

Tobacco use disorder and treatment: new challenges and opportunities

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Introduction

Tobacco use is the cause of over 5 million deaths per year globally,¹ over twice as many deaths due to alcohol and illicit drugs combined. If current consumption rates continue, tobacco is projected to kill 1 billion people this century, with the majority of deaths occurring in low- and middle-income countries,² although there is good evidence for the effectiveness both of pol-

Tobacco use remains a global problem, and options for consumers have increased with the development and marketing of e-cigarettes and other new nicotine and tobacco products, such as “heat-not-burn” tobacco and dissolvable tobacco. The increased access to these new products is juxtaposed with expanding public health and clinical intervention options, including mobile technologies and social media. The persistent high rate of tobacco-use disorders among those with psychiatric disorders has gathered increased global attention, including successful approaches to individual treatment and organizational-level interventions. Best outcomes occur when medications are integrated with behavioral therapies and community-based interventions. Addressing tobacco in mental health settings requires training and technical assistance to remove old cultural barriers that restricted interventions. There is still “low-hanging fruit” to be gained in educating on the proper use of nicotine replacement medications, how smoking cessation can change blood levels of specific medications and caffeine, and how to connect with quitlines and mobile technology options. Future innovations are likely to be related to pharmacogenomics and new technologies that are human-, home-, and community-facing.

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icies² and pharmacological interventions³ in developing countries. An important subgroup of smokers that continues to use tobacco at a high rate includes those with mental illness or other addictions. A recent publication by the Royal College of Physicians (2013) provides an excellent summary of this previously neglected and overlooked population of tobacco users. Tobacco-use disorders are usually not isolated *Diagnostic and Statistical Manual of Mental Disorders (DSM)* diagnoses. Tobacco use is two to three times more prevalent among patients with other psychiatric disorders, including anxiety, attention-deficit, mood, and other substance-use disorders. Forty-four percent of all cigarettes in the United States are consumed by smokers with mental illness,⁴ and in mental health and addiction treatment settings, 50% to 95% are smokers.⁵ Unfortunately, smoking rates in this vulnerable population remain high despite the general trend for decreasing smoking rates in the United States as a whole.

This article will focus on important new issues in the assessment and treatment of tobacco-use disorders, including those with comorbid psychiatric disorders; new emerging tobacco and nicotine products, mobile technologies, and social media interventions; and future possibilities for pharmacogenomics and integrating technologies. Nicotine-receptor pharmacology and genetic variations have been a fruitful area in understanding the fundamental neuroscience of tobacco-use disorders, and they open windows to tailoring treatment based on genetic subtypes of fast/slow metabolism of nicotine and by specific pharmacotherapy agents. Assessment of nicotine and tobacco now must consider new delivery devices beyond cigarettes, including e-cigarettes, heat-not-burn delivery systems, and global products of other nicotine- and tobacco-related products.

Nicotine is a naturally occurring pesticide found on tobacco leaves and is the addictive substance in tobacco or cigarette smoke. When nicotine or tobacco is administered orally (nicotine-replacement therapy [NRT] medication, dissolvable tobacco, tobacco chew, snuff, etc), absorption is slow and takes 10 to 15 minutes. When nicotine is inhaled as smoke, it quickly reaches the alveoli of the lungs, and within 11 seconds of a puff, reaches the brain through the blood stream and crossing the blood-brain barrier. Nicotine then binds to nicotinic acetylcholine receptors (nAChRs) found throughout the brain. nAChRs have several α and β subunits, arranged in a pentamer configuration. One of the most

common subtypes is $\alpha 4\beta 2$ (which has two or three $\alpha 4$ units and three or two $\beta 2$ units) and has a high affinity for nicotine. Animal models and pharmacologic agents have identified the $\alpha 4$ and $\beta 2$ subunits of the nicotine receptor as contributing to nicotine-reinforcing effects.^{6,7} These ligand-gated receptors open with nicotine or acetylcholine and allow for the flow of ions.⁸

Nicotine arrives more quickly, and exhibits higher brain peaks, with cigarettes and e-cigarettes than other tobacco products, such as water pipes, dissolved nicotine, or the wide range of NRT products (oral gum, lozenge, inhaler, nasal spray, dermal patch). Smokers can also modulate their nicotine intake through the amount they smoke and how they smoke, for example, how deeply they inhale and whether they cover venting holes on cigarettes.⁹ In dependent smokers, repeated exposure to nicotine peaks can desensitize nAChRs so that they are less responsive, requiring a smoker to smoke more.¹⁰ In contrast, nicotine replacement patches release a stable amount of nicotine in the blood, eliminating peaks and alleviating dependence.

A newer version of diagnostic criteria was released in 2013 with the *DSM-5*,¹¹ the fifth edition of the *DSM*, which now classifies “tobacco addiction” or “nicotine dependence” as a “tobacco-use disorder,” similar to other substances. Diagnostic criteria for substance-use disorder require that at least two of 11 conditions listed (such as using more than intended, unsuccessful effort to cut down, time spent using, failure to fulfill life obligations, or giving up activities and use despite knowledge of the consequences) occur within a 12-month period. The *DSM-5*¹¹ criteria for tobacco-use disorder continue the tradition of blending the dependence syndrome¹² and biological symptoms of tolerance and withdrawal while adding a new diagnostic criterion of craving. The latter addition illustrates the growing acceptance that craving is a central component in substance use,¹³ despite a systematic review suggesting that craving is a poor predictor of relapse.¹⁴

Alternative modes of nicotine delivery

Cigarette smoking is the most prevalent form of nicotine delivery. However, alternative modes are becoming more common, including e-cigarettes and heat-not-burn and dissolvable-tobacco delivery systems. Between 2010 and 2013, lifetime use of e-cigarettes among US adults increased significantly from 3.3% to

8.5%.¹⁵ Rates of lifetime use are even higher in current cigarette smokers, 36.5% in 2013, whereas only 1.3% of nonsmokers report having tried e-cigarettes. Sixty percent of current smokers report lifetime use of e-cigarettes, and half report regular use.¹⁶ Even though e-cigarettes were initially promoted as a safer alternative to cigarettes, they are still a direct method of nicotine exposure. Compared with traditional cigarettes, nicotine exposure varies based on experience level of the user, whereby nicotine and cotinine are less concentrated for inexperienced users.¹⁷ A cigarette has about 6 to 11 mg of nicotine, resulting in 1 to 2 mg absorbed per cigarette.¹⁸ Cigars can contain 100 to 444 mg of nicotine, resulting in 9 to 68 mg absorbed. A nicotine cartridge for an electronic nicotine delivery system has 6 to 24 mg per mL of nicotine, and a whole cartridge can yield 2.5 to 7.7 mg inhaled nicotine.¹⁹ Contemporary electronic cigarettes have been shown to match or even exceed the nicotine delivery of a regular cigarette.

Nicotine causes release of dopamine and upregulation of receptors, resulting over time in nicotine dependence and craving with the drive to return to consuming nicotine. *Table I* summarizes the main effects of the other neurotransmitters that are released by nicotine binding.¹⁸ Nicotine's short half-life of 1 to 2 hours leads to withdrawal symptoms of irritability, frustration, anxiety, difficulty concentrating, restlessness, depressed mood, insomnia, increased appetite, weight gain, and cravings.

While e-cigarette cartridges have 6 to 24 mg of nicotine per mL, a study of 32 of the most popularly manufactured e-cigarette products in the US-made cartridges found trace nicotine in three products labeled as nicotine free and found that nine products showed differences

between labeled and detected nicotine concentrations larger than 20%.²⁰ In the European Union, regulations have recently been introduced to improve the accuracy of labeling of e-cigarettes. A recent study showed that next-generation e-cigarettes may even exceed the nicotine delivery of a regular cigarette.²¹ Another concern that may make these devices more addictive is the flavored options, which can appeal to youth, who are more vulnerable to addiction. Past-month e-cigarette use nearly tripled from 2013 to 2014 among high school students (4.5% to 13.4%), surpassing all other tobacco use.²² An ongoing study of these newer products confers an over four times greater risk of cigarette smoking 1 year later in adolescents.²³ Heat-not-burn products are a very recent addition to the smokeless tobacco market, though not yet available in the United States. Initial evidence suggests that smoke from these products, which were developed by tobacco companies, still contains volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide, as well as 84% of the nicotine found in conventional cigarette smoke.²⁴ Recent research shows that e-cigarette dual use is of concern in current smokers and is not a definitive method of quitting. A recent systematic review and meta-analysis found that in three cohort studies, there was no evidence that nicotine or non-nicotine electronic delivery systems helped people quit smoking.²⁵ In a meta-analysis of clinical trials and observational real-world studies, 20 controlled studies were analyzed,²⁶ and the odds of quitting cigarettes were 28% lower in those who used e-cigarettes than in those who did not use e-cigarettes, regardless of whether or not smokers were interested in quitting. In contrast, a systematic review from 2015²⁷ identified only six studies and reported that nicotine-filled e-cigarettes were more effective for cessation than those without nicotine. Similarly, a systematic review published last year²⁸ identified 62 studies of mostly lower quality and reported that e-cigarettes may be helpful for some smokers in smoking cessation or reduction. Taken as a whole, research to date does not support use of e-cigarettes for cessation; there is a need for more research on this topic. E-cigarettes can trigger use of traditional cigarettes.²⁹ Finally, although e-cigarettes may potentially reduce harm from the combustible products of traditional cigarettes, there is still not enough known about the byproducts and effects of e-cigarettes. Access and ingestion of nicotine in high doses, especially for nonsmokers and children, can be dangerous and even fatal.

Neurotransmitter	Effect
Dopamine	Pleasure, appetite suppression
Norepinephrine	Arousal, appetite suppression
Acetylcholine	Arousal, cognitive enhancement
Glutamate	Learning, memory enhancement
Serotonin	Mood modulation, appetite suppression
β-Endorphin	Reduction in anxiety and tension
GABA	Reduction in anxiety and tension

Table I. Main effects of neurotransmitters that are released by nicotine binding. GABA, γ -aminobutyric acid
Adapted from reference 18: Benowitz. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther.* 2008;83(4):531-541.

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Treatment of tobacco-use disorder/ nicotine dependence

There are seven evidence-based US Food and Drug Administration (FDA)-approved pharmacotherapies for tobacco-use disorder, as well as several evidence-based psychosocial interventions with the need for further study of emerging new options of person-, home-, and community-facing technologies (*Table II*).³⁰⁻³⁸ With the highest rates of tobacco-use disorders among people with psychiatric disorders, there is a need to continue to consider adapted and innovative treatments for this subgroup of users, especially given the increased associated morbidity and mortality, including the shorter

life span—by as much as 25 years—among those with serious mental illness.⁵

Medication options

There are seven FDA-approved medications for smoking cessation, including two non-nicotine replacement pill options of bupropion (Zyban) and varenicline (Chantix) and five nicotine-replacement therapies (NRTs). NRT patches, gum, and lozenges are available over-the-counter, whereas, in the United States, NRT inhaler and nasal spray are available by prescription only. Varenicline (Chantix) appears to be the most effective compared with placebo, followed by bupropi-

Intervention	Details	Appraisal	Setting	Key references
Integrated/ combined treatment	<p>Examples</p> <ul style="list-style-type: none"> - Using a combined psychosocial and pharmacological approach - Treating tobacco-use disorder concurrently with other illnesses and psychiatric disorders - Concurrently pairing a long-acting NRT (ie, nicotine patch) with a short-acting NRT (ie, gum, lozenge, inhaler, or nasal spray) - Concurrently pairing a long-acting medication, such as varenicline or bupropion, with a rescue medication, such as the gum or lozenge 	<ul style="list-style-type: none"> - Integrated treatment delivers the best outcomes - Medications can complement each other, and combined psychosocial and pharmacological approaches can address both psychological and biological dependence 	Clinical	Lancaster et al, ³⁰ 2000 Stead et al, ³¹ 2015 Stead et al, ³² 2016
Constituent treatments				
Nicotine replacement therapies (NRT)	Five types: patch, gum, lozenge, inhaler, and nasal spray	<ul style="list-style-type: none"> - FDA-approved - Relatively low cost - Marginally less effective than Varenicline and Bupropion - Offer more steady delivery of nicotine than cigarettes, reducing reinforcement - Patch, gum, lozenge over-the-counter - Inhaler and nasal spray by prescription only in the United States 	Clinical; nonclinical	Lawrence et al, ³³ 2009
Varenicline (Chantix)	Relieves craving and withdrawal, reducing the reinforcing effects of nicotine	<ul style="list-style-type: none"> - Most effective of the pharmacological interventions - FDA-approved - Be aware of black-box warning for cardiovascular adverse events - Be aware of possible neuropsychiatric symptoms in some patients (depressed mood, agitation, suicidality) 	Clinical	Lawrence et al, ³³ 2009

Table II. Recommended treatment for nicotine dependence. CBT, cognitive behavior therapy; FDA, US Food and Drug Administration; MAOI, Monoamine oxidase inhibitors; NicA, Nicotine Anonymous; NRT, nicotine replacement therapy; SR, sustained release

on and NRTs.³⁹ Varenicline is a partial agonist at the $\alpha 4\beta 2$ neuronal nAChR; as a partial agonist, it relieves craving and withdrawal, but reduces the reinforcing effects of nicotine by blocking dopaminergic stimulation (less smoking reinforcement/reward). Bupropion (Zyban) is the other medication that can affect dopamine, norepinephrine, and nicotinic-cholinergic receptors to decrease cravings and withdrawal symptoms. NRTs function to satisfy nicotine receptors while being less reinforcing. Whereas plasma nicotine sharply peaks within 5 minutes of cigarette use, NRTs offer a more steady delivery of nicotine, thereby satisfying but not reinforcing. In addition to having slower delivery, NRT only offers 30% to 75% of the amount of nicotine that would be acquired from smoking. To achieve substitution, the NRT should roughly match the individual's pretreatment level of nicotine. Many factors influence what amount of nicotine replacement might be needed to reduce or eliminate craving for nicotine, including the range of smoking behaviors, which effect levels of nicotine consumed from a cigarette (individuals can have longer or shorter inhalation breaths and longer or

shorter time periods between puffs); external environmental triggers (living with a smoker or working with smokers, etc); and genetic variation on the metabolism of nicotine (faster/slower metabolism).

Choice of medication depends on history, patient input, cost, previous attempts, and severity of dependence/withdrawal and breakthrough symptoms. Although cost effectiveness has yet to be verified,⁴⁰ these therapies can be effectively used in combination, for example, by concurrently pairing a long-acting NRT (ie, nicotine patch) with a short-acting NRT (ie, gum, lozenge, inhaler, or nasal spray) or combining a long-acting medication, such as varenicline or bupropion, with a rescue medication, such as the gum or lozenge.³⁰

Whereas smoking exposure during pregnancy is well recognized as a risk factor for premature birth, growth retardation and adverse long-term neurobehavioral effects, the effects of prenatal exposure to nicotine are less well known. We do know that nicotine is metabolized more quickly in pregnant women, easily passes the placental barrier, and accumulates in breast milk. Moreover, there is emerging evidence that prenatal nicotine

Bupropion SR (Zyban)	An antidepressant that reduces cravings and other withdrawal effects	<ul style="list-style-type: none"> - Effective, but less so than Varenicline - FDA-approved - Do not use with seizure disorders, current use of bupropion, or MAOIs, electrolyte abnormalities, eating disorders 	Clinical	Lawrence et al, ³³ 2009
Individual psychological intervention	Examples include brief counseling, motivational interviewing, cognitive behavior therapy	<ul style="list-style-type: none"> - Addresses psychological motivation to use tobacco and to quit - Even brief interventions have been shown to be effective 	Clinical	Stead et al, ³⁴ 2013 Lindson-Hawley et al, ³⁵ 2015
Group support	NicA, online support groups, CBT-based groups	<ul style="list-style-type: none"> - Leverages social support and social modeling in quitting - Aligns with other peer-support models for substance dependence - More effective than self-help, but not more effective than individual counseling 	Community, clinical, online	Stead et al, ³⁶ 2005
Mobile technologies	Text-message support, limited number of mobile apps	<ul style="list-style-type: none"> - Limited evidence for publicly available apps - Text-messaging support has been shown to be effective 	Community, online	Free et al, ³⁷ 2011 Abroms et al, ³⁸ 2013
Organizational interventions	Smoke-free institutions, workplace counseling	<ul style="list-style-type: none"> - Provides environmental supports for quit attempts, reducing cues and increasing motivation - Effective when combined with individual interventions 	Community	Abroms et al, ³⁸ 2013

Table II. Continued

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exposure is associated with premature birth, stillbirth, and abnormal brain development.^{41,42}

Patient education

Clinicians have an opportunity to greatly impact treatment outcomes by enhancing patient education on key issues. Often, nicotine replacement products are used incorrectly, particularly the “chewing” of nicotine gum as opposed to the recommended “bite and park” technique. Patients are often not told that blood levels of caffeine and many specific medications rise when someone quits smoking; thus, patients may experience symptoms of caffeine intoxication (doubling of caffeine levels in the blood with no change in caffeine intake⁴³) or side effects from specific medications (such as sedation, rigidity, etc, from specific antipsychotics and other medications). These interactions are a result of tobacco-smoke-metabolism interactions and not nicotine itself. The clinical encounter is an opportunity to educate patients on the appropriate way to take medications and also how to access quitlines available in the state, Nicotine Anonymous phone meetings, and Internet sites and mobile technology options, including texting and numerous apps.

There is strong evidence that combining psychosocial and pharmacological approaches is most effective.^{31,32} Important psychosocial or community-based interventions can be used without medications, including individual and group counseling with behavioral therapy, phone counseling (quitlines), and text messaging interventions. Individual interventions, such as brief counseling and motivational interviewing in health settings, are particularly effective,^{34,35} although a systematic review of patients hospitalized for coronary heart disease showed they required a longer duration of engagement.⁴⁴

Adjusting for psychiatric comorbidity

Treatment approaches may need to be adjusted slightly when addressing tobacco-use disorders among individuals with co-occurring psychiatric disorders; these individuals have disproportionately high rates of tobacco use. Those living with serious mental illness have a life expectancy that is 25 years lower than the general population,⁴⁵ a difference largely due to tobacco use as well as obesity and poor engagement in medical care.⁴⁶⁻⁴⁸ Those experiencing mental illness are about twice as

likely to be a smoker as the general population^{4,33} and have lower rates of quitting.⁴ Moreover, smoking tobacco can affect the metabolism of certain antidepressant and antipsychotic medications, particularly accelerating those primarily metabolized by cytochrome P450 1A2 (CYP1A2). Inequalities in tobacco-related mortality and morbidity are mutable with changes in clinician behavior to engage these individuals through willingness to engage, provision of treatment planning, and multiple treatment efforts. Nicotine may function, in the short term, to reduce certain psychiatric symptoms; however, there are no long-term benefits to ongoing tobacco use, and there are clear benefits from quitting. Individuals with schizophrenia may exhibit impaired sensory gating (related to polymorphisms on the $\alpha 7$ nicotinic receptor gene on the chromosome 15q14 locus), which can improve temporarily after nicotine use.⁴⁹ On the other hand, smoking cessation leads to significant reductions in anxiety, depression, and stress in both psychiatric and nonpsychiatric populations.⁵⁰

There is a growing literature on treatment options for tobacco users with comorbid psychiatric disorders, and there is consensus that clinical care of those with serious mental illness should include tobacco cessation and implementation of evidence-based interventions for smoking cessation. Earlier fears of chaos and deterioration after smoking cessation in this group have proven unfounded. Studies show comparable⁵¹ or improved⁵⁰ mood and quality of life among quitters, with few adverse individual or treatment program organizational effects.⁴⁶ Common smoking cessation treatments, such as bupropion and varenicline, have been shown to be well tolerated and effective in those with serious mental illness.^{51,52} Psychosocial strategies, such as pragmatic goal-setting and self-monitoring, may be particularly helpful adjuncts for individuals whose mental illness is associated with lower motivation and self-efficacy. “Learning about Healthy Living” is an example of a psychoeducational program for psychiatric patients, addressing how tobacco use enhances recovery and wellness.⁵³ Other interventions for smoking cessation leverage social support, which appears to be particularly helpful for men.^{54,55}

Use of mobile technology

There is increasing interest in the potential of mobile technologies in aiding smokers to quit. Programs range

from simple text messaging to applications that allow for interactive progress tracking. A Cochrane review⁵⁶ showed that mobile phone interventions significantly increase the long-term quit rates compared with control programs. Most of the existing evidence-based interventions in this area use text messaging, for example, the “txt2stop” intervention.³⁷ At comparatively low cost, mobile applications have the potential to bolster self-management with instantaneous measurement and feedback; but at present, it is too early to endorse any mobile applications as being truly evidence based. The quality of publicly available mobile applications is low, as few of these have been tested or even have adequate face validity. One study located a total of 252 smoking-cessation apps for iPhone and 148 for Android, reporting that popular apps scored low on adherence to the US Public Health Service’s Clinical Practice Guidelines for Treating Tobacco Use and Dependence.³⁸ Very few publicly available apps recommended medications, and no apps recommended calling a quitline, despite the effectiveness of these services. Although there is much potential in this area, there is still a need for further research on this rapidly growing technology option that now is including home- and community-facing technology through carbon-monoxide meters and real-time changes in measurements. There is a need for evidence-based mobile applications for smoking cessation to be more readily available.

Organizational-level approaches

New tobacco products and the potential for “personalized medicine” imply that potential changes must be part of the treatment culture to increase awareness and the willingness to integrate new treatments. Fundamentally, each treatment agency has a culture that supports addressing tobacco or not. Since tobacco-use-disorder treatment is often not reimbursed, there is often no incentive to treat, and indeed, there are disincentives pertaining to clinician time and agency resources. Historically, mental health and addiction treatment programs have been lenient and even supportive of tobacco use by their clients and staff. There is a need to improve staff training, to help staff quit smoking, to provide a tobacco-free campus, and to offer services including patient education on medications, side effects, changes in blood levels of caffeine and medication, and on how to engage in psychosocial and community-based op-

tions, such as quitlines, mobile technology, and Nicotine Anonymous. Having carbon-monoxide meters as standard equipment supports assessment and management. Rxforchange.ucsf.edu, for example, is a free and evidence-based training resource online with a curriculum specifically for psychiatric providers who want to change culture and treat tobacco use. There are also curricula on the website for other types of providers, including those in cardiology, respiratory care, and general medicine.

Organizational-change interventions, such as the Addressing Tobacco Through Organizational Change (ATTOC) model, have been used to help many mental health and addiction treatment programs in changing clinicians’ attitudes and organizational readiness to address tobacco; however, more research is needed. Having agency leadership support, local champions, work-group teams, enhanced communication, trainings, practical changes to support more interventions, and monitoring of changes in both organizational processes and individual client outcomes is feasible and can lead to changes in staff attitudes, skills, and services provided at these agencies.⁵⁷

Emerging medications

There are seven FDA-approved medications, which are discussed above, and emerging science may result in additional options in the future. For example, cytisine is a naturally occurring plant alkaloid, like nicotine, and functions similarly to varenicline, with strong binding affinity for the nAChR. It is considered first-line therapy in many Eastern European countries. Other targets may inhibit cytochrome P450 2A6 (CYP2A6), which is the major metabolizer of nicotine. Medications that are used for opiate-use disorder may reduce nicotine intake, suggesting that opioid receptors modulate the reinforcing effects of nicotine.⁵⁸ Two other medications of interest are mecamylamine, a noncompetitive antagonist of nicotinic cholinergic receptors and lobeline, an alkaloid and nicotine receptor agonist. These medications work in different ways with the former blocking nicotine effects, as well as reinforcement, and the latter satisfying the nicotine receptor. Currently, phase 1 and phase 2 clinical trials are looking at nicotine vaccines, which produce antibodies that can bind to nicotine to prevent nicotine from acting on receptors,⁵⁹ with limited effects. Research is relatively recent, and a potential

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concern is that with such a vaccine users might increase their intake of nicotine to overcome the effects of the vaccine.

Pharmacogenomics and tobacco-use disorders: insights that may lead to new treatments

Genome-wide association studies are now identifying single nucleotide polymorphisms on specific genes that are implicated in tobacco-use disorders. *CHRNA5* (cholinergic receptor nicotinic $\alpha 5$ subunit) was the first gene of interest in 2007,⁶⁰ and shortly thereafter, *CHRNA3* (cholinergic receptor nicotinic $\alpha 3$ subunit) was identified.⁶¹ The *CHRNA5-CHRNA3-CHRNA4* gene cluster on chromosome 15 encodes for most of the α - and β -receptor subunits of interest in nicotine dependence, and changes in specific amino acids of these genes lead to varying levels of nicotine agonist response.⁶² In human studies, homozygosity for a *CHRNA5* major allele is associated with reduced volume of smoke inhaled per puff when the nicotine content of a cigarette is increased.⁶³ Also, variants of the *CHRNA5-CHRNA3-CHRNA4* gene cluster are associated with cotinine levels in smokers.⁶⁴ *CHRNA2* (encodes the $\beta 2$ subunit) are important for the $\beta 2$ nAChR subunit function, which can be protective against the initiation of regular smoking by decreasing dopamine release during early smoking experiences.⁶ This is relevant because roughly one-third of people who try smoking go on to become dependent. Targeting specific receptor subunits, most involved in addiction, may help with medication development in the future.

In addition to susceptibility to nicotine and nicotine dependence, genetic studies also can inform responsiveness to the currently FDA-approved medication treatments. For example, *CHRNA5* markers may indicate response to nicotine replacement therapy.⁶⁵ Such insights could lead to precision-medicine targets; however, medications such as NRT are underutilized, and increasing access and use of these medications, regardless of allele, is also imperative.

Nicotine clearance is also important for mediating nicotine's effects and is mostly metabolized in the

liver; individual variation in liver metabolism leads to different smoking behaviors.⁶⁶ Most nicotine is cleared through CYP2A6 metabolism, converting nicotine into cotinine and then to *trans*-3'-hydroxycotinine (3HC). Both metabolites are detectible in the urine; generally, cotinine is a biomarker for nicotine exposure, with a long half-life of about 16 hours.⁶⁷ Different rates of CYP2A6 (loss of alleles *2 and *4) metabolism can be associated with varying degrees of addiction risk, quit rates, and medication efficacies.^{68,69}

Conclusion

Tobacco use continues to increase morbidity and mortality with high rates of tobacco-use disorders among individuals with psychiatric disorders resulting in severe health disparities for that population. New nicotine and tobacco products will continue to be developed, as will new treatments, with increasing person-, home-, and community-facing technologies. The dialogue must include how to effectively implement the existing evidence-based resources that are available, which will require more training, support tools, technical assistance at the organizational level, and a hopeful attitude.

Reducing tobacco use in the broader population requires a multipronged approach. In terms of prevention, initiating use of emerging nicotine delivery systems, such as e-cigarettes, should continue to be discouraged, with early interventions among children and adolescents. Treatment of tobacco-use disorder is optimized by the integration of evidence-based pharmacological and psychosocial treatments, as well as effective implementation in real-world settings. Special attention must be paid to organizations treating individuals with mental illness and substance-use disorders because of the long traditions of ignoring tobacco use and the persistent clinical indifference to the disease burden caused by tobacco use in these populations. Our knowledge of the effects and effective treatments of nicotine use has increased rapidly in the last decades, but there is much yet to do. □

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El trastorno por uso de tabaco y su tratamiento: nuevos desafíos y nuevas oportunidades

El uso de tabaco sigue siendo un problema mundial, y las opciones para los consumidores han aumentado con el desarrollo y comercialización de cigarrillos electrónicos y otros nuevos productos de la nicotina y del tabaco, como el tabaco que “calienta pero no quema” y el tabaco soluble. El aumento del acceso a estos nuevos productos está yuxtapuesto con el desarrollo de la salud pública y de las opciones de intervenciones clínicas, incluyendo las tecnologías móviles y los medios de comunicación social. El persistente aumento en la frecuencia de los trastornos por uso de tabaco entre los pacientes con trastornos psiquiátricos ha atraído una mayor atención mundial, incluyendo intervenciones exitosas a nivel de los tratamientos individuales y en las organizaciones. Los mejores resultados se obtienen cuando se combinan medicamentos con terapias conductuales e intervenciones a nivel de la comunidad. El tratamiento del tabaquismo en los ambientes de salud mental requiere entrenamiento y asistencia técnica para remover las antiguas barreras culturales que restringen las intervenciones. Todavía hay posibilidades fáciles para enseñar la utilización correcta de medicamentos que reemplacen a la nicotina, para saber que el dejar de fumar puede modificar los niveles plasmáticos de determinados fármacos y de cafeína, y para conocer cómo conectarse con aplicaciones de tecnologías móviles y líneas telefónicas orientadas a dejar de fumar. Es probable que las futuras innovaciones estén relacionadas con la farmacogenómica y con nuevas tecnologías orientadas a los humanos, a la casa y a la comunidad.

Nouveaux défis et nouvelles opportunités du traitement et des troubles de l'usage du tabac

L'usage du tabac reste un problème mondial, de nouvelles options se présentant aux consommateurs avec le développement et la commercialisation des cigarettes électroniques et d'autres nouveaux produits dérivés du tabac et de la nicotine, comme le tabac « qui chauffe mais ne brûle pas » et le tabac soluble. L'accès accru à ces nouveaux produits se juxtapose au développement de la santé publique et aux options d'intervention clinique, telles que les technologies mobiles et les médias sociaux. L'attention générale s'est focalisée sur le taux élevé persistant des troubles liés au tabac parmi les patients qui ont des troubles psychiatriques, et notamment sur le succès des traitements individuels et des interventions organisationnelles. Les résultats sont meilleurs quand les traitements sont intégrés à des thérapies comportementales et à des interventions de proximité. Le traitement du tabagisme dans le cadre de la santé mentale nécessite une formation et une assistance technique pour supprimer les barrières culturelles qui restreignent les interventions. Il existe encore des solutions faciles à mettre en œuvre pour éduquer les patients à l'utilisation correcte des substituts nicotiniques, leur expliquer comment l'arrêt du tabac change les taux sanguins de certains médicaments spécifiques et de la caféine et leur apprendre à se connecter aux applications mobiles et aux lignes téléphoniques dédiées à l'arrêt du tabac. De futures innovations seront probablement liées à la pharmacogénomique et à de nouvelles technologies qui seront tournées vers l'humain, la maison et la population.