapeutic use. J Clin Pharm Ther 2007; 32: 209-231.
[66] Le Foll B, Forget B, Aubin HJ and Goldberg SR. Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: insights from pre-clinical and clinical studies. Addict Biol 2008; 13: 239-252.
[67] Raffa RB and Ward SJ. CB_1-independent mechanisms of Δ^9-THCV, AM251 and SR141716 (rimonabant). J Clin Pharm Ther 2012; 37: 260-265.
[68] French ED, Dillon K and Wu X. Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport 1997; 8: 649-652.
[69] Le Foll B and Goldberg SR. Rimonabant, a CB1 antagonist, blocks nicotine-conditioned place preferences. Neuroreport 2004; 15: 2139-2143.
[70] Kodas E, Cohen C, Louis C and Griebel G. Cortico-limbic circuitry for conditioned nicotine-seeking behavior in rats involves endocannabinoid signaling. Psychopharmacol (Berl) 2007; 194: 161-171.
[71] Nashmi R and Lester HA. CNS localization of neuronal nicotinic receptors. J Mol Neurosci 2006; 30: 181-184.

[72] McCallum SE, Parameswaran N, Bordia T, Fan H, McIntosh JM and Quik M. Differential regulation of mesolimbic alpha 3/alpha 6 beta 2 and alpha 4 beta 2 nicotinic acetylcholine receptor sites and function after long-term oral nicotine to monkeys. J Pharmacol Exp Ther 2006; 318: 381-388.
[73] Auerbach A. Agonist activation of a nicotinic acetylcholine receptor. Neuropharmacol 2015; 96: 150-156.
[74] Araki H, Suemaru K and Gomita Y. Neuronal nicotinic receptor and psychiatric disorders: functional and behavioral effects of nicotine. Jpn J Pharmacol 2002; 88: 133-138.
[75] Wilens TE, Verlinden MH, Adler LA, Wozniak PJ and West SA. ABT-089, a neuronal nicotinic receptor partial agonist, for the treatment of attention-deficit/hyperactivity disorder in adults: results of a pilot study. Biol Psychiatry 2006; 59: 1065-1070.
[76] Esterlis I, Cosgrove KP and Batis JC. Quantification of smoking-induced occupancy of beta2-nicotinic acetylcholine receptors: estimation of nondisplaceable binding. J Nucl Med 2010; 51: 1226-1233.
[77] Rose JE, Behm FM, Westman EC, Levin ED, Stein RM and Ripka GV. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. Clin Pharmacol Ther 1994; 56: 86-99.
[78] Coe JW, Brooks PR and Vetelino MG. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005; 48: 3474-3477.
[79] Wilkerson JL, Deba F, Crowley ML, Hamouda AK and McMahon LR. Advances in the in vitro and in vivo pharmacology of Alpha4beta2 nicotinic receptor positive allosteric modulators. Neuropharmacol 2020; 168: 108008.
[80] Maurer P and Bachmann MF. Therapeutic vaccines for nicotine dependence. Curr Opin Mol Ther 2006; 8: 11-16.
[81] Cerny EH and Cerny T. Anti-nicotine abuse vaccines in the pipeline: an update. Expert Opin Investig Drugs 2008; 17: 691-696.
[82] Hall W and Gartner C. Ethical and policy issues in using vaccines to treat and prevent cocaine and nicotine dependence. Curr Opin Psychiatry 2011; 24: 191-196.
[83] Cerny EH and Cerny T. Vaccines against nicotine. Hum Vaccin 2009; 5: 200-205.
[84] Maramai S, Gemma S and Brogi S. Dopamine D3 receptor antagonists as potential therapeutics for the treatment of neurological diseases. Front Neurosci 2016; 10: 451.
[85] Scendoni R, Bury E, Ribeiro ILA, Cameriere R and Cingolani M. Vaccines as a preventive tool for substance use disorder: a systematic review including a meta-analysis on nicotine vaccines' immunogenicity. Hum Vaccin Immunother 2022; 18: 2140552.
[86] Goniewicz ML and Delijewski M. Nicotine vaccines to treat tobacco dependence. Hum Vaccin Immunother 2013; 9: 13-25.
[87] Xi ZX and Gardner EL. Hypothesis-driven medication discovery for the treatment of psychostimulant addiction. Curr Drug Abuse Rev 2008; 1: 303-327.
[88] Kiss B, Laszlovszky I and Krámos B. Neuronal dopamine D3 receptors: translational implications for preclinical research and CNS disorders. Biomolecules 2021; 11: 104.
[89] Lawrence AJ, Cowen MS, Yang HJ, Chen F and Oldfield B. The orexin system regulates alcohol-seeking in rats. Br J Pharmacol 2006; 148: 752-759.
[90] Le Foll B, Goldberg SR and Sokoloff P. The dopamine D3 receptor and drug dependence: effects on reward or beyond? Neuropharmacol 2005; 49: 525-541.
[91] Mahler SV, Moorman DE, Smith RJ, James MH and Aston-Jones G. Motivational activation: a unifying hypothesis of orexin/hypocretin function. Nat Neurosci 2014; 17: 1298-1303.
[92] Azizi F, Fartootzadeh R, Alaei H and Reisi P. Electrophysiological study of the response of ventral tegmental area non-dopaminergic neurons to nicotine after concurrent blockade of orexin receptor-2 and cannabinoid receptors-1. Brain Res 2019; 1719: 176-182.
[93] Roecker AJ, Cox CD and Coleman PJ. Orexin receptor antagonists: new therapeutic agents for the treatment of insomnia. J Med Chem 2016; 59: 504-530.