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Optimizing treatments for nicotine dependence by increasing cognitive performance during withdrawal

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Abstract

Introduction—Current FDA-approved smoking cessation pharmacotherapies have limited efficacy and are associated with high rates of relapse. Therefore, there is a clear need to develop novel antismoking medications. Nicotine withdrawal is associated with cognitive impairments that predict smoking relapse. It has been proposed that these cognitive deficits are a hallmark of nicotine withdrawal that could be targeted in order to prevent smoking relapse. Thus, pharmacotherapies that increase cognitive performance during nicotine withdrawal may represent potential smoking cessation agents.

Areas covered—The authors review the clinical literature demonstrating that nicotine withdrawal is associated with deficits in working memory, attention and response inhibition. They then briefly summarize different classes of compounds and strategies to increase cognitive performance during nicotine withdrawal. Particular emphasis has been placed on translational research in order to highlight areas for which there is strong rationale for pilot clinical trials of potential smoking cessation medications.

Expert opinion—There is emerging evidence that supports deficits in cognitive function as a plausible nicotine withdrawal phenotype. The authors furthermore believe that the translational paradigms presented here may represent efficient and valid means for the evaluation of cognitive-enhancing medications as possible treatments for nicotine dependence.

Keywords

cognition; nicotine; reinstatement; relapse; self-administration; smoking; tobacco; withdrawal

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Declaration of interest

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1. Background

More than 400,000 people die annually of smoking-related illnesses in the USA [1]. Despite this enormous public health problem, only 3% are able to quit smoking successfully [2]. More than half of smokers try to quit each year, and approximately one-third use medication to assist their quit attempt. There are currently three FDA-approved pharmacological treatments for nicotine dependence: nicotine replacement therapy (NRT), bupropion and varenicline. However, among those treated with varenicline, 44% are abstinent at the end of treatment, and at 6 months, this number drops to 27%. Abstinence rates for combination NRT (e.g., patch plus inhaler) at 6 months are only slightly higher at 32% [3]. Therefore, there is a critical need to develop novel, efficacious pharmacotherapies for smoking cessation. The majority of smokers who relapse, do so during the first week of a quit attempt [4,5]. Moreover, the ability to maintain smoking abstinence during the first week of a quit attempt is a strong predictor of success at end of treatment and at 6 months [6]. Thus, the early withdrawal period is a vulnerable time for most smokers and represents a critical window in which to evaluate novel smoking cessation treatments.

The nicotine withdrawal syndrome is complex as the time course and nature of symptoms vary across smokers. In nicotine-dependent smokers, abstinence produces a variety of physiological, psychological and cognitive symptoms. One approach to further our understanding of nicotine dependence and identify novel pharmacotherapies is to dissect the withdrawal syndrome into its component symptoms in order to target research on more focused core phenotypes [7,8]. Increasingly, attention has focused on cognitive impairments that emerge during smoking abstinence. Indeed, there is a high prevalence of cognitive deficits among treatment-seeking smokers that may predict relapse. Although the mechanisms that mediate nicotine withdrawal-induced cognitive impairments are not clear, evidence suggesting that higher order cognitive control is critical for maintaining goal-directed behaviour [9,10] and may provide a theoretical framework for explaining why cognitive deficits may be associated with smoking relapse.

In this review, we highlight the neurobiological, preclinical and clinical evidence supporting cognitive enhancers as promising candidates for smoking cessation. First, we will discuss evidence supporting the repurposing of pharmacotherapies that may enhance cognition in disorders that share cognitive symptoms with nicotine withdrawal (Table 1). Next, we will review the translational approaches for testing novel treatments using animal, human and neuroimaging paradigms. Specifically, we review human laboratory models of smoking relapse, which focus on the critical early withdrawal period. These models may represent more efficient methods for screening novel medications and provide a means for testing mechanisms of a medication's efficacy [8,11,12]. We conclude with a discussion of the potential for this strategy to facilitate the development of novel treatments for nicotine dependence, challenges and limitations to this approach and recommendations for future research.

2. Potential treatments for nicotine withdrawal-induced cognitive deficits

2.1 Drugs that modulate cholinergic transmission

Smoking cessation and nicotine withdrawal are associated with drug craving and cognitive impairments [13]. A growing literature indicates that cognitive deficits represent a core symptom of nicotine withdrawal that predict relapse during abstinence [14]. Thus, it has recently been proposed that cognitive-enhancing medications may prevent drug craving and relapse, in part, by reversing or normalizing nicotine withdrawal-induced cognitive impairments [15,16]. Consistent with these findings, nicotine re-exposure [17,18] and administration of the α4β2* nicotinic acetylcholine receptor (nAChR) partial agonist and α7 nAChR full agonist varenicline [19,20] reverse abstinence-induced cognitive deficits and blunt relapse in both humans and rodents. Taken together, these findings suggest that other cognitive-enhancing drugs that increase endogenous acetylcholine levels and/or cholinergic transmission in the brain may prevent smoking relapse.

2.1.1 nAChR agonists—Nicotine is the principal psychoactive chemical in tobacco that mediates tobacco's reinforcing effects [21]. Nicotine binds to and stimulates nAChRs, ligand-gated ion channels activated by the endogenous neurotransmitter acetylcholine. Twelve nAChR subunits have been identified in the brain (α2 – α10, β2 – β4). These subunits combine to form cation channels. The most abundant nAChRs in the brain are heteromeric α4- and homomeric α7-containing receptors [22]. There is clear evidence that α4β2* nAChRs play a critical role in nicotine addiction [23-25]. Recent studies have also demonstrated that nAChRs containing α4, α5 and α6 subunits also mediate nicotine reinforcement [23]. In contrast, studies examining the functional significance of α7-containing nAChRs in nicotine dependence have yielded mixed results [23]. Due to an extensive literature demonstrating a role for α4β2* nAChRs in nicotine taking, the majority of drug discovery programs aimed at identifying novel nAChR-based pharmacotherapies for smoking cessation have focused on compounds that target α4β2* nAChRs.

nAChR agonists substitute for the reinforcing effects of nicotine, alleviate some of the adverse symptoms associated with nicotine withdrawal and are generally well tolerated [26]. While NRTs have been the mainstay of smoking cessation pharmacotherapies, partial agonists of nAChRs have gained increasing attention as potential treatments for smoking relapse. Compared to full agonists, partial agonists produce less than maximal stimulation of nAChRs thereby substituting for the reinforcing effects of smoking with less abuse liability. Partial agonists of nAChRs also function as antagonists in that they reduce nicotine reinforcement and nicotine-evoked neurotransmitter release in the brain.

Varenicline is an α4β2* nAChR partial agonist and full agonist at α7 nAChRs that fully substitutes for nicotine in drug discrimination studies and attenuates nicotine taking and seeking in rats [27,28]. Varenicline increases cognitive performance during smoking abstinence and reduces the subjective rewarding effects of nicotine in humans [20,29,30]. Despite these effects, approximately one in four smokers successfully maintain long-term abstinence when treated with varenicline [3,31]. Moreover, varenicline treatment is associated with adverse events including depressed mood and suicidal ideation in some patients [32]. Varenicline, similar to nicotine, increases expression and desensitization of

α4β2* nAChRs in the brain. These processes are thought to facilitate persistent smoking behaviour and smoking relapse [33,34]. It has been proposed that the limited efficacy of varenicline for smoking cessation is due, in part, to increased expression and desensitization of nAChRs [33,34].

Sazetidine-A is a partial agonist that binds selectively to α4β2* nAChRs with high affinity, which results in desensitization of these receptors [35]. Sazetidine-A administration attenuates nicotine self-administration and increases cognitive performance in rats [36,37]. Unlike varenicline and nicotine, sazetidine-A administration desensitizes α4β2* nAChRs without a concomitant increase in α4β2* nAChR expression in the brain [33]. If increased expression of α4β2* nAChRs is a critical neuroadaptation that promotes smoking relapse and limits the efficacy of varenicline for smoking cessation then nAChR partial agonists such as sazetidine-A that do not increase α4β2* nAChR expression may be more efficacious smoking cessation medications. Future clinical studies are needed to investigate the efficacy of sazetidine-A in treatment-seeking smokers.

α7 nAChRs have a clear role in cognition [38] and modulators of α7 nAChRs are currently being investigated as treatments for cognitive dysfunction. For example, the α7 antagonist ABT-126 is currently being investigated for attenuating cognitive symptoms in Alzheimer's disease (NCT01527916) and schizophrenia (NCT01678755). In addition, one study demonstrates beneficial effects of TC-5619, an α7 agonist, on cognitive dysfunction in schizophrenia. Interestingly, these effects are more pronounced in smokers with schizophrenia [39]. EVP-6124 is an α7 partial agonist that improves cognition in patients with Alzheimer's disease [40] and is currently being investigated as a smoking cessation aid (NCT01480232). However, it is important to note that cognitive deficits observed in patients with Alzheimer's disease and schizophrenia are likely to be distinct from nicotine withdrawal-induced cognitive impairments. Thus, therapeutic responses (i.e., improved cognitive performance) in these patient populations may not be predictive of efficacy in smoking cessation trials.

2.1.2 Acetylcholinesterase inhibitors—Acetylcholinesterase inhibitors (AChEIs) increase extracellular levels of acetylcholine in the brain and augment cholinergic transmission through inhibition of acetylcholinesterase, a catabolic enzyme responsible for metabolizing acetylcholine in the synapse. Galantamine and donepezil are two AChEIs that are FDA-approved for treating cognitive impairments associated with mild-to-moderate Alzheimer's disease [41]. Given that one hallmark of nicotine withdrawal is cognitive impairments, AChEIs may improve nicotine withdrawal symptoms in abstinent smokers and prevent smoking relapse. Consistent with this hypothesis, recent preclinical studies demonstrate that acute galantamine or donepezil administration during withdrawal attenuates the reinstatement of nicotine of nicotine-seeking behaviour, an animal model of relapse [42,43]. Moreover, galantamine administration improves cognitive performance following nicotine withdrawal in mice [44]. Taken together, these studies are provocative and suggest that AChEIs could be repurposed as pharmacotherapies for smoking cessation.

Although there has been great interest in prescribing cognitive enhancers, including AChEIs, for treating drug addiction and/or drug-associated cognitive deficits, there is a paucity of

clinical data directly assessing the efficacy of AChEIs and other cognitive enhancing compounds on drug-seeking and withdrawal-induced cognitive deficits [16]. Preliminary studies indicate that AChEI administration increases cognitive performance in non-treatment-seeking smokers [45,46]. AChEIs also partially substitute for the discriminative stimulus properties of nicotine in humans [46] and rats [47]. Although these findings suggest that AChEIs may prevent smoking relapse, studies examining the effects of AChEIs on tobacco craving and smoking behaviour are mixed [45,46,48-50]. These conflicting clinical results are likely due to different patient populations (i.e., genetic variability, neuropsychiatric disorders, etc), comorbid drug use and small sample sizes. Therefore, the efficacy of AChEIs in treating smoking relapse remains to be defined in healthy, treatment-seeking smokers without comorbidities.

2.1.3 Positive allosteric modulators of nAChRs—In addition to inhibiting acetylcholinesterase, galantamine also functions as a positive allosteric modulator (PAM) of α7 homomeric and α4β2* heteromeric nAChRs [51]. PAMs bind nAChRs at allosteric sites that are distinct from the binding sites for nicotine and acetylcholine. The binding of PAMs to nAChRs facilitates nicotine- and acetylcholine-evoked receptor responses [52]. PAMs of nAChRs have recently been proposed as potential smoking cessation medications based on studies demonstrating that hypofunction of nAChRs is associated with increased smoking rates [53].

PAMs of α7 and α4β2* nAChRs increase cognitive performance in drug-naive rats [54,55]. These findings suggest that PAMs of α7 and α4β2* nAChRs may reverse nicotine withdrawal-induced cognitive deficits and attenuate nicotine seeking. No studies, however, have examined the role of PAMs of α7 and α4β2* nAChRs on cognitive function and the reinstatement of nicotine seeking during nicotine withdrawal. A recent study demonstrated that systemic administration of a PAM of α4β2* nAChRs attenuated nicotine self-administration in rats [56]. Although these results suggest that PAMs of α4β2* nAChRs may attenuate nicotine consumption in humans, more studies are needed to determine the effects of PAMs of nAChRs on aberrant behavioural phenotypes during withdrawal.

2.2 Glutamatergic agents

The neurotransmitter glutamate plays an important role in learning and memory [57]. There is also evidence that nicotine enhances the release and function of glutamate, particularly in brain regions important for cognitive function including the prefrontal cortex (PFC) [58]. Of the several types of glutamatergic receptors, the NMDA receptors are thought to be integral to learning processes [57]. For example, memantine, which is FDA-approved for the treatment of cognitive deficits in patients with Alzheimer's disease, is a noncompetitive antagonist at the NMDA receptor and blocks the serotonin type 3 receptor ($5\text{-}HT_3$) and nAChRs [59]. A recent meta-analysis concluded that memantine improved cognition and clinician's global impression in patients with Alzheimer's disease [60]. Although it is not clear whether memantine improves cognitive performance in healthy adults [61], memantine attenuated nicotine self-administration in rats [62] and decreased the subjective effects of cigarette smoking in adult smokers [63]. Another study found no effect of memantine on cognition or smoking behaviour [63]. There is also evidence that combined treatment of

memantine and AChEIs may be more effective at reducing cognitive decline in Alzheimer's patients [64]. Compounds such as MDX-8704, which is a fixed-dose combination of memantine and donepezil from Adamas pharmaceuticals, are being investigated for Alzheimer's disease. Thus, combined pharmacotherapy may be a useful strategy to explore for nicotine dependence treatment.

D-Cycloserine (DCS) is an antibiotic that acts as a partial agonist of the NMDA receptor. More recently, it has been studied for its role in promoting extinction of conditioned fear responses in patients with anxiety disorders [65]. To date, the majority of clinical research with DCS has demonstrated efficacy for treating obsessive–compulsive disorder and post-traumatic stress disorder [66]. However, several preclinical studies found that DCS enhanced function in other cognitive domains including working memory and episodic-like memory [67,68]. A few studies have begun to investigate the role of DCS in nicotine dependence. For instance, DCS attenuated nicotine self-administration in rats with low-baseline levels of self-administration suggesting that DCS may be most effective for helping lighter smokers to quit smoking [69]. In humans, DCS reduced reactivity to smoking cues and cigarette cravings but exerted little effect on smoking behaviour [70]. In another study, when DCS was combined with smoking, it improved response inhibition but not attention or cognitive flexibility [71]. DCS also had differential effects on the subjective symptoms of smoking depending on whether smokers were in a nicotine-deprived or satiated state [71]. It is possible that DCS only improves specific domains of cognitive function, although this hypothesis warrants further exploration. Furthermore, DCS may be most efficacious when given to smokers prior to a quit attempt and used in combination with another cholinergic medication (e.g., varenicline).

2.3 Adrenergic agents

2.3.1 α_2 adrenergic receptor agonists—There is strong evidence that the adrenergic system is critical in cognitive function [72]. Guanfacine, an α_2 adrenergic (α_2A) receptor agonist, improves working memory performance in nonhuman primates and humans [73]. Guanfacine was FDA-approved for treating symptoms of attention-deficit/hyperactivity disorder (ADHD) in 2009 [74] and has been shown to attenuate stress responses and improve multiple domains of cognition, including spatial working memory, behavioural flexibility and reversal learning [75]. Using a laboratory paradigm of stress-precipitated smoking, guanfacine reduced smoking behaviour and craving, enhanced PFC activity associated with improved attention and self-control and improved treatment outcome during a brief follow-up period [76]. Although larger clinical trials are necessary to replicate these results, these data suggest stimulation of α_2A receptors may be a useful strategy for nicotine dependence.

In addition, clonidine is an α_2A agonist that also binds to the 2B and 2C receptors. It is FDA-approved for the treatment of ADHD and demonstrates beneficial effects on inattention and hyperactive/impulsive symptoms [77]. Initial evidence also supports its efficacy as a smoking cessation medication, at least among women [78]. However, the unfavorable side-effect profile of clonidine limits its use and there is at least some evidence that it may impair cognition among nonsmoking control subjects [79]. Future studies of

smoking cessation may focus on newer adrenergic receptor agonists, such as AR08 from Arbor pharmaceuticals, which is currently being investigated as a treatment for ADHD (NCT01876719).

2.3.2 Norepinephrine reuptake inhibitors—The norepinephrine reuptake inhibitor, atomoxetine, is also an approved treatment for ADHD and has been shown to improve response inhibition in both healthy controls [80] and individuals with ADHD [81,82]. Although initial studies in mice indicated that atomoxetine may attenuate nicotine withdrawal-induced deficits in contextual fear conditioning [83], it had no effect on withdrawal-related attentional deficits or smoking behaviour in a placebo-controlled human laboratory study of smokers following overnight abstinence [84,85]. Nortriptyline, a tricyclic antidepressant, which acts as a norepinephrine and serotonin reuptake inhibitor, has demonstrated some efficacy for smoking cessation [86], but another norepinephrine reuptake inhibitor, venlafaxine, had no effect on abstinence [87]. These equivocal findings may be partially explained by the fact that, similar to dopamine, norepinephrine has an inverted U-like relationship with PFC function. That is, either too much or too little norepinephrine may impair function. Prolonged elevation of norepinephrine levels during chronic stress may contribute to deficits in cognition and blockage of norepinephrine receptors may reverse stress-induced cognitive deficits [88]. Thus, the effects of atomoxetine and other adrenergic agents may be dose-dependent and this may partially explain the mixed effects observed on cognitive performance. One direction for clinical research may be to establish a dose-response curve to evaluate whether there is an optimal dose at which atomoxetine may be an efficacious smoking cessation medication.

3. Translational strategies for designing and optimizing nicotine dependence treatment

Thus far, we have reviewed several classes of medications that have demonstrated: i) some efficacy for either improving cognitive function under certain conditions (e.g., stress) or in particular groups (e.g., patients with ADHD); and ii) have some impact on the cholinergic system suggesting they may have some impact on smoking behaviour. The majority of the medications reviewed above have undergone rigorous testing for safety and tolerability prior to FDA approval. Repurposing medications that have been ‘de-risked’ through prior development removes a key reason for drug failure (i.e., safety) and substantially reduces the time and cost associated with typical drug development strategies [89]. Below, we review translational approaches for evaluating novel treatments for nicotine dependence. We begin with preclinical studies that are critical for examining the neurobiological mechanisms underlying nicotine taking and seeking, identifying novel targets for drug discovery programs aimed at developing smoking cessation medications and screening potential smoking cessation pharmacotherapies. We then review strategies for translating preclinical data for the development of clinical studies to evaluate the efficacy of novel treatments in humans.

3.1 Preclinical models of nicotine addiction

3.1.1 Nicotine self-administration and the reinstatement of nicotine seeking-behaviour—The overarching goal of translational research focused on identifying medications for nicotine addiction is to screen novel therapeutics for potential efficacy in preclinical animal models before proceeding to more costly clinical trials in human smokers. The rat nicotine self-administration model has played a critical role in understanding the biological mechanisms underlying nicotine addiction. Drug self-administration is a behavioural paradigm used commonly to measure the reinforcing effects of nicotine. Briefly, nicotine self-administration requires that an animal perform an operant response (i.e., pressing a lever) in order to obtain a drug infusion. While nicotine self-administration studies in human subjects typically study cigarette-smoking behaviour, the majority of nicotine self-administration studies in rodents utilize an intravenous route of administration. Intravenous self-administration is used primarily because this route simulates the rapid rise in arterial nicotine and rapid distribution of nicotine to the brain that occurs via the typical pulmonary route of exposure in humans [90]. Despite procedural differences, data from both human and rodent self-administration studies depict an inverted U-shaped dose-response curve, with maximal rates of responding occurring at intermediate doses of nicotine [91]. Nicotine self-administration has the highest degree of face validity of all animal models of nicotine addiction primarily because it mimics voluntary tobacco consumption in humans [8]. Plasma nicotine levels are similar in animals self-administering nicotine and human tobacco smokers, further validating this animal model of nicotine addiction [92]. Furthermore, the predictive validity associated with nicotine self-administration and the effectiveness of smoking cessation medications appear to be relatively high [8]. For example, all three FDA-approved treatments for smoking cessation decrease nicotine self-administration in rodents [93-95]. Finally, it is thought that nicotine self-administration has good construct validity and an emerging literature indicates that changes in dopaminergic, cholinergic, GABAergic, glutamatergic, serotonerigc, and cannabinoid systems mediate the reinforcing effects of nicotine in humans and laboratory animals [96].

Drug craving and relapse of drug-taking behaviour in humans are precipitated by three major factors: a stressful life-event, an environmental stimulus previously associated with drug taking or re-exposure to the drug itself [97]. Relapse in humans is typically modeled in animals as follows: following a period of drug self-administration and the subsequent extinction of the drug reinforced behaviour, the ability of stress, drug-associated stimuli or re-exposure to the drug itself to reinstate drug seeking is assessed [97]. For example, following extinction of nicotine self-administration, systemic injections of relatively low doses of nicotine or cues previously paired with nicotine taking reinstate operant responding in the absence of drug reinforcement in rodents [42,43]. The rein-statement model's validity as an *in vivo* medication screen appears promising for relapse to nicotine taking [98]. For example, varenicline administration attenuates nicotine seeking in rats [28,99].

3.1.2 Preclinical models of nicotine withdrawal-induced cognitive deficits—As reviewed above, cognitive deficits are a hallmark of nicotine withdrawal that may promote smoking relapse. Therefore, it has been proposed that cognitive-enhancing drugs may attenuate nicotine seeking by improving cognitive deficits during periods of smoking

abstinence [16]. Previous studies examining the effects of nicotine withdrawal on cognition utilized subcutaneous osmotic minipumps to deliver chronic nicotine [44,100,101]. Continuous delivery of nicotine in rodents does not model pulsatile delivery in human smokers and produces neuroadaptations in the brain that are distinct from episodic smoking [102] and nicotine self-administration [103]. Therefore, nicotine self-administration in rats is a more homologous model of voluntary nicotine taking in humans and cognitive deficits that appear during withdrawal from nicotine self-administration are more likely to model cognitive deficits in abstinent human smokers.

While rat nicotine self-administration studies clearly demonstrate withdrawal-induced changes in behaviour as measured by overt somatic signs of withdrawal [104], changes in intracranial self-stimulation thresholds [105] and anxiety [106], no studies have examined withdrawal-induced cognitive deficits in rats following voluntary nicotine self-administration. Withdrawal following continuous nicotine exposure via osmotic minipumps in mice results in cognitive impairments that are reversed/normalized by increased nAChR signaling in the brain [17]. Moreover, administration of galantamine improves cognitive performance following nicotine withdrawal in mice [44]. Markou and colleagues have shown that nicotine withdrawal is associated with increased impulsivity [107] and deficits in attention [108] in rats. These studies, however, are limited in that osmotic minipumps were used to deliver continuous nicotine and, therefore, do not model voluntary, episodic nicotine consumption in human smokers. Thus, there is a clear need for preclinical models of withdrawal-induced cognitive deficits following nicotine self-administration that can be used to screen the efficacy of cognitive-enhancing compounds to reverse/normalize theses impairments.

3.2 Clinical

3.2.1 Laboratory studies of acute nicotine withdrawal—A necessary step in evaluating potential novel treatments is to examine whether they attenuate cognitive deficits during nicotine withdrawal. Many human laboratory paradigms have been developed to test a variety of cognitive functions after some period of withdrawal. Typically, the duration of abstinence ranges from overnight (~ 9 – 12 h) to 24 h [109,110], although some have required smokers to undergo longer periods of abstinence (e.g., up to 72 h [111]). Because the majority of smokers who make a quit attempt relapse within the first week [6], most studies have focused on the early withdrawal period. Thus, one limitation is that little is known about the persistence of cognitive deficits during prolonged abstinence. Furthermore, these laboratory studies often only examine smokers with low motivation to quit smoking, which may reduce the generalizability to the broader population of smokers who want to quit.

Nicotine withdrawal-associated cognitive deficits can be assessed via self-report using standard rating scales [112] or objective measures using computerized tasks that assess executive cognitive function. Objective measures reduce the bias associated with self-report and enhance the translational potential because many of the computerized assessments have been adapted for animal models. We will briefly discuss the most common tasks used in animals and humans (Table 2). For reviews of the effects of nicotine and nicotine

withdrawal on cognitive function, see [34,113,114]. For example, sustained attention, or vigilance, refers to the ability to discriminate between targets and distractors [115]. In humans, attention is commonly assessed with a Continuous Performance Test (CPT) [116] or a Rapid Visual Information Processing [117]. The five-choice serial reaction time task (5-CSRTT) is a commonly used analogue in animals [118]. Working memory is a multi-component process responsible for the active maintenance and manipulation of information [119]. In humans, working memory is often assessed using the *n*-back task [120] and in animals, performance on Morris water maze and radial-arm maze tasks are considered indices of working memory [121]. Response inhibition refers to the ability to inhibit prepotent responses [122]. Assessments of response inhibition in humans include the stop signal task, the go/no-go task and commission errors on a CPT [110,122]. In animals, indices of response inhibition include premature responding on the 5-CSRTT and the more recently developed stop signal task [123]. Recently, a rodent five-choice CPT paradigm was established that is more analogous to the human CPT. Studies of five-choice CPT in rodents and human patients with schizophrenia indicate that this animal model has translational validity and relevance [124,125]. Reversal learning, sometimes referred to as cognitive or behavioural flexibility, requires the ability to adapt to changes in reward contingency and respond to stimuli that were previously not associated with reward. Although less studied than the other domains mentioned, reversal learning paradigms have been developed for animals and humans and have demonstrated clear links with addictive behaviours [126]. Importantly, there is substantial overlap in the assessment of these cognitive domains and their underlying neurocircuitry. Therefore, comprehensive test batteries may help to isolate specific treatment targets.

3.2.2 Laboratory models of smoking relapse—A critical limitation of laboratory studies of cognitive deficits during nicotine withdrawal is that they cannot establish whether medication effects are related to the ability to abstain from smoking. Because Phase III clinical trials are costly and time intensive, human laboratory models of smoking relapse may represent more efficient methods for screening novel medications [8,11,12]. Using early Phase II approaches, these models require smaller sample sizes and shorter duration of testing. Critically, these laboratory paradigms focus on abstinence as an outcome and therefore can provide an early signal for medication efficacy, which can be tested in a clinical trial. This can reduce the likelihood of wasting valuable resources on a large clinical trial. One model, developed by Perkins and colleagues [127-130] focuses on smokers with high motivation to quit using a within-subject crossover design during week-long ‘practice quit attempts’. In this model, smokers undergo a 7-day abstinence period during which they receive small monetary incentives ($15/day) for providing biochemical verification of abstinence. The significance of the week-long quit period is based on evidence that abstinence during the first week is highly predictive of long-term abstinence [6]. This model has been validated using existing treatments for nicotine dependence including NRT, varenicline and bupropion and has demonstrated specificity using ineffective treatments (e.g., modafinil) [127,128,130].

Another model for early medication screening focuses on the ability to resist the first cigarette and subsequent smoking [12]. This model is based on the premise that a ‘slip’,

defined as smoking even one puff of a cigarette that often occurs soon after quitting, is one of the best predictors of smoking relapse [4]. Following exposure to common triggers of smoking relapse (e.g. nicotine deprivation, alcohol, stress), smokers are given the opportunity to smoke or to delay smoking for up to 50 min in exchange for money (e.g., modeling the first 'slip'). Once participants 'give in' (or 50 min passes), smokers are given 60 min to smoke cigarettes or receive money for cigarettes not smoked (e.g., modeling subsequent smoking after the first 'slip'). This model has been validated with evidence that both varenicline and bupropion increased the ability to resist smoking and reduced ad-libitum cigarette consumption, compared with placebo [131]. Both the models described above combine the validity of clinical trials with the practical advantages of laboratory tests and a means for evaluating mechanisms of efficacy [8,11]. For instance, McKee and colleagues found that their model is sensitive to stress- and alcohol-precipitated smoking relapse [132,133]. Furthermore, Perkins and colleagues [130] found that one mechanism of bupropion's efficacy may be attenuation of withdrawal-related cognitive deficits.

3.2.3 Neuroimaging approaches—In addition to the behavioural paradigms reviewed above, advances in neuroimaging techniques may provide a more sensitive test of pharmacological agents to better understand their mechanisms. These strategies include blood-oxygen-level-dependent functional magnetic resonance imaging (fMRI) to examine neural activity associated with treatment targets such as attention, working memory, and response inhibition and positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to estimate receptor availability and neurotransmitter levels in the brain. Although fMRI techniques provide better temporal resolution, PET and SPECT provide a means for examining *in vivo* receptor binding and occupancy. Imaging techniques can be used to characterize brain activation and receptor density patterns that may represent biomarkers that can be used to identify neural pathways from which novel medications can be screened for nicotine dependence or predict treatment outcome. Furthermore, these techniques may also be used to examine individual differences in treatment response to identify those most likely to benefit from a particular treatment. Although a full review of the studies examining the neural substrates of cognitive function during nicotine withdrawal and in response to current treatments is beyond the scope of the present manuscript, for reviews see [134-136].

4. Expert opinion

Despite the clear negative consequences of smoking, the majority of smokers who make a quit attempt fail within the first week. Thus, there is a clear need to identify novel treatments to help more smokers quit smoking. We have focused our review on medications that target cognitive function as a core phenotype of nicotine withdrawal. Although medications that alter cholinergic function may show the most promise, further research is necessary to determine their efficacy at promoting abstinence and their safety profile in smokers. Importantly, we do not suggest that targeting cognitive function is a strategy that will work for all smokers. Rather, we propose that improving withdrawal-related cognitive deficits represents one treatment option. Indeed, one area for future research is to characterize subgroups of smokers most likely to experience cognitive deficits and therefore most likely to benefit from cognitive-enhancing treatments.

Although there is consistent evidence in the preclinical and clinical literature that nicotine withdrawal produces cognitive deficits, an outstanding question is whether treatments that enhance cognition in treatment-seeking smokers also prevent smoking relapse. The evidence from studies with varenicline or NRT suggests that these treatments do have beneficial effects on cognition, but whether improved cognition *mediates* treatment effects has not been determined. It is possible that these medications may prevent or normalize nicotine withdrawal-induced cognitive deficits and have limited efficacy for smoking relapse. If this is the case, these treatments may serve as adjunctive treatments for smoking cessation. That is, cognitive enhancers may facilitate the ability of first-line pharmacotherapies including NRT, varenicline and bupropion to promote smoking cessation. The use of combination pharmacotherapy may also provide a means for individualizing treatment to a particular smoker's needs. This also highlights the importance of individual differences, including genetics and gender, and their role in susceptibility to relapse, withdrawal-induced cognitive deficits and treatment response.

Much of the evidence reviewed here regarding the cognitive enhancing effects of these medications is equivocal and suggests that the effects are small, at best. However, the majority of these studies have not focused on cigarette smokers and it is not clear how smoking may impact the complex interactions among cholinergic, noradrenergic, glutamatergic and estrogen function. Furthermore, chronic smoking has adverse effects on many of these systems, including inflammation. Changes in cognition, particularly among healthy individuals, may be subtle and the current assessments may not be sensitive enough to detect changes. Indeed, the cognitive enhancing effects of the medications reviewed above may be more pronounced in patient populations and may not be predictive of efficacy in smoking cessation trials with smokers without comorbidities. Therefore, we emphasize the importance of translational research in identifying and evaluating novel treatments for nicotine dependence. It is vitally important that: i) preclinical studies identify novel compounds that can be tested in human laboratory paradigms; ii) human imaging studies identify neural substrates that can be evaluated in pre-clinical models; and iii) imaging studies identify biomarkers of treatment response that can be used to develop more sensitive cognitive assessments. Here, we use the role of nAChR subtypes in nicotine withdrawal-induced cognitive deficits as an example of this translational model. Both $\alpha4\beta2$ and $\alpha7$ nAChRs have been shown to play important and differential roles in cognitive performance [34]. Although administration of $\alpha4\beta2$ and $\alpha7$ nAChR antagonists into the hippocampus impairs working memory, these effects are not additive suggesting distinct roles for $\alpha4\beta2$ and $\alpha7$ nAChRs in cognition [137]. In contrast, cognitive deficits produced by administration of an $\alpha7$ nAChR antagonist into the amygdala are blocked by pretreatment with a $\alpha4\beta2$ nAChR antagonist [138]. Thus, there is a clear need to further define the role of specific nAChR subtypes in the neuroanatomy-mediating cognition. One direction for future research would be to evaluate $\alpha7$ and $\alpha4\beta2$ nAChR antagonists using the human laboratory paradigms to examine how nicotine withdrawal impacts performance on a battery of cognitive tasks. This information could then inform brain imaging studies to explore potential biomarkers of treatment efficacy to identify subgroups of smokers most likely to benefit from a particular treatment.

Indeed, more focused translational research programs can expedite identification of novel smoking cessation medications. While preclinical studies can inform clinical trials, animal models of nicotine addiction have limitations and may not recapitulate the addiction process in human smokers. For example, multiple factors including poly-drug use, co-morbid neuropsychiatric disorders and environmental stimuli influence compulsive smoking behaviour and propensity to relapse. While operant paradigms model voluntary nicotine consumption in humans, they do so under defined conditions (an inherent advantage to these models as well). Therefore, integrating preclinical studies into translational programs should be done cautiously. Nevertheless, we suggest that it is imperative to develop models of cognitive deficits following voluntary nicotine self-administration in animals to enhance the predictive validity for using preclinical models to screen new compounds.

We identified several classes of medication that may have cognitive-enhancing properties as possible treatment for nicotine dependence. These compounds include cholinergic, glutamatergic and adrenergic agents. However, there are likely other systems involved that should be addressed in future research. For example, estrogen's effect on cholinergic function has been proposed as a neurobiological mechanism to explain its effects on cognitive function [139] suggesting estrogen receptor agents may be targets for future research (Table 1). There are also well-established links between smoking and inflammation [140] and between cognition and inflammation [141]. However, no study to our knowledge has explored anti-inflammatory agents as a smoking cessation aid (Table 1). Although our review was primarily focused on repurposing medications approved for other indications, we identified several compounds being tested for their cognitive enhancing properties that may be useful to explore for attenuating nicotine-withdrawal-related cognitive deficits [38,142,143]. To this end, we outline strategies for future research to identify and evaluate novel compounds. These translational models utilize data from preclinical paradigms of nicotine dependence, human laboratory paradigms of withdrawal-induced cognitive deficits and human models of smoking relapse. Emerging evidence supports deficits in cognitive function as a plausible nicotine withdrawal phenotype, and the translational paradigms presented here may represent efficient and valid means for evaluation cognitive-enhancing medications as possible treatments for nicotine dependence.

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Article highlights

- Cognitive deficits are a common nicotine withdrawal symptom that may precipitate relapse.
- Repurposing medications that may enhance cognition may represent an efficient strategy for screening novel medications for nicotine dependence.
- Preclinical models of nicotine dependence can provide valuable data to guide the development of clinical studies.
- Human laboratory models of smoking relapse can provide an early signal for medication efficacy and allow for testing of potential mechanisms of efficacy.
- The nicotine withdrawal syndrome is heterogeneous and targeting cognitive function may only be effective for a subset of smokers.

This box summarizes key points contained in the article.

Table 1

Cognitive-enhancing medications, mechanisms of action and effects on cognition and nicotine dependence

Drug class/target	Medication	Mechanism	Indication	Effects on nicotine taking and seeking in rats	Effects on nicotine withdrawal-induced cognitive deficits	Effects on nicotine dependence
Cholinesterase inhibitors						
	Galantamine	AChEl and PAM of α4|β2 nAChRs and agonist at α7 nAChRs	Alzheimer's disease	Decreases nicotine taking and seeking [43,56]	Decreases nicotine withdrawal-induced cognitive deficits in mice [44] Improved response inhibition in nicotine-deprived smokers [46]	Reduced cigarette consumption among alcohol-dependent smokers [48] No effect on smoking behaviour among smokers with schizophrenia [50]
	Donepezil	AChEl	Alzheimer's disease	Decreases nicotine taking and seeking [42]	Improved working memory in nonabstinent smokers [45]	No effect on smoking behaviour among healthy smokers [45]
	Rivastigmine	Nonselective cho linesterase Inhibitor	Alzheimer's disease	No studies to date	No studies to date	No change in smoking behaviour or urges to smoke among methamphetamine-dependent smokers [144] Reduced cigarette consumption and craving in alcohol-dependent smokers [49]
nAChR PAMs						
	dFBr	α4β2 nAChR PAM		Decreases nicotine taking [56]	No studies to date	No studies to date
	PNU 120596 and others	α7 nAChR PAM		No studies to date	No studies to date	No studies to date
nAChR agonists						
	Varenicline	α4β2 nAChR par tial agonist	Nicotine dependence	Decreases nicotine taking and seeking [27,28]	Decreases nicotine withdrawal-induced cognitive deficits in mice [19]	FDA-approved treat ment for nicotine dependence [3]
	Sazetidine-A	α4β2 nAChR par tial agonist		Decreases nicotine taking in rats [36]	No studies to date	No studies to date
Glutamatergic agents						

Drug class/target	Medication	Mechanism	Indication	Effects on nicotine taking and seeking in rats	Effects on nicotine withdrawal-induced cognitive deficits	Effects on nicotine dependence
	Memantine	NMDA receptor antagonist	Alzheimer's disease	Decreased nicotine taking in mice [62]	No effect on cognition, but effects may depend on smoking status (deprived vs nondeprived) [63]	Reduced subjective effects of smoking but did not alter smoking behaviour [63]
	D-Cycloserine	NMDA partial agonist	Antibiotic; off-label use for OCD and other anxiety disorders	Attenuated self-administration in rats with low-baseline levels of responding for nicotine [69]	Improved response inhibition but not attention or cognitive flexibility in humans [71]	Reduced craving and reactivity to smoking cues; no effect on behaviour [70]
Adrenergic agents						
	Guanfacine	α_2 adrenergic receptor agonist	ADHD	No studies to date	Increased prefron tal brain activity associated with attention and response inhibition [76]	Reduced smoking behaviour and craving [76]
	Atomoxetine	Norepinephrine reuptake inhibitor	ADHD	No studies to date	Attenuated withdrawal-induced cognitive deficits in mice [83] but not in humans [84]	Reduced withdrawal and craving [84,85] No effect on smoking behaviour [84], modest effect in another study [85]
Steroid hormone	Estrogen	Estrogen receptor	Oral contraceptive; hormone replace-ment therapy	Estrogen levels positively associ-ated with increased rates of self-administration in female rats [145]	Reverses anticholin-ergic cognitive deficits [146,147] but has not been tested in abstinent smokers	No studies to date
Anti-inflammatory	NSAIDs	Inhibition of the enzyme cyclo-oxygenase (COX)	Pain; inflammation	No studies to date	No studies to date	No studies to date

ADHD: Attention-deficit/hyperactivity disorder; CEE: Conjugated equine estrogens; CGI-C: Clinical global impression of change; dFBr: Desformylflustrabromine; nAChR: Nicotinic acetylcholine receptor; OCD: Obsessive-compulsive disorder; PAM: Positive allosteric modulator; SIB: Severe impairment battery.

Table 2
Commonly used preclinical and clinical laboratory models of cognition

Cognitive domain	Preclinical model	Human laboratory model
Attention	Five-choice serial reaction time task (5-CSRTT)	CPT hits (correct targets) rapid visual information processing
Vigilance	Five-choice CPT	Five-choice CPT
Working memory	Morris water maze	N-back digit span
Response inhibition; inhibitory control	Premature responses on the 5-CSRTT Stop signal task	Stop signal reaction time task Go/no-go task CPT false alarms Stroop task
Learning, declarative memory	Novel object recognition task	Recall or recognition tasks
Spatial working memory, discrimination	Spatial object recognition task T-maze, Y-maze	Spatial span
Pavlovian learning, fear memory	Fear conditioning	Cue exposure therapy

Cognitive domains listed here are a subset of those described in the Research Domain Criteria initiative from the National Institute of Mental Health [113,121], 5-CSRTT: Five-choice serial reaction time task; CPT: Continuous performance test.