



Current pharmacological treatments for nicotine dependence

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There are nearly 1.1 billion users of nicotine and tobacco products worldwide. Tobacco use through cigarette smoking is the leading preventable cause of death in the world and kills nearly four million people annually. However, although some cigarette smokers are able to quit, many are not, and standard medications to assist in smoking cessation (e.g. nicotine-replacement therapies and sustained-release bupropion) are ineffective in many remaining smokers. Recent developments in our understanding of the neurobiology of nicotine dependence have identified several neurotransmitter systems that might contribute to the process of smoking maintenance and relapse, including dopamine, noradrenaline, 5-hydroxytryptamine, acetylcholine, endogenous opioids, GABA, glutamate and endocannabinoids. Several existing medications are being tested as treatments for nicotine dependence and novel investigational agents are under development as effective treatments for nicotine dependence in the 'hard to treat' tobacco user.

In the USA, ~23% of the general population smoke cigarettes, which is the most common (>98%) method of tobacco use [1,2], and ~430 000 people die each year as a result of smoking-attributable medical illnesses such as lung cancer, chronic obstructive pulmonary disease, cardiovascular disease and stroke [2]. Worldwide, it is estimated that nearly two billion people use tobacco on a regular basis [1], but rates of smoking appear to be highly sensitive to tobacco control interventions such as limiting access to particular groups (e.g. adolescents), advertising the health dangers of continued use (e.g. US Surgeon General's Report) and increases in tobacco excise taxes. As a result of implementing such tobacco control policies in the USA, the prevalence of cigarette smoking has reduced from 45% in the 1960s to ~22.9% in 2002 [1]. However, it appears the remaining smokers have more difficulty quitting smoking, and today's smoker has often failed numerous attempts to quit, frequently with the combined use of behavioral therapies and pharmacological interventions, such as nicotine replacement therapies (NRTs) and sustained-release bupropion. During the past 15 years, quit rates with NRTs in controlled clinical trials appear to be declining [3]. The remaining population of smokers has characteristics that are associated with smoking

persistence and quit-attempt failures, such as lower educational attainment, less interest in behavioral treatments that assist cessation, and medical, substance abuse and psychiatric comorbidities [4]. Furthermore, a higher proportion of women are smoking now than in the past, and women might have more intense nicotine-withdrawal symptoms and depressed mood during quit attempts than men [5], and might be less responsive to quitting with NRTs [6]. Smokers who have failed initial attempts to quit generally embrace pharmacotherapies and, given that a large proportion of these smokers do not respond to conventional drugs, the development of novel and more effective medication for smoking cessation is crucial to treat nicotine dependence. Recent advances in our understanding of the effects of nicotine on CNS neurotransmitter systems are guiding basic and clinical pharmacologists to develop medications for new pharmacological targets that will treat nicotine dependence.

Neurobiology and pharmacology of nicotine and tobacco

Nicotine alters the function of several CNS neurotransmitters, including dopamine (DA), noradrenaline (NA), 5-hydroxytryptamine (5-HT), glutamate, GABA and endogenous opioid peptides (EOPs) [7]. In the brain, nicotine acts via nicotinic acetylcholine (nACh) receptors, which are diverse members of the neurotransmitter-gated ion-channel superfamily and have crucial neuromodulatory roles in the CNS [8,9]. The endogenous neurotransmitter at nACh receptors is ACh. In general, there are two families of nACh receptors in the CNS [7,9]: high-affinity nACh receptors, which contain β 2-subunits, form a heteropentameric configuration of α -subunits and β -subunits and are sensitive to the antagonists mecamylamine and dihydro- β -erythrodine; and low-affinity nACh receptors, which are homopentameric complexes that contain α 7-subunits and are sensitive to the snake-venom toxin α -bungarotoxin and the selective antagonist methyllycaconitine. Both high-affinity and low-affinity nACh receptors are present on mesocorticolimbic DA-containing neurons [10], and low-affinity nACh receptors are enriched in the hippocampus and cortex and where they facilitate information processing and sensory integration [11]. Stimulation by nicotine of presynaptic nACh receptors on these neurons increases neurotransmitter release and metabolism. Unlike most agonists, which down-regulate receptor numbers with chronic exposure, chronic

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administration of nicotine leads to desensitization and inactivation of nACh receptors, and a 'paradoxical' upregulation of nACh receptor sites. After overnight abstinence, these nACh receptors are likely to resensitize and are thought to be fully responsive to nicotine as an exogenous agonist. This might explain why most smokers report that the most satisfying cigarette of the day is the first one in the morning. Mesolimbic DA-containing neurons, which form part of the reward pathway, are particularly important because they project from the ventral tegmental area (VTA) in the midbrain to anterior limbic forebrain structures such as the nucleus accumbens and cingulate cortex and mediate the rewarding effects of nicotine. These neurons possess high-affinity nACh receptors on their cell bodies and terminals [12], and they receive inputs from glutamate-containing and GABA-containing neurons, which have low-affinity and high-affinity nACh receptors on their terminals, respectively [13]. Similarly, stimulation of presynaptic nACh receptors on DA-containing neurons that project from the VTA to the prefrontal cortex evokes DA release and DA metabolism [14]. Chronic nicotine administration is thought to lead to post-receptor changes (e.g. changes in gene expression, and protein synthesis and degradation) in CNS neurons (such as the mesolimbic DA system), which lead to the complex processes of nicotine dependence and withdrawal [8].

In addition to nicotine, there are ~4000 chemical constituents in tobacco, some of which have psychopharmacological effects and, thus, contribute to the nicotine dependence state in humans. For example, an unidentified component of tobacco smoke (not nicotine) inhibits both A and B subtypes of monoamine oxidase (MAO-A and MAO-B), which are responsible for the metabolism of monoamine neurotransmitters such as NA and 5-HT (MAO-A) and DA (MAO-B) [15,16]. This might contribute to the reinforcing properties of tobacco.

Clinical features of nicotine dependence

Most tobacco users (>98%) are smokers of cigarettes. Although a subset of cigarette smokers do not smoke daily, most do and are physiologically dependent on nicotine [17]. Typically, nicotine dependence is determined clinically by documenting daily smoking (typically 10–40 cigarettes per day) for several weeks, evidence of tolerance (e.g. lack of aversive effects of nicotine such as nausea) and the presence of symptoms of nicotine withdrawal on smoking cessation, including dysphoria, anxiety, irritability, decreased heart rate, insomnia (waking in the middle of the night), increased appetite and craving for cigarettes [18]. In addition, most dependent smokers state that they smoke their first cigarette of the day within 30 min of waking. Scales such as the Fagerstrom Test for Nicotine Dependence (FTND) assess the level of nicotine dependence (scores of ≥ 4 on a scale of 0–10 are consistent with physiological dependence on nicotine) and have been validated empirically [19].

In addition to positive reinforcement (e.g. smoking satisfaction), withdrawal and craving, several secondary effects of nicotine and tobacco use could contribute to both the maintenance of smoking and smoking relapse, including mood modulation (e.g. reduction of negative affect),

stress reduction, antinociception, weight control and cognitive enhancement. In addition, conditioned cues can elicit the urge to smoke, even after prolonged periods of abstinence. Specific effects might be most relevant to individuals high on dietary restraint (weight reduction), psychiatric disorders (cognitive enhancement, mood modulation and stress reduction) and chronic pain states (antinociception). These secondary effects might present additional targets for pharmacological intervention. These potential primary and secondary contributory factors to nicotine dependence are depicted in Figure 1.

Standard pharmacotherapies for nicotine dependence: NRTs and bupropion

Extensive, randomized, double-blind, placebo-controlled clinical trials have established the efficacy and safety of NRTs and bupropion in the treatment of nicotine dependence (Table 1). Standard treatment outcomes include measures, such as 7-day point prevalence smoking abstinence at the end of the treatment trial (i.e. no report of smoking in the preceding week, confirmed by objective surrogate measures of smoking such as the concentrations of carbon monoxide in the breath and cotinine in plasma), continuous abstinence from the target quit date (TQD), and prolonged abstinence after a grace period [20]. Long-term abstinence is typically evaluated at either 6 month or 12 month follow-ups. However, in terms of identifying novel anti-smoking medications, relatively few validated human laboratory models have been developed that predict efficacy in clinical trials [21,22]. Although not fully realized, human laboratory studies have great potential for defining the mechanisms by which a standard pharmacotherapy enhances abstinence rates [21] and for screening new compounds [22].

NRT

Five NRTs have been approved as first-line agents to treat nicotine dependence in the USA and other countries, including the slow-acting transdermal nicotine patch (TNP) formulation, and faster-acting formulations such as nicotine gum, nicotine nasal spray, nicotine vapor inhaler and, most recently, the nicotine lozenge [23–25] (Table 1). When smokers use these products, they must cease all tobacco use before starting the NRT (e.g. the TQD) because of concerns about nicotine toxicity with concurrent NRT and tobacco use. The faster-acting NRTs appear to be helpful in satiating the positive effects of nicotine administration through smoking (e.g. smoking satisfaction, desire to smoke and anticipation of positive effects) and reducing acute craving [21], whereas the slow-acting TNP formulation supplies constant, low levels of nicotine which, when adequately dosed, can relieve nicotine-withdrawal symptoms [25,26]. All NRT formulations have demonstrated superior efficacy in placebo-controlled clinical trials, with Odds Ratios of 1.5–2.5 [23,26] at both end-of-trial and long-term (e.g. 6-month and 12-month) assessments.

Sustained-release bupropion

The phenylaminoketone atypical antidepressant agent bupropion, in the sustained-release formulation (Zyban[®]),

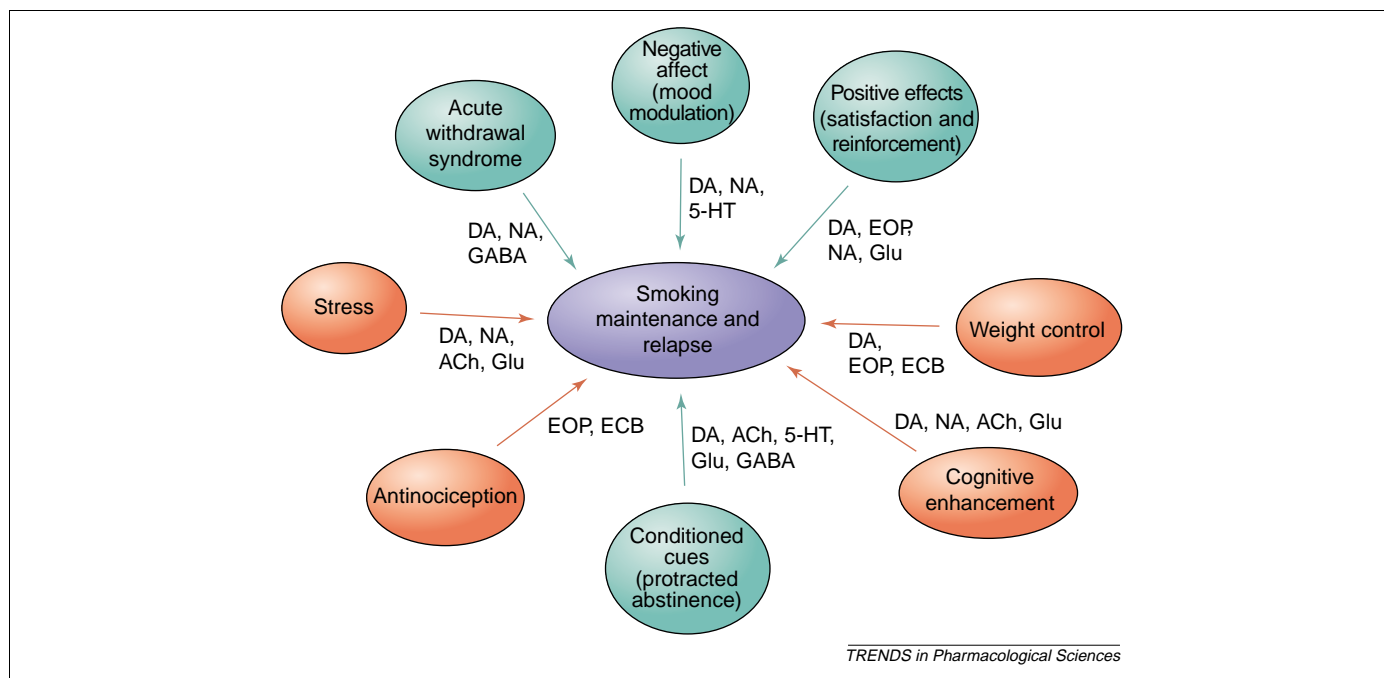


Figure 1. State, trait and environmental factors, and neurotransmitter systems that mediate smoking maintenance and relapse. The green circles represent primary contributors to smoking maintenance and relapse, whereas the red circles represent secondary contributors to these processes. Abbreviations: ACh, acetylcholine (nicotinic ACh receptor); DA, dopamine; ECB, endocannabinoid (CB₁ receptor); EOP, endogenous opioid peptide; Glu, glutamate; 5-HT, 5-hydroxytryptamine; NA, noradrenaline.

Table 1. Current pharmacotherapies for nicotine dependence and clinical and neuropharmacological mechanisms of action^a

Medication	Route of administration and dose range	Clinical and pharmacological mechanisms	Refs
Nicotine patch	Transdermal (7–22 mg day ⁻¹)	NRT: reduces nicotine craving and withdrawal	[26]
Nicotine gum	Buccal (20–40 mg day ⁻¹ ; 2–4 mg pieces up to 10 times daily)	NRT: reduces nicotine craving and withdrawal	[21,23]
Nicotine lozenge	Buccal (20–40 mg day ⁻¹ ; 2–4 mg pieces up to 10 times daily)	NRT: reduces nicotine craving and withdrawal	[17]
Nicotine nasal spray	Intranasal (16–32 mg day ⁻¹ ; 1–2 mg spray ⁻¹ in each nostril up to 16 times daily)	NRT: nACh receptor stimulation rapidly reduces nicotine craving and withdrawal symptoms	[17,25]
Nicotine vapor inhaler	Inhalational and buccal (6–16 mg day ⁻¹ ; constant puffing up to 120 times daily)	NRT: nACh receptor stimulation rapidly reduces nicotine craving and withdrawal	[17,25]
Bupropion hydrochloride (sustained-release)	Oral, 300 mg day ⁻¹ in bid dosing	Blocks reuptake of DA and NA; high-affinity, noncompetitive nACh receptor antagonist reduces nicotine reinforcement, withdrawal and craving	[29]
Clonidine	Oral (0.6–1.2 mg day ⁻¹) in bid-tid dosing	α_2 -Adrenoceptor agonist reduces nicotine withdrawal symptoms	[50,51]
Tricyclic antidepressants (nortriptyline, doxepin)	Oral (100–250 mg day ⁻¹), once or twice daily	Blocks reuptake of NA and 5-HT; probably reduces withdrawal symptoms and comorbid depressive symptoms	[38–41]
Mecamylamine	Oral (5–20 mg day ⁻¹), in bid dosing (in combination with patch)	Noncompetitive, high-affinity nACh receptor antagonist combined with TNP reduces nicotine reinforcement, withdrawal and craving	[34,35]
Naltrexone	Oral (50–100 mg day ⁻¹) in once daily dosing	Endogenous mu opioid peptide receptor antagonist appears to reduce nicotine craving and withdrawal in combination with TNP; might reduce comorbid alcohol use	[36,37]
Buspirone	Oral (15–40 mg day ⁻¹) in bid-tid dosing	Partial agonist of 5-HT _{1A} receptors reduces 5-HT release; might be effective in smokers with comorbid anxiety symptoms	[49]
Moclobemide	Oral (400 mg day ⁻¹) in bid dosing	Reversible MAO-A inhibitor increases NA and 5-HT levels; might be helpful for smokers with comorbid mood disorders	[42]
Selegiline	Oral (10 mg day ⁻¹) in bid dosing	Irreversible MAO-B inhibitor increases synaptic DA levels; might reduce nicotine reinforcement, withdrawal and craving	[43]

^aAbbreviations: bid, twice daily; DA, dopamine; 5-HT, 5-hydroxytryptamine; MAO, monoamine oxidase; NA, noradrenaline; nACh receptor, nicotinic acetylcholine receptor; NRT, nicotine replacement therapy; tid, three times a day; TNP, transdermal nicotine patch.

was approved by the Food and Drug Administration (FDA) in the USA in 1997 as the first non-nicotine pharmacotherapy for smoking cessation. It is now considered a first-line pharmacological treatment for nicotine-dependent smokers. Although not proven, its mechanism of action in the treatment of nicotine dependence is likely to involve its modest blockade of DA and NA reuptake [27], and might also relate to its antagonism of high-affinity nACh receptors [28]. The target dose of this agent in nicotine dependence is 300 mg day⁻¹. It is started 7 days before the TQD at 150 mg day⁻¹, and increased to 150 mg twice daily after 3 days so that steady-state levels are achieved before the quit attempt. It is not known whether the major metabolite 6-hydroxybupropion, which is formed by cytochrome P450 2D6 metabolism [27], contributes to the anti-smoking actions. Unlike the NRTs, there is no absolute requirement that smokers cease smoking by the TQD, although many smokers report a significant reduction in urges to smoke and craving, which facilitates cessation. Some smokers gradually reduce their cigarette smoking over several weeks before quitting. The anti-smoking actions of this drug were first observed in US veterans taking the antidepressant formulation of this drug, but its anti-smoking and antidepressant effects appear to be independent [27]. The main contraindication for the use of bupropion is a past history of seizures of any etiology; the rates of *de novo* seizures are low with this agent (~0.1%), and observed mainly when the dose exceeds 450 mg day⁻¹. The primary side-effects associated with bupropion are headache, jitteriness, dry mouth, initial insomnia and gastrointestinal symptoms. A pivotal study by Hurt and colleagues [29] established the efficacy of bupropion sustained release compared to placebo for smoking cessation, with the most robust anti-smoking effects at a dose of 300 mg day⁻¹. Recent studies have extended its use to preventing smoking relapse after the initial achievement of smoking cessation [30]. However, bupropion has limited effectiveness in many smokers and, given its high cost, there is controversy over the subtypes of smokers that might achieve the most benefit [31].

Combination treatments

In psychopharmacological treatment, if there is a poor response to a single agent it is common to use a combination of agents with distinct mechanisms of action. This approach has been applied in the management of refractory nicotine dependence and one controlled study that combines fast-acting and slow-acting NRTs has been published. Bohandana and colleagues [32] conducted a 12-week study that demonstrated superior efficacy of the active combination of TNP plus nicotine inhaler over TNP plus placebo inhaler. Most recently, sustained-release bupropion (Zyban[®]) at 300 mg day⁻¹ combined with TNP was shown to be superior to placebo bupropion plus TNP but, interestingly, was not significantly different from cessation outcomes with active bupropion plus placebo patch [33]. Other studies have combined TNP with non-approved antagonist drugs such as mecamylamine [34,35] and naltrexone [36,37], with promising results (see later). This indicates that the combination of NRT (to alleviate nicotine withdrawal symptoms) and antagonists (to reduce

rewarding effects of cigarette smoking) could be useful to treat nicotine dependence. Further studies are needed.

Non-approved, clinically available pharmacological treatments for nicotine addiction

Indirect monoamine agonists

As mentioned previously, there is evidence that monoamines are involved in the neurobiology of nicotine dependence. Several tricyclic antidepressants (TCAs), which inhibit the reuptake of NA and 5-HT, such as nortriptyline [38–40] and doxepin [41], might facilitate smoking cessation in combination with behavioral treatment. However, TCAs have significant side-effects, such as anticholinergic toxicity and frequent lethality in overdose. MAO degrades monoamine neurotransmitters: MAO-A, degrades 5-HT and NA preferentially and MAO-B preferentially metabolizes DA. Traditional MAO-A inhibitors, which are older-generation antidepressants (e.g. phenelzine and clorgyline) and irreversible inhibitors of MAO-A, are associated with hypertensive crises (e.g. 'cheese reactions') because they inhibit the metabolism of the dietary pressor tyramine in the gastrointestinal tract. However, a reversible MAO-A inhibitor, moclobemide (Manerix[®]), which is available in Europe and Canada to treat major depression, has demonstrated efficacy at 400 mg day⁻¹ in a French placebo-controlled study for smoking cessation [42]. In support of DA-related mechanisms in nicotine dependence, our group at Yale have found that the selective MAO-B inhibitor and indirect DA agonist selegiline hydrochloride (Eldepryl[®]), an FDA-approved drug for Parkinson's disease that selectively increases synaptic DA concentrations, is superior to placebo in a preliminary trial [43]. Further studies with these agents are in progress.

5-HT agents

A better tolerated and safer class of antidepressants, 5-HT-selective reuptake inhibitors (SSRIs), have also been studied, given the role of 5-HT in modulating smoking behavior [7,44]. Most studies yield either equivocal or negative results with the SSRI fluoxetine (Prozac[®]) alone [45] and in combination with NRT [46,47]. Subsequent post hoc analysis of the negative trial with fluoxetine indicated some benefit in the subset of smokers who had a history of major depression [48].

Buspirone (Buspar[®]), an anxiolytic agent used to treat generalized anxiety disorder, is a 5-HT_{1A} partial agonist. 5-HT_{1A} receptors are inhibitory autoreceptors that occur both presynaptically and postsynaptically. Thus, stimulation of the 5-HT_{1A} receptor by buspirone leads to a reduction in presynaptic release of 5-HT, which appears to mediate its anxiolytic effects. Buspirone does not cause physical dependence, which makes it an attractive candidate for treating nicotine dependence, especially in anxious smokers. However, a placebo-controlled trial failed to support its efficacy in smoking cessation [49].

α₂-Adrenoceptor agonist

Clonidine is a α₂-adrenoceptor agonist that was approved originally for the treatment of hypertension and found to

be effective in the treatment of opioid withdrawal, which is associated with hyperactivity of CNS adrenoceptors. Several clinical trials conducted between 1985 and 1993 demonstrate that clonidine has modest efficacy in smoking-cessation trials, and two meta-analyses that cover a total of 13 placebo-controlled clinical trials indicate that it is superior to placebo, with Odds Ratios of 2.4 (1.7–32.8) and 2.0 (1.3–3.0) [50,51], and that it might be beneficial in female smokers [50]. However, significant side-effects, such as sedation, constipation and orthostatic hypotension, might limit its use. More recent trials of transdermal [52] and oral [53] formulations indicate modest efficacy for this drug. Thus, clonidine is considered a second-line cessation pharmacotherapy.

EOPs

There is strong evidence in humans for a role of endogenous opioids in mediating the nicotine-dependence state [54,55]. However, evidence that the mu opioid peptide receptor antagonist modifies smoking behavior is mixed [56]. There is little evidence that naltrexone alone facilitates smoking cessation in the small-scale studies conducted to date [36]. More encouraging results using the combination of TNPs and naltrexone, as compared to TNP and placebo naltrexone have been reported in one recent preliminary study [37]. This study also indicated that naltrexone reduces weight gain, which potentially is an important benefit for smokers whose weight concerns might contribute to the maintenance and relapse of smoking (Figure 1). Larger studies of this combination are in progress (S.S. O'Malley *et al.*, unpublished).

Nicotinic receptor antagonists

At doses of $\leq 10 \text{ mg day}^{-1}$, the ganglionic blocker mecamylamine is a noncompetitive antagonist at the ion-channel site of the high-affinity nACh receptor [57], a property shared by bupropion, TCAs and SSRIs [57]. The rationale for using mecamylamine to aid smoking cessation is that it should reduce the satisfaction associated with smoking and the urge to smoke. When this drug is given to smokers who do not want to quit, smoking consumption increases in an attempt to overcome this blockade [58,59], and early attempts to use mecamylamine alone were unsuccessful, probably because of side-effects that include abdominal pain, constipation, dry mouth and headaches. However, two studies have suggested that mecamylamine in combination with TNP produces a superior outcome compared to TNP plus placebo [34,35]. Whereas the combination of agonist (TNP) and antagonist (mecamylamine) seems paradoxical, chronic administration of either upregulates nACh receptors [7,60], and they might have distinct sites of action on the high-affinity nACh-receptor-subunit complex. Further studies of mecamylamine in combination with NRTs are needed.

Other promising agents with novel sites of action

Although both GABA and glutamate appear to be important mediators of the actions of nicotine [7,22,61], few clinical studies have tested their utility in the treatment of nicotine dependence. A human laboratory study by Cousins and colleagues [62] with the GABA_B

receptor agonist baclofen indicates that this agent could reduce the rewarding effects of smoking, and it appears to be a promising agent for further development. Several promising novel agents are either undergoing preclinical testing or in early clinical development for smoking cessation. These include selective cannabinoid (CB₁) receptor antagonists [63], metabotropic glutamate (mGlu₅) receptor agonists [64], 5-HT_{1A} receptor antagonists [65], DA D3 receptor antagonists [66], β 2-subunit-selective nACh receptor agonists [67] and GABA_B receptor agonists [68]. Vaccines, which involve injection of a nicotine-like hapten conjugated to a strong immunogen [69] and lead to the production of anti-nicotine antibodies and sequestration of intravascular nicotine after cigarette smoking, are being developed and Phase I studies are in progress. These novel treatments could provide more effective options for the pharmacological management of nicotine addiction, in terms of both initiating smoking abstinence and preventing relapse.

Matching medications to populations of smokers

There is evidence that many refractory smokers have comorbid psychiatric and drug-abuse disorders that might make them less amenable to standard treatments for nicotine dependence. The high rates of smoking in some comorbid disorders, such as schizophrenia, major depression and alcoholism, might be an attempt to 'self-medicate' clinical features of these disorders. In addition, the pathophysiology of these disorders (e.g. shared genes) might confer a vulnerability to the initiation and maintenance of smoking behavior [70]. In fact, there is evidence that pharmacological treatments for depression [71], schizophrenia [72] and alcoholism [73] might reduce smoking and facilitate smoking cessation. Furthermore, there is increasing evidence that pharmacogenetic approaches can match anti-smoking pharmacotherapies to smokers, as shown in a recent study of in which the CYP2B6 genotype was used to predict the response to bupropion [74].

Concluding remarks

Evidence from preclinical and clinical studies indicates that several neurotransmitter systems mediate the neurobiology of nicotine dependence, and that the pathophysiology of some comorbid conditions could increase the risk of vulnerability to smoking. Several agents used for other indications (e.g. depression, alcoholism, Parkinson's disease and epilepsy) might be used to treat smokers who are unable to quit using standard, approved, pharmacological interventions for nicotine dependence. Furthermore, several medications act on novel pharmacological targets (e.g. selective DA, nACh and GABA receptors), and these novel strategies offer considerable promise to refractory smokers for achieving cessation. This could lead to a significant reduction in the most insidious, but preventable, cause of death in modern humans, tobacco-related disease.

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