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Tobacco Use Disorder

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Abstract

Tobacco use disorder is highly prevalent and over a billion individuals use tobacco worldwide. Popular views on the addictive potential of tobacco often underestimate the complex neural adaptations that underpin its continued use. While sometimes trivialized as a "minor" substance, the effects of nicotine on behavior invariably lead to profound morbidity over a lifetime of exposure. Innovations in tobacco processing have led to potent forms of tobacco, and delivery devices that maximize the reinforcing capacity of nicotine. Most recently, proactive treatment strategies have emerged that focus on pharmacotherapeutic interventions to address tobacco use disorder. Innovations on the horizon hold significant promise for helping clinicians address this problem in a more phenotypically-tailored manner. However, efforts will be needed to prevent use of tobacco for future generations.

Introduction

Plants of the genus *Nicotiana* are members of the nightshade family, originating primarily in the Central and South Americas well before the appearance of humans. Genus *Nicotiana* encompasses at least 70 naturally occurring species, but the cultivated species *N. tabacum L.* is of primary economic importance.(1,2) The product of chance hybridization between several other species, natural genetic drift, and agricultural selection pressures, *N. tabacum L.* is prized for its ability to deliver relatively high concentrations of nicotine directly to the respiratory tract.

Ancient civilizations across the Americas used tobacco in a variety of religious and cultural ceremonies. Tobacco was chiefly smoked in cigars and pipes or chewed with lime (primarily calcium oxides) to produce stimulating, then emetic, and ultimately hallucinatory effects. In the 16th century, European explorers disseminated and cultivated tobacco for recreational use throughout North America, systematically creating markets for trade by promoting its

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medicinal properties and overall salutary effects to western European society. The French ambassador to Portugal, Jean Nicot, introduced tobacco to the French royal family, and methodically promoted its use throughout the world, resulting in the adoption of his name for both the plant's genus and its principle active salt, nicotine.(3) As a result, potions and salves made from the decoction of tobacco leaves have been used as diuretics, emetics, anthelmintics and antibiotics by a variety of cultures worldwide, with an estimated use by 1.25 billion individuals scattered throughout every nation on Earth.(4–6)

Tobacco use in the United States began to transition into tobacco use disorder during the industrial revolution. During the antebellum period, agricultural tobacco production was generally part of a diversified, regionally integrated system of farming that focused on growing small allotments for local consumption alongside larger volumes of staples like wheat, corn, and oats. Following the emancipation of slaves, Southern farm owners sought ways to maintain profits within their new labor paradigm and began systematically shifting from staples to products with higher profitability per cultivated acre.(7) The arrival of an expanding network of railways through small southern towns made distribution to a wider audience possible, transforming tobacco from local market offering to a nationally commoditized product.

In 1881, a twenty-one-year-old James Bonsack patented the world's first automated cigarette rolling machine. The Bonsack machine was so effective, its daily output matched the output of 48 experienced, and otherwise costly, human hand-rollers. James Buchanan "Buck" Duke and his American Tobacco Company capitalized on the convergence of nascent industrial technologies and evolving social norms to market inexpensive product to densely populated urban communities in the North. This included the bustling immigrant populations of New York City where concern over the potential spread of tuberculous through spitting had stigmatized chewable forms of tobacco, and a blossoming suffrage movement placed a premium on tobacco forms that could be marketed as "lady-like."(8,9) By the end of the 19th century, Buck Duke was able to decrease the cost of production from 96 cents to just under 8 cents per thousand cigarettes, marking the onset of the tobacco industry's golden period in the United States.(10)

Transition to modern era tobacco use disorder

Several 19th century agricultural advances made *N. tabacum L* increasingly popular, effective, and profitable. For example, the application of potash - high-pH potassium salts derived from the combustion of hard woods - to the crop increased yields and improved the balance of sugars and nicotine content to make smoked tobacco delivery more palatable and ubiquitous.(11) Flue-curing - the steady application of heat to the mature green plant - resulted in a bright leaf product with increased sugar content and a reduced acridity that was more amenable to being used in cigarette form. Potash application and flue-curing arguably produced a more addictive end product by producing a more deeply inhalable smoke and a more reinforcing experience.(12)

Nineteenth century work with mild bases like lime and potash led to 20th century experimentation with ammonization as a method of changing the pH of inhaled smoke.

Though there are several minor alkaloids in tobacco that have known reinforcing effects, the major pharmacologically active component is nicotine.(13) While all tobacco species contain small amounts of intrinsic ammonia-producing compounds, it was direct ammonization that allowed producers to fine-tune their product's "impact" by altering the proportion of free-base nicotine elaborated from the leaf upon heating.(14–16) Upon dissociation from the acid component of the salt, free-base nicotine is volatilizable and delivered more readily to the alveolar-capillary interface of the lungs where a massive surface area allows for more efficient absorption.(17) Free-base nicotine quickly reacts with water in the airway to form a protonated molecule that is absorbed rapidly and carried by transport proteins across the blood-brain barrier at a rate much faster than simple diffusion.(18,19) As with other free-base stimulant substances, free-base nicotine produces rapid changes in blood concentrations and significantly amplifies the reinforcing effects of nicotine, resulting in the rather impressive pharmacodynamic effects of the modern cigarette.(20)

Epidemiology of tobacco use disorder

Tobacco use disorder remains responsible for the majority of preventable deaths in the Western world.(37) Worldwide, nearly 1.4 billion people regularly use tobacco.(38) In 2019, the World Health Organization announced its first-ever projected reduction in the number of men who use tobacco, with a total anticipated reduction of nearly 60 million individuals who use tobacco.(38) Of course, the prevalence of tobacco use disorder varies significantly across demographic, economic, and cultural groups, but the highest burden is borne by people from lower socioeconomic individuals, as well as people with mental health and substance use disorders.(39–42) A number of important social-environmental factors have been identified as predictors of tobacco use; higher density of tobacco retailers, peer and/or parental tobacco use modelling, and divorced marital status have all been associated with higher rates of continued tobacco use.(43–45)

While cigarette smoking remains the most common method of tobacco use, other forms including flavored cigars, hookah, and electronic delivery devices have become increasingly attractive to young consumers in recent years. For example, following a long period of slowly declining prevalence, use of tobacco in any form increased considerably among U.S. middle and high school students from 2017–2018, primarily due to a remarkable increase in use of fourth-generation electronic cigarette use.(46) Early prospective observations of U.S. adolescent tobacco use were recently confirmed in European cohorts, and seem to support concerns that early adolescent exposure to electronic cigarettes confers substantially increased risk of going on to later use of combustible tobacco products.(47,48) A U.S. Surgeon General Report concluded that e-cigarette use among youths and young adults is an emerging public health concern.(49)

Neurobiology of Tobacco Use Disorder

Like other substances, the dominant neural system affected by nicotine is the mesolimbic survival system. Nicotine's main effect is through stimulation of the nicotinic cholinergic receptors located throughout the mesolimbic system, but it also has both direct and

indirect effects on noradrenergic, dopaminergic, serotonergic, vasopressin and glutamatergic systems, as well as the stress response regulation of the hypophyseal-pituitary-adrenal axis.(21,22) The Ventral Tegmental Area (VTA) of the midbrain is extensively equipped with the α4β2 variety of cholinergic receptor, highly sensitive to the natural acetylcholine ligand, and with a high affinity for the agonist nicotine.(23–25) Stimulation of cholinergic receptors in the VTA by the exogenous ligand confers abnormal survival salience to otherwise non-survival sensory inputs.(26) Nicotinic stimulation of striatal pathways projecting from the VTA begins the transduction of sensory inputs into motor response.(27) Dopaminergic projections from the VTA result in an increased activation of the Nucleus Accumbens (NA) shell, resulting in a generalized appetitive state and an ineluctable consummatory motor drive.(28) Tobacco use behaviors that are forbidden or foregone induce a negative prediction error signal in the NA core, which amplifies negative affect, increases aggressiveness and facilitates automaticity of response.(29,30) Activation of the pre-frontal and orbitofrontal areas of the cortex constrain cognition so that thoughts and reactions are consistent with the instinct to act.(31)

On a molecular level, nicotine's repeated stimulation of ion-gated cholinergic channels begins the process of translocating cyclic-AMP response element binding protein (CREB) to the nucleus of the cell.(32,33) Nicotine also blocks the enzymatic activity of histone deacetylase (HDAC), which regulates CREB activity.(34) Through translocation and disinhibition of CREB, nicotine facilitates the expression of ΔFosB, a transcription factor known as the molecular switch of addiction, increasing expression of genes coding for endogenous opioid neurotransmitters.(35) Endogenous opioids, including endorphin, enkephalin and dynorphin, are used to regulate the strength of connections between cells, reinforcing some striatal connections and pruning others.(36)

Pharmacologic treatment of tobacco use disorder

Early approaches to tobacco use disorder treatment were essentially reactive, with people encouraged to use the support after making their decision to change the behavior. This perspective inevitably led to unrealistic outcome expectations and normalized the custom of delaying cessation interventions. As a result, clinicians engage in tobacco use disorder treatment infrequently, despite the high morbidity and mortality related to tobacco use.(49–51) In pilot work investigating clinical decision-making, primary care clinicians strongly agreed with statements suggesting a comfort with tobacco counseling and a prioritization of treatment in patients with comorbid conditions. However, they disagreed with statements suggesting effective counseling would lead patients to quit, even if additional institutional resources were made available to address the problem. Underestimation of the probability of treatment success appears to be the result of a complex set of social motivations, including several important cognitive biases that influence clinical decision-making.(52–54)

The US Surgeon General first described tobacco use as the cardinal sign of addiction to nicotine in 1988, beginning the slow clinical shift away from episodic advice to quit toward an understanding that tobacco use disorder requires long term management due to the profound neuroadaptations that occur with long term use.(55) Ten years later, the US Public Health Service (USPHS) published the first comprehensive tobacco use disorder treatment

guideline, providing the evidential basis for both clinical workflow change and aggressive pharmacologic treatment.(56,57) Since then, a “first principle” of tobacco use disorder treatment has been to both encourage behavior change and recommend pharmacotherapy for all people who use tobacco. Most recently, medication pre-treatment strategies have been recommended as a means of controlling the root source of compulsive behavior even *before* attempting behavior change. Pharmacologic pre-treatment strategies have been proposed to help patients manage impulsivity and reduce the anticipatory anxiety of predicted tobacco cessation.(58,59)

To facilitate the use of tobacco use disorder treatments in the clinical setting, tailored guideline recommendations have emerged emphasizing clinical decision-making based on relative pharmacotherapeutic effectiveness.(59,60) Straightforward clinical paths help to reduce hesitancy and provide specific guidance on managing common clinical scenarios. For example, medications with different pharmacokinetic profiles are categorized into controller and reliever classes based on their dominant effect.(61) Pharmacologic agents with different mechanisms of action are no longer seen as therapeutically equivalent. Mechanistic combinations and longer duration of treatment are now preferred strategies in pursuit of improved outcomes. Perhaps most consequentially, current guidelines recommend use of medication treatments to treat the underlying tobacco use disorder even in individuals who have not yet stopped smoking, thus facilitating long term tobacco cessation and reduce tobacco withdrawal symptoms. This simple shift alone was estimated to result in up to 300 additional patients achieving tobacco cessation per thousand treated.(59)

Although the exact mechanism of action remains unclear, nicotine replacement therapies (NRT) are generally felt to work as an adjunct to behavioral management techniques by decreasing the intensity of signaling in the VTA and NA, blunting the downstream appetitive drive and anxiety response.(62–64) The transdermal nicotine patch has the slowest onset of action, but provides the longest and most constant rate of delivery (Table 1). Blood levels of nicotine peak 2 to 4 hours after applying the patch, compared with 5 to 10 minutes after using the nasal spray.(65) The patch is best positioned as a controller medication, and used in combination with one or more relievers like nicotine gum, lozenge, or spray based on patient preference.(66) For example, when used in conjunction with the nicotine patch, a piece of 4mg gum may be used every 1 to 2 hours as needed to address breakthrough nicotine cravings.(67) For patients unable to use the gum properly, or who cannot tolerate its taste, the nicotine lozenge can also be used to relieve withdrawal symptoms in a fashion similar to that of the gum.(68) Fear of overdose is common, and both clinicians and patients tend to underestimate how much NRT is required to produce the desired effect.(69) Concerns over acute cardiac events also undermine clinical confidence, yet NRT is considered safe even in populations at risk for coronary artery disease.(70,71) Fortunately, patients who continue to smoke while using NRT will reproduce baseline blood levels of nicotine, not higher.(72)

Bupropion SR is a tetracyclic antidepressant that acts in part by inhibiting uptake of dopamine from the accumbal synapse.(73) Bupropion SR is approximately equivalent in efficacy to NRT monotherapy, but most effectively promotes abstinence and controls withdrawal symptoms when combined with NRT and counseling.(74,75) Patients should

begin bupropion SR at least 7 to 10 days before the anticipated quit date; however, it is not uncommon for patients to require longer pretreatment to see the full effect. Varenicline, an agonist-antagonist of the nicotinic cholinergic receptors of the mesolimbic system, is purported to work by partially stimulating the VTA while limiting the effectiveness of the nicotine ligand. However, its actual mechanism of action remains unclear; outcomes counterintuitively improve when varenicline is combined with NRT.(76,77) Varenicline also requires an initial pretreatment period longer than labelled, exerting maximum effect with at least 4 weeks of treatment before attempting behavior change.(78,79) Despite popular concerns, the rate of neuropsychiatric side effects with varenicline appears to be quite low. Varenicline should be considered safe and efficacious, even in patients with pre-existing mental illness.(80)

Future directions

Nicotine is primarily metabolized into its 3'hydroxycotinine (3HC) and cotinine metabolites by the liver P450 enzyme CYP2A6.(81) Functional polymorphisms have been associated with slower nicotine clearance, and are more prevalent among individuals who do not smoke and people who find it easier to quit.(82) Conversely, faster nicotine metabolism has been associated with increased cigarette consumption (83), and difficulty achieving cessation in response to nicotine pharmacotherapy.(84) The 3HC/cotinine nicotine metabolite ratio (NMR) is a promising biomarker that reflects both CYP2A6 genetic variation and the gene-by-environment interactions known to influence nicotine clearance *in vivo*.(85,86) In a retrospective examination of clinical trial data derived from subjects randomized to receive either transdermal nicotine patches or nicotine nasal spray, individuals with slower nicotine metabolism experienced a significantly higher cessation rate when treated with nicotine patch than their counterparts who are fast-metabolizers.(87) This relationship was later confirmed in a double-blind, cohort-randomized clinical trial where slow metabolizers were nearly twice as likely to respond to nicotine patch, while no difference in clinical effectiveness was observed among subjects receiving varenicline.(88) Strategies aimed at personalizing pharmacologic treatment for tobacco use disorder have the potential to maximize pharmacotherapeutic effectiveness while minimizing adverse events.(89)

In the future, the way we think about measuring the effect of pharmacotherapy is likely to change substantially. Given the shift to chronic disease management paradigm, it's easy to imagine a number of intermediate outcomes becoming increasingly relevant to refinement of treatment strategies. For example, objective measures of the degree of control over compulsion, predictive models that quantify risk of relapse, and bio-measures of reduction in harms induced by tobacco smoke are all likely to provide clinicians with finer-grain information about the effects of their interventions.(90) Clinical phenotypes, defined by variables such as prior response to therapy, smoking behavior topography and biomarker status, will continue to move clinicians away from a monolithic approach to smoking and toward a more refined, precision therapeutic approach.(91)

The future also holds significant threats to achieving control over the epidemic of tobacco use. Innovations in alkaloid chemical production have resulted in tailoring of highly efficient salts that dissociate at more easily achievable pH and temperature and are increasingly

palatable to the individual using tobacco.(92,93) The introduction of progressively more efficient electronic delivery devices have also increased the availability of nicotine to the adolescent brain, with kinetic profiles and addictive liabilities that rival, and potentially exceed, that of traditional cigarettes.(94,95) The ever-growing variety of inexpensive and available nicotine delivery devices has resulted in an unfortunate shift away from evidence-based therapies among populations of individuals who smoke seeking complete tobacco cessation.(96) Finally, innovative processes have made commercial production of synthetic nicotine more cost-effective. These synthetic products potentially fall into regulatory gaps that threaten to place them outside the purview of agencies responsible for ensuring their safety - unless new oversight frameworks can be adopted before their widespread availability.(97)

Discussion

Tobacco use disorder continues to be popularly understood from a 19th century perspective. Popular assumptions regarding the euphoric requirement for drugs of abuse have at times clouded our communal perspective on the impact of tobacco use disorder, trivializing both the behavior and approach to treatment. Compared to other chronic relapsing and remitting illnesses, healthcare systems often lack the appropriate infrastructure and resources to treat substance use disorders in the most effective manner.(98) Unfortunately, much of the current dilemma is a derivative of public perceptions of addiction, and the stigmatization of tobacco use.(99,100) There is a growing sense that stigma and inadequate public policies that limit access to treatments for tobacco use disorder are unacceptable and unethical, particularly in circumstances like lung cancer where the afflicted suffer stigmatized tobacco-related illnesses.(101–103) Solving the seemingly intractable and tragic problem of nicotine addiction should be a core component of strategies to improve 21st century public health.

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Table 1 –

Tobacco Use Disorder Pharmacotherapy.

Medication	Dosage	Clinical Considerations	Side Effects	Cautions
Controller Medications				
Bupropion SR	150mg twice daily	• Consider starting 4–6 weeks before planned quit attempt. • Can cause insomnia if taken at bedtime - advise patients to take second dose with evening meal. • May help prevent relapse. • Often useful in preventing negative affect of withdrawal in patients with history of depressed mood.	• Agitation • Dry mouth • Vivid Dreams / Insomnia • Can decrease seizure threshold in alcohol withdrawal	• Current use of MAO inhibitors or other bupropion-containing meds. • Seizure disorder. • Eating disorder.
Nicotine Patch	7–21mg patch daily	• Most useful when used in combination with other medications. • Frequently under-dosed - consider start with 21mg for all patients with signs of tobacco dependence. Should be dosed for response. • Longer duration of treatment may be clinically beneficial.	• Local skin irritation. • Rarely nausea.	• No absolute contraindications. • Consider alternative in patients with skin conditions such as eczema.
Varenicline	Titrate to 1mg twice daily	• Consider starting 4–6 weeks before planned quit attempt. • Can cause insomnia if taken at bedtime - advise patients to take second dose with evening meal. • Can cause nausea if taken on empty stomach - advise patients to take with meals. • Safe in patients with mental illness.	• Nausea is relatively common upon initiation. Encourage patients to take with food. • Vivid Dreams / Insomnia • Depressed mood - may indicate dose is too high.	• Dose adjustment required for renal impairment.
Reliever Medications				
Nicotine Gum or Lozenge	2mg or 4mg every hour as needed	• Most effective when ‘parked’ against oral mucosa. • Consider starting with 4mg dose, reduce to 2mg only in patients with difficulty tolerating oral irritation. • Most useful as adjunct to controller medication.	• GI symptoms usually indicate excessive saliva ingestion. • Oral irritation.	• No absolute contraindications. • Use caution in patients with dentures or significant periodontal disease.

Medication	Dosage	Clinical Considerations	Side Effects	Cautions
Nicotine Inhaler	10mg cartridge every 1 −2 hours as needed	• Flexible dosing, used in response to cravings. • Consider start with 5–10 puffs every hour as baseline routine. • Particularly useful in conjunction with patch.	• Cough if inhaled too deeply. • Oral irritation.	• Consider alternative in patients lacking manual dexterity or hand strength necessary to load the device.
Nicotine Nasal Spray	1 spray each nostril every hour as needed.	• Flexible dosing, used in response to cravings. • May require period of accommodation to nasal irritation / sneezing.	• Nasal irritation. • Coughing • Vivid Dreams • Headache	• About 10% of patients develop dependence syndrome due to rapid absorption.