HHS Public Access

Author manuscript

Addict Neurosci. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

Addict Neurosci. 2023 September ; 7: . doi:10.1016/j.addicn.2023.100103.

New medications development for smoking cessation

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Abstract

Diseases associated with nicotine dependence in the form of habitual tobacco use are a major cause of premature death in the United States. The majority of tobacco smokers will relapse within the first month of attempted abstinence. Smoking cessation agents increase the likelihood that smokers can achieve long-term abstinence. Nevertheless, currently available smoking cessation agents have limited utility and fail to prevent relapse in the majority of smokers. Pharmacotherapy is therefore an effective strategy to aid smoking cessation efforts but considerable risk of relapse persists even when the most efficacious medications currently available are used. The past decade has seen major breakthroughs in our understanding of the molecular, cellular, and systems-level actions of nicotine in the brain that contribute to the development and maintenance of habitual tobacco use. In parallel, large-scale human genetics studies have revealed allelic variants that influence vulnerability to tobacco use disorder. These advances have revealed targets for the development of novel smoking cessation agents. Here, we summarize current efforts to develop smoking cessation therapeutics and highlight opportunities for future efforts.

1. Introduction

Tobacco smoking is a leading cause of preventable disease and premature death globally [1]. In the United States, over 480,000 deaths each year are attributable to smoking-related illnesses, such as chronic obstructive pulmonary disorder (COPD), lung cancer, cardiovascular disease, and diabetes [2]. In addition to the devastating health consequences, tobacco use disorder also has a staggering economic impact. More than $300 billion is spent in the United States each year on the treatment of smoking-related illnesses, accounting for approximately 12% of annual healthcare expenditures [3]. Evidence suggests that those who achieve long-term abstinence from tobacco use have a greatly reduced risk of developing

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Disclosures

P.J.K. is a co-founder of Eolas Therapeutics Inc., which has a licensing agreement with AstraZeneca to develop small molecule treatments for substance use disorders.

Declaration of Competing Interest

The authors declare no conflicts of interest.

lung cancer and other smoking-related illnesses than those who persist in their use tobacco products [4,5]. Despite the well-known negative health impact of tobacco use, and the clear benefits of quitting, the majority of smokers are often unsuccessful in their attempts to achieve long-term abstinence. Indeed, approximately 80% of smokers will relapse within the first month of a quit attempt [6]. Medications approved by the US Food and Drug Administration (FDA) as aids to smoking cessation include various forms of nicotine replacement therapy (NRT), such as gum, patch, spray, and lozenges, as well as Zyban (bupropion) and Chantix (varenicline). These medications demonstrate limited efficacy in the majority of smokers attempting to quit [6], and there remains a high residual risk of relapse despite the use of these medications. Use of bupropion and varenicline was thought to be associated with risk of serious mental health side effects in smokers [7], resulting in the inclusion of boxed warnings on their labeling. However, findings from a large-scale clinical trial indicated that these risks may in fact be lower than previously thought [8]. This prompted the FDA to remove boxed warnings from Chantix and Zyban drug labels. Nevertheless, negative perceptions about the safety and efficacy of these medications have limited their use [7,9]. Most recently, safety concerns related to high levels of an *N*-nitroso-varenicline impurity triggered a nationwide recall of Chantix and the approval of genetic formulations of varenicline. Collectively, this underscores the critical need to develop new safe and effective smoking cessation medications to mitigate the deleterious health consequences of tobacco dependence. Such medications are likely to derive from advances in our understanding of the neural mechanisms of tobacco dependence. Here, we briefly summarize the neurobiological mechanisms of tobacco use disorder, highlight ongoing efforts to develop new smoking cessation agents, and identify opportunities to leverage advances in our understanding of tobacco dependence from preclinical studies to establish new medications development programs for smoking cessation. While the focus of the article is on the mechanisms of tobacco use disorder within the context of pharmacological medications development for smoking cessation, ongoing work on other innovative approaches to treat tobacco dependence, including nicotine-based vaccines [10,11], are also briefly considered.

2. Clinical features of tobacco use disorder

Nicotine is considered the major psychoactive component of tobacco smoke that promotes the development and maintenance of tobacco use in those who suffer from tobacco use disorder [12]. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tobacco use disorder is characterized by three primary features: (1) a gradual increase in the amount of tobacco consumed over time; (2) the development of tolerance to the pharmacological actions of nicotine; and (3) the onset of withdrawal symptoms upon cessation of the use of nicotine-containing tobacco products. Thus, tobacco use disorder is also characterized by the consumption of progressively greater doses of nicotine in order to obtain the desired pharmacokinetic response; continued use despite adverse social, economic, or interpersonal consequences; and unsuccessful efforts to quit. The abrupt cessation or reduction in the amount of tobacco intake can precipitate an aversive nicotine withdrawal syndrome, which is characterized by physical, cognitive, and mood disturbances including difficulty concentrating, increased anxiety, and depression-like

negative mood states. Avoidance and alleviation of the nicotine withdrawal syndrome is thought to contribute to the persistence of the tobacco habit and the high risk of relapse during periods of attempted abstinence [13]. Craving during abstinence has been included as a diagnostic criterion of tobacco use disorder in DSM-5. Craving in abstinent smokers reflects “a strong desire or urge to use tobacco” and is thought to be an important component of the withdrawal syndrome that contributes to the resumption of tobacco use. Indeed, the extent of craving during the early stages of abstinence is closely linked with the likelihood of relapsing to tobacco use [14–17]. This suggests that interventions that can attenuate craving and other components of the nicotine withdrawal syndrome in smokers during the early stages of abstinence may facilitate long-term abstinence.

Until recently, most efforts to develop smoking cessation medications were focused on pharmacological modulation of nicotinic acetylcholine receptors (nAChRs), which are the primary substrate for the actions of nicotine in the brains of smokers. Indeed, the efficacy of most of the currently available smoking cessation agents is thought to reflect their pharmacological actions at nAChRs in the brain [18,19]. Evidence has accumulated over recent years that signaling events beyond nAChR-mediated cascades contribute to the reinforcing properties of nicotine. For example, agents that modify the actions of endogenous opioids, hypocretin/orexin, and other neuropeptide systems, glutamatergic receptors, and γ-aminobutyric acid (GABA) receptors, have shown promise as smoking cessation pharmacotherapies (Table 1). Preclinical and clinical studies have been designed to test the effectiveness of novel compounds targeting these systems in regulating various behaviors thought to be important in maintaining tobacco use disorder, including the positive reinforcing actions of nicotine, craving-related behaviors, and aspects of the nicotine withdrawal syndrome that may contribute to negative reinforcing actions of nicotine.

3. Human genetics-based discovery of novel targets for smoking cessation

There is now considerable preclinical, clinical, and human genetics evidence implicating nAChRs located in the central nervous system (CNS) in regulating the abuse liability of nicotine-containing tobacco products [12,38,39] (Fig. 1). nAChRs are ligand-gated cationic channels that are widely distributed throughout the CNS [40]. nAChRs contain five membrane-spanning subunits (α and β subunits) [41,42]. Eight isoforms of the neuronal α subunit ($\alpha2$–$\alpha7$, $\alpha9$, and $\alpha10$) and three isoforms of the β subunit ($\beta2$–$\beta4$) have been identified in mammalian brain [43]. Within the CNS, combinations of $\alpha2$–$\alpha6$ and $\beta2$–$\beta4$ subunits can form functionally distinct subtypes of hetero-oligomeric nAChRs that display distinct pharmacological, kinetic, and other functional properties, whereas $\alpha7$ subunits form homo-oligomeric receptor subtypes [44]. nAChRs containing the $\alpha4$ and $\beta2$ subunits (denoted $\alpha4\beta2*$ nAChRs) are the most abundantly expressed subtype in the mammalian CNS [45]. and are thought to account for the majority of the high-affinity nicotine binding sites in the mammalian brain [46–49]. $\alpha4\beta2*$ nAChRs usually combine in a 2:3 stoichiometry, but can also combine in other stoichiometries (for example 3:2), and sometimes incorporate accessory subunits such the $\alpha5$ nAChR subunit that influence the properties of the mature receptor complex [45]. $\beta2*$ nAChRs are necessary for the

positive reinforcing properties of nicotine in rodents, reflected by the fact that genetic deletion of the $\beta 2$ subunit eliminates high-affinity nicotine binding sites in the brain and abolishes reward-related behavioral responses to nicotine in mice [46,50]. Furthermore, genetically modified mice that express a mutant version of the $\alpha 4$ subunit that renders $\alpha 4*$ nAChRs hyper-responsive to nicotine demonstrate increased sensitivity to nicotine reward, even at "subthreshold" doses of nicotine that are too low to elicit reward-related behavioral responses in wild-type mice [51]. $\alpha 4\beta 2*$ nAChRs are thought to play an important role in the efficacy of currently available smoking cessation agents. Indeed, varenicline (Chantix) is a partial agonist at $\alpha 4\beta 2*$ nAChRs [52]. Varenicline is thought to compete with nicotine to bind to $\alpha 4\beta 2*$ nAChRs expressed by midbrain dopamine neurons, thereby attenuating the stimulatory effects of nicotine on mesoaccumbens dopamine transmission [53,54]. In this manner, varenicline is thought to attenuate the stimulatory actions of nicotine on dopamine transmission in brain reinforcement circuits that is considered critical for the establishment and maintenance of tobacco smoking behavior. Varenicline is a derivative of the nAChR partial agonist (−)-cytisine, a natural product derived from *Cytisus laburnum* and other plant species [53]. Cytisine has shown mixed results in human clinical trials assessing its efficacy as a smoking cessation agent [55–57]. This likely reflects the fact that cytisine has poorer absorption and brain penetration properties than varenicline [58,59]. Varenicline and related partial agonists exert low levels of $\alpha 4\beta 2*$ nAChR-mediated signaling in the brain during periods of nicotine abstinence and thereby at least partially substitute for the pharmacological actions of nicotine in smokers attempting to quit [53]. This action is thought to counteract the decrease in dopamine transmission and other reward-relevant signaling events in the brains of smokers during abstinence, the avoidance and alleviation of which contributes to relapse to tobacco use [53,60]. Thus, the clinical efficacy of NRT and nAChR partial agonists such as varenicline as smoking cessation agents is likely to reflect their ability to substitute for and/or block the actions of nicotine at $\alpha 4\beta 2*$ nAChRs [60,61]. Thus, next generation smoking cessation agents could be developed that more efficiently target the specific populations of $\alpha 4\beta 2*$ nAChRs involved in nicotine reinforcement and/or modify the activity patterns of these receptors in a manner that results in greater clinical efficacy. Bupropion is an atypical antidepressant that is clinically efficacious as a smoking cessation agent, which acts primarily by inhibiting the reuptake of dopamine and other monoamine neurotransmitters in the brain [62]. Intriguingly, bupropion is also an antagonist at $\alpha 4\beta 2*$ nAChRs in the brain [63–65]. Whether the direct actions of bupropion on nAChR signaling contributes to its efficacy as a smoking cessation agent is currently unknown.

In addition to $\alpha 4$ and $\beta 2$ nAChR subunits, other lesser studied nAChR subunits have also been implicated in the addiction-related actions of nicotine [46]. Most notably, the *CHRNA5-CHRNA3-CHRNB4* gene cluster, which encodes the $\alpha 5$, $\alpha 3$, and $\beta 4$ nAChR subunits, respectively, has been heavily implicated in tobacco dependence by human genome-wide association studies (GWAS) [66–69]. Evidence from GWAS indicates that allelic variation in this gene cluster increases the risk of tobacco dependence and smoking-related diseases [66,70,71]. In animals, genetic manipulations that decrease the expression and/or function of $\alpha 3$, $\alpha 5$, or $\beta 4$ subunits result in striking alterations in behavioral responses to nicotine [72–74]. For example, mice with a null mutation in the *Chrna5* gene consume greater quantities of nicotine than wild-type mice, which is reversed by

re-expressing α5 nAChR subunits in the medial habenula (MHb) - interpeduncular nucleus (IPN) circuit [75]. More broadly, the MHb-IPN circuit has been heavily linked to the regulation of nicotine intake [75]. RNA interference-mediated knockdown of *Chrna5* gene transcripts in this region does not alter the rewarding properties of nicotine in rats but instead attenuates the aversive properties of nicotine that are thought to limit consumption of the drug [72–75]. α3* nAChRs in the brain are almost exclusively expressed in the MHb-IPN circuit [74]. Mice engineered to express constitutively low levels of α3* nAChRs are less sensitive to nicotine aversion and self-administer greater quantities of the drug than wild-type mice [74]. These findings suggest that nAChRs containing subunits derived from the *CHRNA5-CHRNA3-CHRNB4* gene cluster influence tobacco dependence vulnerability by regulating the aversive properties of nicotine that limit consumption and protect against the establishment of regulate tobacco use [46]. Combinations of polymorphisms in the *CHRNA5-CHRNA3-CHRNB4* region that tend to be inherited together, known as haplotypes, have been identified that contribute to different risk levels of nicotine dependence (low, intermediate, and high risk) [76]. A large-scale study of genetic factors that influence the efficacy of smoking cessation agents showed that individuals who carry the high-risk *CHRNA5-CHRNA3-CHRNB4* haplotype were more sensitive to currently available smoking cessation therapeutics than those with the low-risk haplotype [76]. Smokers in the high-risk haplotype group that received placebo medication were also more likely to relapse to tobacco use compared with the low-risk haplotype group [76]. In a subsequent study it was reported that the efficacy of NRT was moderated by genetic variants in the *CHRNA5* gene [77]. These data lend support to the idea that novel pharmacological agents that modulate the activity of nAChRs containing α5, α3, and/or β4 subunits may be effective smoking cessation agents, particularly in those individuals who carry *CHRNA5-CHRNA3-CHRNB4* risk alleles.

Allelic variants in genes that encode the enzymes involved in nicotine metabolism, including cytochrome P450 2A6 (CYP2A6) and cytochrome P450 2B6 (CYP2B6), also influence risk of tobacco dependence and the efficacy of smoking cessation therapeutics [78–81]. Higher abstinence rates with bupropion have been reported in individuals carrying alleles that decrease CYP2A6 function resulting in slower nicotine metabolism [79]. In a randomized smoking cessation trial, an association between CYP2A6 genotype and abstinence was found in individuals receiving NRT, but not those receiving bupropion [82], consistent with altered nicotine but not bupropion metabolism in these individuals. Hence, agents that modify CYP2A6/CYP2B6 activity may have efficacy as smoking cessation medications. Identification of other gene variants that influence the risk of tobacco dependent or vulnerability to relapse may similarly yield novel targets for medications development and catalyze personalized medicine-based approaches to tobacco use disorder [71,83]. Hence, next-generation smoking cessation therapeutics are likely to be derived from advances in our understanding of the genetics of tobacco use disorder. Studies employing cultured human neurons that carry risk-associated gene variants are likely to shed important new light on the molecular mechanisms that influence vulnerability to tobacco use disorders [84,85]. Furthermore, advances in high-throughput screening of cultured human neurons may facilitate the identification of small molecule drugs that reverse the functional consequences of risk-associated gene variants, and thereby have utility as smoking cessation agents.

Finally, rates of tobacco use disorder and amounts of tobacco consumed are much higher in individuals suffering from major depressive disorder, anxiety disorders, schizophrenia, and other neuropsychiatric disorders relative to the general population [86]. Whether the onset of a psychiatric disorder increases the risk of developing tobacco dependence or whether tobacco use increases vulnerability to psychiatric abnormalities is unclear, but the available evidence suggests that both relationships are likely to exist [87,88]. This suggests that tobacco use disorder and neuropsychiatric abnormalities may share some overlap in their genetic underpinnings [86,89–92]. If so, insights into the genetic mechanisms of neuropsychiatric disorders may reveal novel treatment approaches for tobacco use disorders and vice versa. Notably, rates of tobacco use in the general population have steadily decreased in recent years [93,94], but have remained stubbornly high in individuals suffering from neuropsychiatric abnormalities [86,95]. This is important because currently available and newly developed smoking cessation therapies may demonstrate altered efficacy in those smokers who also suffer from comorbid psychiatric disorders [96,97].

4. Pharmacogenetics and personalized medicine in the context of smoking cessation

Accumulating evidence support an important link between genetic factors and vulnerability to nicotine dependence and the effectiveness of different smoking cessation agents. As described above, individuals who carried *CHRNA5-CHRNA3-CHRNB4* risk alleles were more sensitive to currently available smoking cessation therapeutics than those with low-risk haplotypes [76,77,98]. The variation in treatment efficacy between smokers with different genetic phenotypes underscores the potential of personalized smoking cessation medications based on genotype to maximize treatment efficacy, while potentially minimizing potential side-effects [98]. Thus, identifying these genes and understanding how they combine to influence nicotine dependence is an important goal of current research that may be addressed through modern genetic approaches, including transcriptomic analysis in animal models and postmortem human brain tissue. Hopefully, these approaches will expand our understanding of the mechanisms of nicotine dependence, and ultimately facilitate the translation of these findings into more efficacious personalized clinical smoking cessation therapies.

5. Preclinical model-based discovery of novel targets for smoking cessation

Significant efforts have been directed toward the development of new medications for smoking cessation based on a growing understanding of the neurobiological mechanisms of nicotine addiction derived from preclinical models of aspects of tobacco use disorder. Indeed, novel targets have been identified in mouse and rat studies that show considerable promise for the treatment of nicotine dependence, leading to the development of new pharmacotherapies currently being evaluated for their efficacy in human clinical trials (Table 2). In this section, we review recent findings supporting the therapeutic potential of compounds targeting newly identified brain targets for smoking cessation, with a focus on endogenous peptide systems, receptors involved in excitatory and inhibitory

neurotransmission, and peroxisome proliferator-activated receptors (PPARs). We will also highlight new pharmacological approaches for the treatment of nicotine dependence such as positive and negative allosteric modulators (PAM and NAM, respectively) of metabotropic glutamate and GABA receptors, which may possess fewer negative side-effects compared with full orthostatic agonists and antagonists at targeted receptors.

5.1. Endogenous opioid system

The endogenous opioid system in the brain is thought to play an important role in the actions of nicotine that contribute to tobacco dependence [99]. The endogenous opioid system consists of 3 families of peptides (β-endorphins, enkephalins, and dynorphin), and 3 families of opioid receptors (μ/MOR, δ/DOR, and κ/KOR) [100]. Opioid receptors are regionally distributed within brain sites involved in pain processing, reward/aversion, and the modulation of stress responses [100,101]. The influence of endogenous opioids in the addiction-related actions of nicotine has been supported in both clinical studies and animal models. Within the ventral tegmental area (VTA), a brain region known to mediate the facilitatory actions of nicotine on dopaminergic transmission, MORs are predominantly expressed on inhibitory GABAergic neurons and act to suppress the release of GABA [102]. Recruitment of the inhibitory action of MORs on GABAergic neurotransmission may therefore act to potentiate the excitatory effects of nicotine on mesoaccumbens dopamine release, and in turn, its reinforcing actions. Evidence from animal studies supports a role of endogenous opioids in nicotine reward. Nicotine has been shown to increase levels of endogenous opioids within the striatum [103–105], and the opioid receptor antagonist naloxone blocks nicotine-induced increases in food responding [106], nicotine-induced analgesia [107], and aversive behaviors associated with mecamylamine-precipitated withdrawal in nicotine-dependent animals [20]. Studies in MOR knockout mice have further demonstrated that this receptor is critical for nicotine reward [108,109]. Together, these findings suggest that the reward-related actions of nicotine may be mediated in part by MOR activation within the mesoaccumbens dopamine system [109].

Clinical studies also support a link between tobacco smoking and the endogenous opioid system. Evidence from human studies indicates that smoking triggers an increase in plasma levels of endogenous opioids [104]. Numerous clinical studies have evaluated the efficacy of opioid receptor antagonists alone or in combination with NRT on smoking behavior. A systematic review and meta-analysis found no significant beneficial effects of naltrexone, a MOR antagonist, on short-term or long-term smoking abstinence [110]. However, a more recent smoking cessation clinical trial reported that naloxone, an inverse agonist of MORs, decreased the desire to smoke in comparison to placebo treatment [111], although this study had a relatively small sample size. In addition, there is evidence that polymorphisms in the *OPRM1* gene encoding MOR in humans may increase the risk of tobacco dependence. The effectiveness of NRT or placebo was evaluated in participants harboring a single nucleotide polymorphism (SNP) in the *OPRM1* gene, leading to a substitution of asparagine (A) for aspartate (G). Individuals with at least one copy of the G allele (GG or GA phenotype) on active NRT treatment were less likely to remain abstinent relative to placebo compared with individuals in the AA phenotype group [112]. Interestingly, these genotype-treatment interactions were found to be sexually dimorphic; males in the AA group were more likely

to remain abstinent at long-term follow-up periods (up to 8 years), whereas the reverse was true for female participants [112]. In contrast to these findings, another study found that NRT was more effective in promoting abstinence in individuals with at least one copy of the G allele of the OPRM1 gene compared with those with two copies of the A allele [112]. Thus, further research is needed to elucidate genotype- and sex-specific influences of the endogenous opioid system in the efficacy of smoking cessation treatments.

5.2. Hypocretin/Orexin

The hypocretin (aka orexin) system comprises 2 neuropeptides (Hcrt1 and Hcrt1) that are produced almost exclusively by neurons located in the lateral hypothalamus and regulate sleep/wake cycles, arousal, and motivational states [113–115]. Hypocretins act at two receptors, Hcrt receptor 1 and 2 (Hcrtr1 and Hcrtr2, respectively) [114,115]. Accumulating evidence suggests that hypocretin plays an important role in the addiction-relevant actions of nicotine. Nicotine increases the expression of hypocretin and its receptors in the lateral hypothalamus [116], and the selective Hcrtr1 antagonist SB334867 decreases nicotine self-administration in rats [21]. Pre-treatment with SB334867 was also found to block the reinstatement of previously extinguished nicotine-seeking behavior by intracerebroventricular infusions of hypocretin [22] and cue-induced reinstatement of nicotine-seeking behavior [23]. A recent study [117] examining electrophysiological responses of hypocretin neurons in the lateral hypothalamus provided further insight into acetylcholine-hypocretin interactions. Acetylcholine stimulated an increase in the firing frequency of a population of hypocretin neurons in the lateral hypothalamus. Interestingly, these effects were also observed following application of the nAChR antagonist mecamylamine. The authors concluded that phasic acetylcholine release in the lateral hypothalamus enhances the firing of a subset of hypocretin neurons through postsynaptic nAChRs, while simultaneously disrupting presynaptic nAChR-mediated glutamatergic inputs to hypocretin neurons [117]. Hence, the regulation of presynaptic glutamatergic inputs to hypocretin neurons within the lateral hypothalamus by acetylcholine may explain the effects of nicotine exposure on the hypocretin system, and hence, the influence of hypocretin receptor antagonists on nicotine-seeking behaviors.

Promising evidence suggests that hypocretin may be associated with the extent of craving during smoking cessation and the risk for relapse in human smokers. In a large sample of smokers, participants who relapsed within the first 4 weeks exhibited a decrease in hypocretin levels at 24 h of abstinence [118]. Further, lower hypocretin levels during withdrawal predicted shorter time to relapse, even after accounting for potential confounding factors such as stress hormone levels. These findings suggest that a decrease in hypocretin levels during the initial withdrawal period promotes nicotine craving and potentiates the risk for relapse in abstinent smokers. Hence, hypocretin levels during early nicotine withdrawal may be useful as a biomarker of craving and relapse risk in smokers attempting to quit [118]. Notably, the dual Hcrtr1/2 receptor antagonist suvorexant was recently shown to attenuate craving in opioid use disorder (OUD) patients undergoing buprenorphine-facilitated abstinence [119]. A randomized phase 1 clinical trial to evaluate the effect of suvorexant on factors impacting the motivation to smoke is currently recruiting participants (Table 2). Recently completed phase 1 clinical trials sponsored by the NIH and AstraZeneca

established that a selective Hcrt1 receptor antagonist (AZD4041) was safe for assessment as a novel smoking cessation agent (www.clinicaltrials.gov/ct2/show/NCT04076540). The findings from these human clinical studies will yield further insights into the therapeutic potential of medications targeting the hypocretin system for smoking cessation.

5.3. Glutamate - metabotropic glutamate receptors

Glutamate-mediated excitatory transmission plays an important role in the reinforcing actions of nicotine and the establishment of nicotine dependence [120]. Nicotine facilitates excitatory neurotransmission in brain circuits involved in reward and aversion, including the mesolimbic dopamine [121] and MHb-IPN circuits [75]. The positive reinforcing properties of nicotine are driven by nAChR-mediated increases in the activity of dopamine neurons in the VTA, thereby increasing their firing rate and enhancing dopamine release in the NAc [122–124]. The activity of mesolimbic dopamine neurons is further regulated by glutamatergic inputs, including from the prefrontal cortex and lateral hypothalamus [120]. Within the mesolimbic circuit, nicotine facilitates glutamate release from presynaptic terminals in both the VTA and NAc, which is believed to play a role in its reinforcing actions [120]. Evidence suggests that blocking glutamatergic transmission within these brain circuits attenuates nicotine reward-related behaviors in rodents [120,125,126]. Conversely, facilitation of inhibitory GABAergic transmission attenuates nicotine seeking behaviors in rodent models of tobacco dependence [120,127,32]. These actions are thought to be mediated through the regulation of dopaminergic transmission; inhibition of GABA release from local interneurons that provide inhibitory input to VTA dopaminergic neurons thereby facilitates nicotine-induced stimulation of dopamine release [120]. However, the specific receptors and circuit-level mechanisms underlying these effects have only recently been elucidated; these will be discussed in more detail in the next section. Ultimately, a better understanding of how glutamate and GABA mediate the reinforcing actions of nicotine will lead to improved pharmacotherapies targeting these neurotransmitter systems for the treatment of nicotine addiction.

The actions of glutamate are mediated through two separate categories of receptors: the fast-acting ionotropic receptors and the slower-acting G-protein coupled metabotropic receptors [120]. The ionotropic glutamate receptors include the amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), *N*-methyl-D-aspartate (NMDA), and kainite-type glutamate receptors, which mediate fast excitatory glutamatergic neurotransmission. The metabotropic glutamate receptor family consists of 8 receptors (mGluR1–8) that are classified into three groups (I, II, and III) based on their functional properties. Group I receptors (mGluR1 and mGluR5) are primarily located postsynaptically, whereas Group II receptors (mGluR2 and mGluR3) are located presynaptically, and their activation inhibits glutamate release to maintain glutamate homeostasis. A growing body of evidence supports a role of mGluRs in nicotine dependence-related behaviors [120,24,29,128].

Preclinical and human studies support the therapeutic potential of mGluRs as targets for smoking cessation. In animals, compounds that decrease glutamatergic transmission either by inhibiting postsynaptic glutamate receptors (NMDARs, mGluR5) or by activating inhibitory presynaptic glutamate receptors (mGluR2/3) decrease nicotine self-administration

and block the reinstatement of nicotine-seeking behaviors. In nicotine-dependent rats, infusion of the mGluR2 agonist LY314582 into the VTA precipitated withdrawal-like increases in intracranial self-stimulation (ICSS) reward thresholds, reflecting a deficit in reward function. This effect was attributed at least partly to reductions in glutamate-mediated excitatory transmission at postsynaptic AMPARs in the VTA [24]. Similar results have been observed with the use of antagonists that block mGluR5-mediated excitatory neurotransmission [29,30]. While the mGluR5 antagonist 6-methyl-2-[*phenylethynyl*]-pyridine (MPEP) did not affect ICSS reward thresholds in nicotine-dependent mice [24], it was found to decrease nicotine-self administration in rats and mice, without affecting the acquisition of food self-administration [29]. Studies in human subjects have also supported a link between mGluRs and nicotine dependence. A positron emission tomography (PET) imaging study reported a global reduction in mGluR5 distribution volume ratio (DVR) in gray matter, which was particularly evident in the medial orbitofrontal cortex. Further, there were significant differences in mGluR5 DVR between smokers and non-smokers, and between ex-smokers and non-smokers. The authors concluded that this decrease may have been an adaptation to chronic increases in glutamate caused by chronic nicotine use [129]. Thus, medications that opposite the stimulatory effects of nicotine on excitatory glutamatergic signaling in the VTA and other reward-relevant brain sites may represent novel smoking cessation agents.

5.4. $GABA_B$ receptors

GABAergic transmission in reward-relevant brain sites has also been heavily implicated in nicotine dependence, particularly in the nicotine withdrawal syndrome. In rodents, somatic withdrawal symptoms are characterized by behaviors such as scratching, head nods, and body shakes, and can be induced by administration of the nAChR antagonist mecamylamine in nicotine-dependent mice [130,131]. Mecamylamine-precipitated withdrawal has been shown to induce expression of the immediate-early gene product c-Fos in the GABAergic neurons located in the IPN, suggesting that nicotine withdrawal may enhance neural activity in the IPN [132]. Moreover, optogenetic activation of GABAergic neurons in the IPN was sufficient to trigger somatic withdrawal symptoms in mice [132]. Notably, infusion of the NMDA glutamatergic receptor antagonist AP5 directly into the IPN reduced GABAergic activation following mecamylamine, and AP5 infusions during spontaneous withdrawal decreased the expression of somatic withdrawal symptoms [132]. The same study also reported that nicotinic $\beta 3$ and $\beta 4$ receptors were upregulated in somatostatin-expressing GABAergic interneurons in the IPN during chronic nicotine exposure, and that blockade of $\beta 4$ receptors activated somatostatin interneurons and triggered somatic withdrawal symptoms that were more dramatic in nicotine-dependent compared to nicotine-naive mice. These findings suggest that glutamate release in the IPN during nicotine withdrawal may drive increases in the activity of GABAergic neurons in the IPN that contribute to the expression of somatic withdrawal symptoms.

Similar to the glutamatergic system, the actions of GABA are mediated through binding to receptors that can be defined as fast-acting ionotropic receptors ($GABA_A$) and slow-acting G-protein-coupled metabotropic receptors ($GABA_B$) [133]. Evidence from animal studies has supported an important role of $GABA_B$ receptors in animal models of

addiction and craving. Administration of $GABA_B$ receptor agonists or positive allosteric modulators has been shown to decease self-administration of various addictive drugs and inhibit cue-induced reinstatement of nicotine-seeking behavior [127,32,134], presumably by enhancing inhibitory neurotransmission in brain reward circuits and thereby opposing the stimulatory effects of nicotine on those sane circuits. Interestingly, prior studies have found that both agonists and antagonists of $GABA_B$ receptors potentiated somatic and anxiety-like responses to mecamylamine-precipitated nicotine withdrawal [135,34]. While it is unclear why the modulation of $GABA_B$ receptors in opposite directions would yield similar behavioral effects, the authors speculated that these results may reflect differential efficacies of the various $GABA_B$ receptor ligands at distinct receptor subtypes in brain regions involved in reward and aversion [34]. Thus, several lines of evidence suggest that $GABA_B$ receptors may modulate both the reinforcing aspects of nicotine as well as the aversive nicotine withdrawal effects in a complex manner. In human clinical trials, the $GABA_B$ receptor antagonist baclofen was shown to decrease cigarette consumption relative to placebo treatment [136], supporting the potential of the $GABA_B$ receptor as a suitable target for the development of pharmacotherapies for smoking cessation.

5.5. Peroxisome proliferator-activated receptors

PPARs have been proposed as therapeutic targets for the treatment of tobacco use disorder [37,137–140]. PPARs ligand-activated transcription factors that regulate the transcription of genes involved in metabolic function and energy hemostasis [141], and more recently have been implicated in addiction-related behaviors. The PPAR receptor family is composed of three subtypes (PPARα, PPARδ, and PPARγ) which differ in their expression patterns and physiological functions [141]. In laboratory animals, compounds that activate PPARs have been shown to reduce reinforcement-related physiological and behavioral responses to nicotine [37,137–140]. A class of drugs known as fibrates that activate PPARs have been widely used to reduce triglyceride levels and reduce the risk of heart disease [142]. A prior study utilizing nicotine self-administration in rats demonstrated that clofibrate, a type of fibrate drug, decreased nicotine consumption, suggesting that clofibrate blocks the reward-related actions of nicotine that motivate consumption of the drug [36]. Clofibrate also attenuated nicotine-induced responses in dopaminergic neurons in the VTA and dopamine release in the NAc [36]. PPARγ has been shown to have potential as a therapeutic target for the development of smoking cessation medications [37]. During acute withdrawal, the expression of PPARγ was found to be elevated in the hippocampus and amygdala of rodents and microinjections of the PPARγ agonist pioglitazone into these regions attenuated somatic and affective symptoms of nicotine withdrawal [37]. Several clinical studies have also evaluated the effects of PPAR agonists on tobacco dependence. The PPARα partial agonist Gemfibrozil did not modify reactivity to nicotine-related cues or the number of days of abstinence in smokers compared to the placebo group [143]. However, another study reported that the PPARγ agonist pioglitazone significantly reduced measures of nicotine craving in smokers [144], suggesting that medications targeting PPARγ may be effective in promoting abstinence in smokers attempting to quit.

6. Corticostriatal circuits in tobacco dependence

The stimulatory action of nicotine on dopamine transmission in brain reinforcement circuits is thought to play a crucial role in the establishment and maintenance of the tobacco smoking habit [46]. As previously mentioned, nicotine stimulates nAChRs located on the terminals of excitatory inputs to the VTA and also nAChRs located directly on dopamine neurons to facilitate VTA-derived dopaminergic signaling in the NAc, which supports the positive reinforcing properties of the drug [121]. Conversely, avoidance and alleviation of the deficits in dopamine transmission in the NAc and other corticolimbic brain sites during periods of nicotine withdrawal is thought to provide an important source of negative reinforcement that contributes to relapse [145]. α6 nAChR subunits are highly localized to midbrain and hindbrain regions containing dopamine-producing and norepinephrine-producing neurons, respectively [122–124]. α6 nAChR subunits are likely incorporated along with β3 nAChRs subunits into subtypes of $\alpha4\beta2*$ nAChRs, which play particularly important roles in regulating the stimulatory effects of nicotine on mesoaccumbens dopamine transmission [45]. Indeed, the $\alpha6*$ nAChR antagonist α-conotoxin-MII suppresses nicotine-evoked dopamine release in the NAc and decreases nicotine self-administration behavior in rodents [124]. Hence, pharmacological agents that target the nAChR subtypes involved in modulating dopamine transmission may have therapeutic utility as smoking cessation therapeutics. Haloperidol, a dopamine D2 receptor antagonist, was found to reduce cigarette smoking in a clinical study [146]. However, haloperidol and other neuroleptic agents have marked adverse effects and it is unclear whether the effects of such compounds on smoking behavior are secondary to such adverse effects. Concerningly, neuroleptics have been reported to increase tobacco smoking behavior [147,148], which may reflect compensatory increases in tobacco consumption to overcome the inhibitory effects of neuroleptics on D2 dopamine receptor-mediated signaling. A clinical study evaluating the effectiveness of *S*-adenosyl-L-methionine (SAMe), a methyl group donor that stimulates the synthesis of catecholamines including dopamine, failed to identify difference in abstinence rates or withdrawal symptoms between SAMe and placebo treatment groups [149]. Thus, it is presently unclear whether interventions designed to modulate mesoaccumbens dopamine transmission will yield clinically efficacious smoking cessation agents, except perhaps in certain populations of smokers that may be particularly sensitive to beneficial effects of such compounds.

Nicotine-enhanced glutamatergic transmission in the NAc, derived from the higher-order cortical inputs, is thought to contribute to relapse vulnerability during periods of abstinence [126]. In the cue-induced reinstatement model of relapse, nicotine-seeking behavior was associated with an increase in glutamate release in the NAc core of rats [126]. Furthermore, cue-induced reinstatement led to an increase in spine diameter along with an increase in AMPA/NMDA glutamatergic receptor ratio in medium spiny neurons in the NAc core, indicative of increased synaptic plasticity. These changes were associated with reductions in the expression of the GluN2A and GluN2B subunits, and pharmacological inhibition of GluN2A or GluN2B in the NAc core prevented nicotine reinstatement [126]. It was also demonstrated that the mGlu2/3 receptor agonist LY379268 decreased cue-induced reinstatement of nicotine-seeking responses in rats after infusion into the VTA or NAc

[25]. As mGlu2/3 receptors act as presynaptic autoreceptors, these manipulations would be expected to decrease phasic increases in glutamatergic transmission in the NAc derived from the cortex and other reward-relevant brain sites [25]. An mGlu2 receptor positive allosteric modulator, AZD8529, similarly decreased nicotine self-administration and cue-induced reinstatement of nicotine-seeking responses in rats [27] and squirrel monkeys [150]. AZD8529 advanced to a phase 2 clinical trial to test whether it facilitates smoking cessation in tobacco users [151]. Reports of an efficacious response to AZD8529 have not appeared in the published literature and its development as a novel smoking cessation agent appear to have ceased. However, other pharmacological interventions that attenuate cortically derived glutamatergic transmission in the mesoaccumbens dopamine system may represent novel treatment strategies to prevent relapse to tobacco use.

7. Habenular circuits in tobacco dependence

Evidence has accumulated over the past 15 years implicating the MHb-IPN circuit in the motivational properties of nicotine and other addictive drugs. The habenula is a diencephalic structure that is comprised of two anatomically and functionally distinct medial (MHb) and lateral (LHb) subnuclei [152]. The LHb receives prominent inputs from limbic, basal ganglia, midbrain, and cortical regions, and sends reciprocal projections to many of these same regions. In contrast, the MHb receives input almost exclusively from just a few regions of the septum, and projects almost exclusively to the IPN [152]. The MHb contains a large population of acetylcholine-producing neurons and contains some of the highest densities of nAChRs in the brain [153]. In particular, the expression of $\alpha 3$, $\alpha 5$, and $\beta 4$ subunits are highly enriched in the MHb-IPN circuit [154]. As mentioned above, RNA interference-mediated knockdown of $\alpha 3$ or $\alpha 5$ nAChR subunits in the MHb-IPN circuit attenuated the aversive effects of nicotine and increased nicotine self-administration behavior in rats [75]. Evidence suggests that the vesicular transporters for acetylcholine and glutamate are co-localized within synaptic vesicles of MHb axonal terminals in the IPN, and that acetylcholine and glutamate are co-released in the IPN [155]. Notably, the elimination of acetylcholine in MHb neurons by the conditional deletion of the acetylcholine-synthesizing enzyme choline acetyltransferase (ChAT) led to a reduction in the amplitude of miniature excitatory post-synaptic potentials (mEP-SCs) and deceased the vesicular content of glutamate but did not affect nicotine-evoked responses in IPN neurons [155], reflecting a reduction in acetylcholine-glutamate co-release. Moreover, nicotine-induced increases in mEPSC frequency were absent in ChAT-KO mice, indicating a decrease in the function of presynaptic nAChRs [155]. Together, these findings demonstrate that acetylcholine facilitates the packaging of glutamate into synaptic vesicles and glutamate transmitter release through the activation of presynaptic nAChRs in the MHb. These acetylcholine-dependent actions may explain the reduction of nicotine dependence in ChAT-KO mice [155]. These findings support that in addition to glutamate neurotransmission within the mesolimbic circuit, glutamate neurotransmission in the MHb-IPN circuit is also an important mediator of the reinforcement-related actions of nicotine. Hence, pharmacological agents that modulate MHb-derived cholinergic and/or glutamatergic transmission in the IPN may represent novel classes of smoking cessation agents. Specifically, pharmacological agents that modify the activity of the MHb-IPN circuit could promote avoidance of

nicotine contained in tobacco smoke and thereby facilitate smoking cessation efforts. Therefore, identification of other "druggable" receptors that are expressed by neurons in the MHb-IPN circuit could serve as targets for development of smoking cessation agents. Using microarray-based RNA profiling to characterize gene expression it was reported that neurons in the MHb densely express the orphan G-protein–coupled receptor (GPCR) GPR151 [156]. Subsequently, Ibanez-Tallon and colleagues used Translating Ribosome Affinity Purification (TRAP) to profile the transcriptomes of MHb cholinergic neurons and confirmed that GPR151 is very densely and almost exclusively expressed MHb cholinergic neurons in rodent and human brain [157], with modest expression also detected in the dorsal root ganglion [158]. The concentrated expression of GPR151 in the MHb has been confirmed by other groups [159,160]. Using electron microscopy, it was reported that GPR151 accumulates at the presynaptic terminals of MHb neurons in the IPN in close proximity to the synaptic "active zones", thereby positioning GPR151 to regulate MHb-derived neurotransmitter release into the IPN [157]. It was also shown that GPR151 colocalizes nAChRs on the terminals of MHb neurons in the IPN [157]. Most importantly, GPR151 knockout mice were shown to self-administer greater quantities of nicotine than their wild-type littermates [157]. Hence, pharmacological agents that enhance the activity of GPR151 in the MHb-IPN circuit may decrease the motivational properties of nicotine and thereby have clinical utility for the treatment of tobacco use disorder.

8. Immune-based therapeutics for smoking cessation

A novel approach to treating tobacco dependence is to recruit the immune system to sequester or degrade nicotine before it can exert its pharmacological actions in the brains of smokers [161]. Vaccines have been developed by several groups that stimulate the immune system to produce antibodies that recognize and bind to nicotine; for example, see [162–164]. Several vaccines and have shown promise as smoking cessation in rodent studies of nicotine reinforcement [162–167]. However, the development of a safe and effective vaccine for smoking cessation in humans has proven to be challenging. For example, NicVAX is a nicotine vaccine developed by Nabi Biopharmaceuticals that attenuated many addiction-related physiological and behavioral responses to nicotine in rodents but failed to meet its primary endpoint in a phase III clinical trial of its utility as a smoking cessation agent [168–170]. There is continued interest in developing a vaccine for smoking cessation, and several new approaches are being explored including the use adjuvants to enhance the immune response to a vaccine [171–173]. Novel non-vaccine strategies are also being pursued to sequester and/or metabolize nicotine at sufficiently high levels to prevent behaviorally relevant amounts of the drug from reaching the brain of human smokers. For example, skin grafts harbouring cells that have been gene-edited using CRISPR to secrete enzymes that rapidly metabolize drugs of abuse such as cocaine have been developed [174]. Skin grafts that secrete agents that reduce the motivation to consume nicotine and other drugs of abuse, such as glucagon-like peptide 1 (GLP-1), have also been developed [175,176]. These skin grafts have shown promise as therapeutics strategies for the treatment of substance use disorders in laboratory rodents [174]. The work points to the exciting possibility of developing cutaneous gene-therapy strategies as safe and effective treatments for tobacco use disorder [177].

9. Future approaches for the identification of therapeutic targets for smoking cessation

In addition to the targets highlighted in this article, which have compounds that are in development or clinical assessment as smoking cessation therapeutics, there is on-going research into discovering additional mechanisms that may be beneficial for the treatment of tobacco use disorder and other substance use disorders. There is clear evidence for a robust genetic component to tobacco dependence, although the specific genes mediating risk have not yet been fully characterized. Nevertheless, findings from GWAS over the past decade have begun to elucidate potential genes associated with the risk for nicotine addiction, although the identified genes typically contribute only a small amount to the overall risk, highlighting the complexity of the phenotype [178]. Indeed, the genetic basis of addiction may be influenced by several hundred genes comprising the risk for addiction. Genetic variations in addiction-relevant genes can also influence the effectiveness of smoking cessation treatments. Thus, identifying risk-associated genes and understanding how they influence vulnerability to tobacco use disorder using animal models, postmortem human brain tissue, and neurons and brain-like organoids derived from human induced pluripotent stem (IPS) cells will likely yield new strategies for medications development. Innovative techniques such as single cell RNA sequencing and spatial transcriptomics, which can provide transcriptional information with unprecedented cellular and brain regions resolution, will enable future studies to identify the genes involved in nicotine dependence-related neuroplasticity and thereby influence risk of tobacco use disorder. Hence, a better understanding of the genetic and transcriptional mechanisms involved in nicotine dependence will be crucial for the identification of novel targets for smoking cessation therapies.

In addition to genetic mechanisms of drug addiction, promising research has implicated a role of microRNAs (miRNA) and other classes of noncoding RNAs that can regulate the expression and/or translation of protein-coding gene transcripts in the mechanism underlying substance use disorders. Previous studies have established a role of miRNAs in the development of dependence on cocaine and alcohol [179]. The contributions of miRNA to nicotine dependence have been less well studied, but a few reports have demonstrated that miR-140–5P regulates the expression of specific genes encoding proteins and receptors important in mediating addiction-related responses to nicotine, including the dopamine D1 receptor and Dynamin-1, a protein that binds to the nAChR β2 subunit. Moreover, neuron-specific miRNAs have been shown to be secreted into the bloodstream in response to tobacco. Several human studies have also reported differences in the expression of specific miRNAs between smokers and nonsmokers. Thus, miRNAs may be useful as biomarkers for addiction in the future. Another example of a novel direction for smoking cessation treatments is targeting neuroimmune mechanisms. Although changes in neural function induced by drug exposure have historically been the focus of substance use disorder research, increasing evidence indicates that glial cells, including microglia and astrocytes, are also impacted by exposure to addictive drugs and may play a role in the behavioral consequences of substance use. There is strong evidence to suggest that addictive compounds such as opioids can lead to increases in surface markers indicative of

glial activation and increase the expression of neuroimmune signaling molecules including pro-inflammatory cytokines [180]. Recent evidence also indicates that nicotine may alter astrocyte morphology through nAChRs [180]. These glial responses to nicotine and other drugs of abuse could influence neuronal function through a number of mechanisms, including structural remodeling or through cytokine and chemokine signaling [181]. Thus, there is a significant need for future studies to investigate the role of microglia and astrocytes in drug self-administration paradigms, which may identify new avenues of therapeutic approaches to treating nicotine addiction as well as other substance use disorders.

10. Conclusions

Despite considerable research efforts over the past two decades, tobacco dependence remains a significant public health concern. Evidence suggests that pharmacotherapy is an effective approach to facilitate smoking cessation, although there is a pressing need to develop new medications with improved efficacy, tolerability, and side effect profiles. Importantly, findings from preclinical animal models and human clinical studies highlight that for tobacco use disorder is complex and multifaceted and influenced by a plethora of variables including genetic factors, sex of the subject, history of drug use, and comorbid neuropsychiatric conditions. Hence, it is unlikely that a “silver bullet” approach exists for the treatment of tobacco use disorder. Accumulating evidence supports the benefits of personalized medicine, wherein smoking cessation treatments are tailored to the specific symptoms and characteristics of the individual seeking treatment. Further research into identifying potential biomarkers of relapse risk, such as hypocretin levels, will be useful for mitigating relapse rates in smokers attempting to quit. Moreover, a better understanding of the interactions between specific genes that contribute to the risk for nicotine addiction and the efficacy of smoking cessation treatments could allow for more effective treatment approaches targeted to individuals with certain genetic phenotypes (e.g., *OPRM1* gene haplotypes).

Our understanding of the mechanisms of nicotine addiction has improved significantly over the past decade. We now have strong evidence that several signaling systems including hypocretin, endogenous opioids, glutamate, and GABA all contribute to the addictive actions of nicotine. These findings have led to the development of novel compounds that have shown to be effective in regulating nicotine-relevant behaviors. A promising new approach to pharmacological treatment for nicotine addiction is the use of allosteric modulators at addiction-relevant targets, such as mGluR2/5 and $GABA_B$ receptors, which display better target specificity and fewer adverse side effects compared with agonists and antagonists. These novel compounds have shown promise in decreasing nicotine self-administration and relapse to nicotine-seeking behaviors in animal models and are now beginning to be evaluated for their efficacy in clinical trials. The findings from these clinical studies will confirm whether these compounds may be a viable approach to facilitate smoking cessation. Thus, these recent advances in our knowledge of the neural mechanisms of nicotine addiction will hopefully translate into new and more effective smoking cessation medications.

Data availability

No data was used for the research described in the article.

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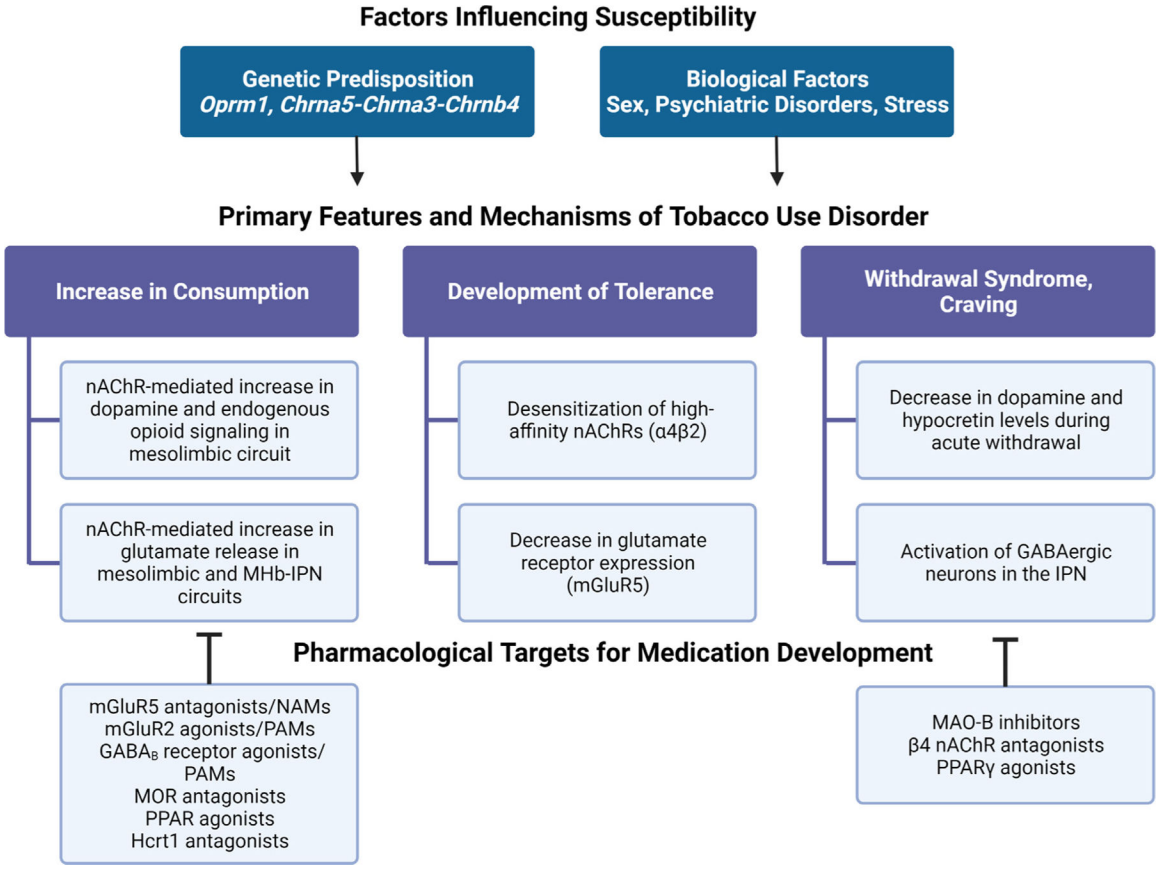

Fig. 1.

Summary of factors that influence vulnerability to tobacco use disorder and opportunities for new medications development. GABA, ϒ-aminobutyric acid; Hcrt1, hypocretin receptor 1; IPN, interpeduncular nucleus; MAO-B, monoamine oxidase B; mGluR; metabotropic glutamate receptor; MHb, medial habenula; MOR, mu opioid receptor; nAChR, nicotinic acetylcholine receptor; NAM, negative allosteric modulator; PAM, positive allosteric modulator; PPAR, peroxisome-proliferator-activated receptor.

Table 1

Compounds that have been shown to alter behaviors relevant to nicotine seeking in laboratory animals.

Compound	Mechanism of Action	Behavioral findings in animal models	Citation
Naltrexone/naloxone	MOR antagonist	Naloxone produced a conditioned place aversion in rats chronically treated with nicotine.	[20]
SB-334,867	Hypocretin receptor 1 antagonist	SB-334,867 decreased nicotine self-administration in rats; pre-treatment with SB-334,867 blocked hypocretin-induced and cue-induced reinstatement of nicotine seeking behavior.	[21–23]
LY314582	mGluR2 agonist	Infusion into the VTA of nicotine-dependent rats precipitated withdrawal-like increases in ICSS reward threshold.	[24–26]
AZD8418, AZD8529	mGluR2 PAMs	Decreased nicotine self-administration and cue-induced reinstatement of nicotine-seeking behavior in rats.	[27,28]
MPEP	mGluR5 NAM	Decreased nicotine self-administration and reinstatement of nicotine-seeking behavior.	[29–31]
CGP44532	$GABA_B$ receptor agonist	Decreased nicotine self-administration in rats.	[32,33]
CGP7930, BHF177, GS39783, KK-92A	$GABA_B$ receptor PAMs	Attenuated nicotine-self administration and cue-induced nicotine-seeking behavior.	[32,34,35]
Clofibrate	$PPAR_{\alpha}$ agonist	Clofibrate abolished nicotine self-administration in both naïve rats and those with a history of self-administering nicotine.	[36]
Pioglitazone	$PPAR_{\gamma}$ agonist	Pioglitazone attenuated somatic and affective symptoms of nicotine withdrawal in rats and mice.	[37]

Table 2

Novel compounds in clinical testing for smoking cessation.

Compound	Mechanism of Action	Sponsor	Status	Phase
Suvorexant	Hcrt1/2 receptor antagonist	University of Texas Health Science Center	Recruiting	Phase 1
Baclofen	$GABA_B$ receptor agonist	University of Pennsylvania	Completed	Phase 2
Naltrexone	MOR antagonist	University of Chicago	Completed	Phase 2
Naltrexone combined with Bupropion	MOR antagonist and antidepressant	Yale University	Completed	Phase 2
Selegiline	MAO-B Inhibitor	NIDA	Completed	Phase 2
AZD8529	mGluR2 PAM	NIDA	Completed	Phase 2
Gemfibrozil	PPARα agonist	University of Texas	Completed	Phase 2
S-adenosyl-L-Methionine (SAMe)	Facilitates monoamine synthesis	Mayo Clinic	Completed	Phase 2/3