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Effective Treatments for Nicotine Addiction

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Abstract
Nicotine dependence as a result of smoking is a chronically relapsing disorder with detrimental effects. However, fortunately for smokers, an armamentarium of smoking cessation aids is available in the forms of nicotine replacement therapy (NRT), non-nicotinic drugs (namely varenicline and bupropion), and the novel nicotine vaccines, each with their own mode of action to moderate nicotine addiction. This paper analyzes the mechanism of action associated with nicotine addiction and the various methods of combat, or at the very least, attenuation of the addiction.

Introduction
Though incognito, nicotine addiction has been proven to be the true killer in the seemingly innocent activity of smoking, for it reinforces the desire to smoke. To prevent the myriad adverse effects of smoking, smokers need to work very hard to break nicotine addiction through smoking cessation. Nonetheless, many smokers find themselves dealing with many ups and downs in the quitting process. It comes as no surprise that nicotine addiction is therefore identified as a “chronic condition” by The US Clinical Practice Guideline, as many smokers need to make several attempts before they successfully wean themselves off completely (Fagerström & Hughes, 2008). Smoking is the second most expensive chronic health condition in the United States, with an estimated economic cost of 300 billion dollars per year (Jordan & Xi, 2018). Yet, stopping smoking can reverse the biological and economical damage caused by smoking (Benowitz, 2010).

Understandably, 70% of smokers admit that they would like to quit. Every year, about 40% quit for at least a day. However, due to the extreme difficulty to abstain, about 45 million Americans currently smoke tobacco. Moreover, the 80% who attempt to quit on their own return to smoking within a month. Each year, only 3% of smokers quit successfully and remain abstinent one year later, highlighting the critical need for effective long-term smoking treatments (Benowitz, 2010).

Methods
This comprehensive review is based on critical analyses of literature obtained using various databases available through The Touro College Library online, such as PubMed and ProQuest. The National Center for Biotechnology (NCBI) website was also useful in providing additional source material.

Nicotine Addiction
Cigarette smoking is a major cause of death, cardiovascular disease, and pulmonary disease. It also presents the risk for various infections, osteoporosis, reproductive disorders, adverse postoperative events, delayed wound healing, duodenal and gastric ulcers, and diabetes (Benowitz, 2010). Although nicotine itself plays a minor role, if any, in causing smoking-induced diseases, the addiction to nicotine, which leads to sustained smoking use, is the proximate cause of these diseases (Onor et al., 2017).

Nicotine (C10H14N2) is a plant alkaloid found in the tobacco plant (Onor et al., 2017) that consists of a pyridine and pyrrolidine ring, each one possessing a tertiary amine (Escobar-Chávez et al., 2011). The pKa of the pyridine nitrogen is 3.04 and the pKa of the pyrrolidine nitrogen is 7.84 under standard conditions. Based on these characteristics, nicotine’s distribution exists among three forms, depending on the pH of the solution. An increase in acidity of solution increases the fraction of protonated molecules; conversely, a more basic environment increases the fraction of the unprotonated, or free base, form (Figure 1). Although all forms of nicotine are highly soluble in water and can easily dissolve in lung fluids and blood, the unprotonated nicotine smoke particles are volatile, whereas the protonated form is not. Conventionally, a sample of particulate matter from cigarette smoke is not acidic enough to cause the protonated form to dominate. Thus, a higher percentage of unprotonated nicotine can rapidly cross biological lipid membranes and be deposited in the respiratory tract (Centers for Disease Control and Prevention, 2010). Nicotine begins to reach the brain ten seconds after inhalation and its concentration continues to increase gradually (Dani et al., 2011).

Blood concentrations of nicotine rise rapidly and peak at the completion of smoking. The rapid absorption of nicotine is attributed to the broad surface area of the alveoli and small airways. This rapid rise allows the smoker to titrate and manipulate the level of nicotine during smoking, which makes smoking the most reinforcing and dependence-producing form of nicotine administration (Benowitz et al., 2009).
Essentially, pharmacologic feedback, learned factors, genetics, and environmental factors (including tobacco product design and marketing, stress, smoking cues, or peers who smoke) contribute to nicotine addiction. Other factors include sex, age, mental illness, and substance abuse. Although each of these features contributes, the one that will be discussed with perspicience is the pharmacological interplay with nicotine addiction (Benowitz et al., 2009).

The pharmacological basis for nicotine use is enhancement of mood and augmentation of mental and physical functions. Inhalation of smoke from a cigarette allows nicotine from the smoke particles to diffuse through the lungs, where it is rapidly absorbed into the pulmonary venous circulation. From there, it moves quickly to the left ventricle of the heart and to the systemic arterial circulation and brain. Based on human autopsy samples from smokers, the liver, kidney, spleen, and lung have the highest affinity for nicotine (Benowitz et al., 2009). Subsequently, the nicotine enters arterial circulation to be moved from the lungs to the brain with high affinity, where it binds to nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels that normally bind a neurotransmitter acetylcholine (Benowitz, 2010).

nAChRs are pentameric structures consisting of a combination of five different subunits, including nine α subunits (α2 through α10) and three β subunits (β2 through β4), resulting in at least 12 unique nAChR subtypes that have been identified thus far. The α4β2 receptor, though, is the prime mediator of nicotine dependence. As seen in positron emission tomography studies in humans, smoking a full nicotine cigarette nearly saturated α4β2 receptor occupancy. In fact, when disruption of the β2 subunit gene was tested in mice, the behavioral effects of nicotine were eliminated. Similarly, the α4 subunit is an important determinant of sensitivity to nicotine. This was confirmed when a mutation affecting a single nucleotide in the pore-forming region of the receptor gene in mice made it hypersensitive to the effects of nicotine. These observations strongly implicate α4β2 nAChRs in nicotine addiction and illustrate the α4β2 receptor as a potentially attractive medicinal target for treatment of the addiction (Jordan & Xi, 2018).

The smoker craves nicotine to propagate dopamine overflow in the pleasure-seeking areas of the brain. The α4β2 are located on the dopamine (DA) cells of the mesolimbic system. The system is comprised of projections from DA neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc), the part of the brain responsible for reward, pleasure, laughter, aggression, and fear, and the prefrontal cortex. Nicotine binding to α4β2 receptors on VTA DA cells increases neuronal excitability and neurotransmitter release, opening the ligand-gated ion channel, and allowing Ca2+ and Na+ to cascade intracellularly, which stimulates DA release to NAc (Figure 2). This is the underlying effect of nicotine’s reward cascade, as dopamine serves as a pleasure signal and mood modulator and is critical for reinforcing nicotinic effects (Jordan & Xi, 2018).

When studied under laboratory conditions, nicotine elicits classic addictive responses (Dani et al., 2011). In order to reap the rewarding feeling associated with nicotine and avoid withdrawal symptoms, smokers must maintain a certain nicotine level. Repetitive exposure to nicotine leads to neuroadaptation and tolerance to nicotine’s effects, and accumulation of nicotine in the body leads to a more substantial withdrawal reaction if cessation is attempted. Common withdrawal symptoms include anxiety, difficulty concentrating, and irritability, all of which can last for days, weeks, or longer (Onor et al., 2017).

As neuroadaptation occurs, the number of binding sites on the nicotinic cholinergic receptors in the brain increases. This causes desensitization, wherein a ligand-induced closure and unresponsiveness of the receptor occurs due to the profusion of ligand infiltration. Thus, the feelings of craving and withdrawal are exacerbated during periods of abstinence due to the mitigated levels of dopamine and other neurotransmitters. However, during a smoking period, binding to the α4β2 cholinergic receptors alleviates the need for nicotine. To circumvent withdrawal symptoms, smokers will sustain sufficient levels of plasma nicotine (Benowitz, 2010).

It comes as no surprise that nicotine withdrawal is extremely taxing on the smoker. Such repercussions are powerful incentives to take up smoking again (Benowitz, 2010). Fortunately for smokers, there is an expansive market of nicotine treatments that promote smoking cessation, some of them in the form of nicotine replacement therapy (NRT), non-nicotinic drugs such as bupropion and varenicline, and finally, the emergence of nicotine vaccines.
Effective Treatments for Nicotine Addiction

Nicotine Replacement Therapy (NRT)
Nicotine's rapid rate of absorption and entry to the brain are key factors responsible for the high abuse potential. Unlike cigarettes, nicotine replacement therapy (NRT) products such as gums, inhalers, and transdermal patches can help relieve the physical withdrawal symptoms by providing gradual increments of nicotine without the damaging chemicals found in cigarette smoke (Jordan & Xi, 2018). The gradual distribution of nicotine results in low abuse liability of NRTs. Although NRT doesn't completely eliminate withdrawal symptoms since it does not provide rapid and high levels of nicotine, NRT may provide a coping mechanism, making cigarettes less enticing to smoke (Molyneux, 2004) and increasing the rate of quitting by 50 to 70% (Stead et al., 2012). NRTs are well tolerated and have minimal adverse effects, but are most effective when used in conjunction with intense behavioral support (Molyneux, 2004).

In 1984, transmucosally delivered nicotine polacrilex, or nicotine gum, was introduced as the first effective NRT to serve as a smoking cessation aid, as approved by the US Food and Drug Administration (FDA). It is not chewed like ordinary confectionary gum, as it must be intermittently chewed and held in the mouth for over 30 minutes to achieve optimal release of nicotine. The absolute dose of nicotine absorbed systemically is much less than the nicotine content of the gum, in part because considerable nicotine is swallowed with first-pass metabolism (Benowitz et al., 2009), where it gets metabolized in a specific location other than the location of interest, reducing the concentration that enters systemic circulation (Herman & Santos, 2019). The dosage is slowly decreased until it is no longer required (Wadgave & Nagesh, 2016).

To satisfy the behavioral hand-to-mouth ritual of smoking, the nicotine oral inhaler was introduced to the NRT market. Contrary to its label, the inhaler is mainly delivered to the oral cavity, esophagus, and stomach, and negligibly to the lungs. Because absorption is mainly through the oral mucosa, a slow absorption rate of nicotine is achieved, akin to that of nicotine gum (Wadgave & Nagesh, 2016).

In a parallel fashion, nicotine patches deliver nicotine at a relatively steady rate when applied to and readily absorbed through the skin. In fact, the patch is the form that delivers nicotine at the slowest rate when compared to the other forms of NRT. A chief advantage of nicotine patches is the simplicity of user compliance, since the patch can be placed on the skin in the morning and worn for the duration of the day. The patches are available in a range of doses, allowing users to gradually decrease their nicotine intake over the span of several weeks or longer to ensure a proper adjustment to lower nicotine levels until they can attain a nicotine-free state. The rate of nicotine release is controlled by the permeability of the skin, rate of diffusion through a polymer matrix, and rate of passage through membranes in the various patches on the market. In all cases, there is an initial lag time of 1 hour before nicotine enters the bloodstream, followed by continued systemic absorption once the patch is removed, the latter due to the vestiges of nicotine in the skin (Benowitz et al., 2009). Current evidence supports the safety of long-term use of nicotine patches for nicotine treatment (Wadgave & Nagesh, 2016).

Non-Nicotinic Drugs
Bupropion (Wellbutrin)
The first non-nicotine drug to treat nicotine addiction was introduced in 1997. Bupropion (amfebutamone), marketed as Wellbutrin and Zyban among others (Fava, et al., 2005), an amphetamine-based drug, is a reuptake inhibitor of dopamine into neuronal synaptic vesicles and a blocker of nicotine's activation of several neuronal nAChRs. Bupropion undergoes metabolic transformation to an active metabolite, 4-hydroxybupropion, through hepatic cytochrome CYP2B6, (Foley et al., 2006). Bupropion’s structure is akin to nicotine, rendering it a compatible competitor (Figure 3). Originally developed as an antidepressant, a systematic review of 44 clinical trials found that sole therapy with bupropion significantly increased long-term (≥6 months) smoking abstinence, affirming its efficacy as an anti-smoking agent (Onor et al., 2017). It should be noted that the antismoking effect does not seem to correlate with its antidepressant effect, as bupropion is equally as effective for smoking cessation for individuals with and without depression (Roddy, 2004).

Figure 3. The chemical structures of bupropion (left) and nicotine (right) (National Center for Biotechnology Information).
When nicotine infiltrates the blood and crosses the blood brain barrier, there is a release of dopamine into the synaptic cleft of neurons in the dopaminergic pathways. After nicotine levels subside, dopamine reuptake into the axon terminal vesicles occurs. Bupropion is thought to inhibit this dopamine reuptake. In vivo studies have also shown that bupropion antagonizes the effects of nicotine at the postsynaptic acetylcholine nicotinic receptor (Wilkes, 2008). During withdrawal, bupropion may attenuate symptoms by mimicking the effects of nicotine on dopamine (Warner & Shoaib, 2005). These effects may explain how bupropion inhibits the reinforcing effects of nicotine, though it is still unclear whether bupropion offers any long-term relapse prevention following termination of treatment. Nonetheless, both pragmatic and observational trials of bupropion have shown that approximately 1 in 5 smokers will successfully remain abstinent for at least a year post-treatment (Wilkes, 2008).

**Varenicline (CHANTIX)**

Cytisine is a naturally occurring insecticide found in the leaves and seeds of Cytisus laburnum (golden rain tree). During World War II, soldiers smoked leaves of this tree in lieu of tobacco. Both varenicline and cytisine target the α4β2 receptor, where varenicline was developed to improve binding to the receptor to enhance efficacy of smoking cessation. However, the cytisine structure did not lead to a viable drug candidate. In due course, a series of efforts based on analgesic bicyclic benzazepines, one of which was unveiled as a potent α4β2 nAChR antagonist, served as a novel template that led to the development of varenicline, branded as CHANTIX. FDA approval was based on randomized clinical trials conducted in 3659 subjects in the United States. The subjects, all of whom were chronic smokers, averaged 43 years of age and reported smoking an average of 21 cigarettes per day for the previous 25 years. The primary outcome measured abstinence from smoking, which came in at a 44% rate, a significant improvement over bupropion (30%) and placebo (18%). Secondary outcomes, such as the urge to smoke and withdrawal symptoms, were likewise improved in varenicline-treated subjects over placebo (Jordian & Xi, 2018). In 2006, varenicline received FDA approval, and it was highly touted as an aid to quit smoking (Fagerström & Hughes, 2008).

Like bupropion, varenicline has a somewhat parallel configuration to its nicotine competitor in order to operate as an appropriate replacement. In fact, in vitro binding assays indicate that varenicline’s affinity for the α4β2 receptor (Ki = 0.15 nM) is higher than that of nicotine (Ki = 1.6 nM) and cytisine (Ki = 0.23 nM) (Jordian & Xi, 2018). Varenicline has the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanediol (1:1) (Figure 4). Varenicline has a molecular weight of 361.35 Daltons and is highly soluble in water (Pfizer Labs, 2016).

With varenicline, dopamine is still released, but less so than with nicotine. Since the α4β2 had been identified to have the highest sensitivity to nicotine, it had become a potential target for the smoking cessation drug. Varenicline was developed to have a high affinity for the α4β2 neuronal nicotinic acetylcholine receptors in the mesolimbic dopamine system and stimulate receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline’s highly selective nature ensures that it will bind more potent to α4β2 receptors than to other common nicotinic or non-nicotinic receptors (Pfizer Labs, 2016).

As a result of being a partial agonist, varenicline displays both agonist and antagonist effects. Partial agonists have been reviewed thoroughly as a method of attenuating nicotine addiction. Partial agonists bind to nAChRs but do not elicit the maximum response of a full agonist, and instead depend on receptor occupancy by other ligands. For instance, in the presence of a full agonist like nicotine, a partial agonist would behave as an antagonist by occupying the receptor site, thereby minimizing nicotine’s effects at the receptor. However, in the absence of nicotine, a partial agonist would behave as an agonist by mitigating nicotine withdrawal symptoms through triggering a degree of dopamine release (Jordian & Xi, 2018).

Given that continuous abstinence rates across studies remain low (18-30% with varenicline; 4-10% with placebo), novel and more effective treatments may be required. However, since FDA approval in 2006, incoming reports have been continuing to demonstrate varenicline’s efficacy for smoking cessation over the alternatives. For example, in a randomized trial involving 376 participants over the span of 52 weeks, varenicline resulted in higher abstinence rates from smoking (55.9%) when compared to transdermal NRT (43.2%), highlighting varenicline’s progress (Jordian & Xi, 2018).
Nicotine Vaccines
With the advent of the novel nicotine vaccines, smokers have an alternative course of action through which they can quit smoking. Currently undergoing clinical trials, the goal of the vaccine is to generate antibodies that sequester nicotine in the blood and hinder the pharmacological effects by preventing access into the brain. Thus, the vaccine brims with potential for treatment of nicotine addiction and relapse prevention (Goniewicz & Delijewski, 2013).

Based on the assumption that a rapid increase in brain nicotine levels induces feelings of reward, preventing nicotine from entering the brain is an intriguing idea with precedent in other, similar treatments. Using antibodies to bind a drug and thus disabling it from crossing the blood-brain barrier was first tested in the realm of heroin addiction and extended to nicotine and cocaine addiction (Raupach et al., 2012).

Since nicotine is too small to elicit a response from the immune system, nicotine is not immunogenic. In order to elicit an immune response, nicotine or a structurally similar hapten needs to be paired with a larger carrier protein, thus producing a conjugate vaccine (Goniewicz & Delijewski, 2013). Vaccination administers an immunogenic substrate that activates T and B cells, leading to the formation of specific antibodies within the individual, imprinting the response in immunological memory. By virtue of this mechanism, this approach has been shown to yield longer lasting protection (Raupach et al., 2012).

When nicotine enters the body, the vaccine causes it to bind to the nicotine-specific antibodies, forming a complex too large to cross the blood-brain barrier. Thus, there is no nicotine-induced cerebral stimulation for the smoker and the impression received by the smoker is comparable to smoking a cigarette without nicotine (Escobar-Chávez et al., 2011).

The success of this immunological strategy hinges on immunogenicity of the vaccine, affinity of antibodies, and specificity of antibodies (Raupach et al., 2012). Immunogenicity refers to the antibody serum concentration. A vaccine must elicit and maintain a high antibody serum concentration throughout the period of interest in order to be maximally effective (Escobar-Chávez et al., 2011).

The primary measure of antibody affinity to the target drug can be measured by the binding equilibrium constant, Ka. The Ka is defined by Ka = [NicAb]/[Nic][Ab]. [NicAb] represents the plasma volume concentration of bound nicotine-antibody complexes, and [Nic] and [Ab] denote the volume concentrations of unbound drug and unbound antibody, respectively. Hence, in order to calculate the percentage of bound nicotine, data regarding the amount of antibody present in circulation must be obtained beforehand. The Ka should be high enough to bind to nicotine and low enough to allow for unbound nicotine release and elimination (Goniewicz & Delijewski, 2013). However, extremely high affinity may be disadvantageous, as saturation of all antibodies compromises efficacy for subsequent nicotine doses (Fahim et al., 2011).

Interestingly, the interaction of antibodies with nicotine is reversible and each antibody binds to and releases nicotine many times, much like a juggler catches and releases multiple sticks many times. Thus, it is observed that the binding capacity of the antibodies for nicotine is far in excess than the expected stoichiometric calculation (Escobar-Chávez et al., 2011).

Specificity refers to the extent to which the elicited antibodies bind to nicotine in preference to other molecules (Raupach et al., 2012). Greater specificity reduces competition from other molecules, thus improving safety and minimizing the likelihood of adverse side effects (Escobar-Chávez et al., 2011). This has practical applications for the design of conjugate vaccines. For example, one recent study showed that using longer rather than shorter linkers, amino acid sequences used to separate multiple domains in a protein (Reddy Chichili et al., 2013), increases antibody selectivity to nicotine. Additionally, linker position influences specificity. Linkers that are distant from the prime sites of metabolism (i.e. attached to the 6- rather than 5- position of the pyridine ring) help enhance antibody selectivity (Raupach et al., 2012).

In order to maintain an ideal serum antibody concentration, repeated administration of the nicotine-conjugate system in the form of the vaccine is required. The first vaccination administered causes a primary immune response, comparable to when the organism had its initial encounter with an infectious antigen. Each subsequent administration acts as a “planned infection,” which uses memory about the antigens during the production of antibodies. Therefore, a faster and more effective response to the subsequent vaccinations is anticipated (Goniewicz & Delijewski, 2013).

Due to the prolonged effect that nicotine vaccines provide, they have an advantage over the existing pharmacotherapies (Shen et al., 2012, as cited in Goniewicz & Delijewski, 2013) and are a critical addition to the pharmacological smoking cessation aids. The relapse rate is minimal since only bimonthly booster shots are required to achieve a high level of antibodies. Thus, patient adherence to the necessary protocol can significantly improve. Nevertheless, early clinical trials have casted some doubts in that many patients may not elicit a sufficient antibody response. To circumvent this issue, novel carriers and/
or adjuvants with immunogenic properties can be introduced to stimulate a more potent immune response (Cerny et al., 2009, as cited in Goniewicz & Delijewski, 2013).

For those who attain high levels of antibodies, vaccination has been shown to be effective in achieving and maintaining abstinence (Goniewicz & Delijewski, 2013). Vaccines against nicotine are at an advanced stage of clinical trials but have not yet been approved for treatment of individuals (Escobar-Chávez et al., 2011). Future strategies for enhanced specificity that the vaccine can provide in conjunction with a high affinity to nicotine and increased antibody level offer an effective avenue for smoking-cessation (Goniewicz & Delijewski, 2013).

Discussion and Conclusion:

After reviewing the various smoking cessation techniques, it seems that a combination of a few would be the most viable option. The smoker can implement preliminary arrangements with the use of NRT. NRT may be useful for those who want to attenuate the smoking habit but do not want to put a halt to it completely, known as quitting “cold turkey.” The choice of NRT can be guided by the patient’s preference, though it may be wise to have a first-line agent in conjunction with NRT; however, healthcare professionals must learn the benefits and potential detriments of different types of NRT before guiding patients in its potential use (Wadgave & Nagesh, 2016).

Smokers who find that they are unsuccessful with NRT can choose an alternative method. Although nicotine vaccines have an advantage over existing pharmacotherapies in that they have a prolonged effect and require substantially less cooperation from patients with bimonthly booster shots, data from clinical trials suggest that many patients may not produce sufficient antibody response (Goniewicz & Delijewski, 2013), suggesting that it may not be the most pragmatic approach.

Since nicotine addiction is primarily responsible in impeding smoking cessation and long-term abstinence, it seems that the most prudent option would be a modality that targets the activity at the α4β2 receptor, the prime mediator of nicotine dependence. Where bupropion therapy aims to alleviate the withdrawal symptoms experienced during the transition state to a steady state of neurotransmitter activity, as does NRT, varenicline was developed to selectively target nicotine activity at the receptor that leads to the addiction, a seemingly more robust approach. Though varenicline presents a surfeit of undesirable side effects, some in the forms of nausea, abnormal dreams, taste perversion, and headaches (Burke et al., 2016), these effects may prove manageable and worthwhile under a cost-benefit analysis. The strong rationale for targeting the α4β2 receptor with a partial agonist, coupled with promising findings from clinical studies, reinforce varenicline’s efficacy and safety as a reliable smoking cessation aid. Upregulation of these receptors and adaptation lead to the compulsive use of nicotine to maintain homeostasis, both of which render the α4β2 receptor an effective candidate for pharmacologic intervention. However, patients and providers should determine whether to use varenicline only after an assessment of the potential risks and benefits. The efficacy of varenicline can be improved in combination with NRT and bupropion, especially for smokers who are more heavily dependent on nicotine (Burke et al., 2016).

Greater understanding of the exact mechanisms of these drugs, particularly bupropion, could lead to the development of drugs that are more effective in promoting smoking abstinence (Warner & Shoab, 2005).

All things considered, nota bene that relapse is often prominent in a patient’s attempt to quit smoking. The average patient will quit four or five times before reaching complete cessation, an important point to convey to patients to prevent disillusionment and hopelessness during recovery (Woody et al., 2008).

Essentially, the adverse health effects associated with cigarette smoking are numerous and continual efforts to reduce the prevalence of smoking are imperative (Onor et al., 2017). Nevertheless, due to futile attempts to quit, many smokers feel demoralized and incapable of taking action towards quitting. However, there are options available to the smoker: Whether in the form of NRT, non-nicotinic drugs (namely varenicline and bupropion), or the novel nicotine vaccines, nicotine addiction can be mitigated to aid the journey towards recovery.

References:

Centers for Disease Control and Prevention (US):
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