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Innovative approaches to support smoking cessation for individuals with mental illness and co-occurring substance use disorders

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Abstract

Introduction—Tobacco remains the leading preventable cause of death in the US, accounting for over 520,000 deaths annually. While the smoking prevalence has declined over the past 50 years, those with mental illness and addictive disorders continue to smoke at high levels and with significant tobacco-related health problems.

Areas covered—This review highlights the epidemiology, contributing factors, and evidence-base for intervening upon tobacco use in those with mental illness and addictive disorders. Historically under-prioritized, a growing body of literature supports treating tobacco within mental health and addiction treatment settings. Critically, treating tobacco use appears to support, and not harm, mental health recovery and sobriety. This review also summarizes novel, emerging approaches to mitigate the harms of cigarette smoking.

Expert commentary—People with mental illness and addictive disorders have a high prevalence of tobacco use with serious health harms. Treating tobacco use is essential. Evidence-based strategies include individual treatments that are stage-matched to readiness to quit and combine cessation medications with behavioral therapies, supported by smoke-free policies in treatment settings and residential environments. Emerging approaches, with a focus on harm reduction, are electronic nicotine delivery systems and tobacco regulatory efforts to reduce the nicotine content in cigarettes, thereby reducing their addiction potential.

Keywords

Tobacco; smoking; nicotine; mental illness; substance use disorders; e-cigarette; dual diagnosis; nicotine replacement therapy; CYP1A2; quit-line

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Declaration of interest

JJ Prochaska has consulted for Pfizer, which makes smoking cessation medications; Carrot Sense, which makes a tobacco cessation device; and has been an expert witness for in litigation against the tobacco industry. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Prevalence and significance of tobacco use in individuals with mental illness and addictive disorders

People with mental illness and addictive disorders consume nearly half the cigarettes sold in the US and are disproportionately affected by tobacco [1]. The smoking prevalence in the general population has declined to 15%, while 50–95% of patients in mental health and addiction treatment settings smoke cigarettes [2–4]. The estimates of smoking prevalence range with study design and psychiatric diagnosis. Higher smoking prevalence is reported in clinical versus community or epidemiologic studies and among patients with bipolar depression, schizophrenia, and substance use disorders. Consistently, clients in methadone maintenance programs and hospitalized psychiatric patients have the highest smoking prevalence [5]. The smoking prevalence is almost fivefold greater among those with schizophrenia, bipolar disorder, post-traumatic stress disorder (PTSD), and alcohol/illicit drug use disorders [6]. Notably, depression is twice as common in smokers as nonsmokers, and four times as common in heavy smokers [7]. Smoking prevalence increases with a greater number of diagnosable mental disorders: 18% for people with no mental illness versus 61% for people diagnosed with three or more mental disorders [8]. People with mental illness tend to smoke more cigarettes, smoke more intensely, and have greater dependence on nicotine, greater withdrawal symptoms when quitting, and lower quit rates [9–14].

Tobacco remains the leading preventable cause of death, accounting for over 520,000 US deaths annually. People with mental illness die on average 25 years earlier than the general population, largely from chronic tobacco-related diseases such as heart and pulmonary diseases and cancers [15]. Tobacco also worsens wound healing, diabetes, asthma, impotence, eye and oral health, and osteoporosis [16].

1.1. Additional considerations for patients with mental illness who smoke

1.1.1. Medication effects—Smoking affects medication levels of several psychotropic medications via the CYP1A2 metabolism interaction. Tobacco smoke (not the nicotine) induces CYP1A2 activity, decreasing the effective levels of caffeine, haloperidol, clozapine, methadone, olanzapine, tricyclic antidepressants, other psychotropics as well as many general medications (e.g. heparin, insulin, warfarin) and caffeine. Tobacco use and patients' efforts at quitting smoking need to be communicated among treatment providers to ensure appropriate medication management, and patients quitting smoking should be counseled to reduce their caffeine intake.

1.1.2. Withdrawal—Symptoms of tobacco withdrawal (i.e. irritability/frustration/anger, anxiety, difficulty concentrating, restlessness/impatience, depressed mood/depression, insomnia, increased appetite/weight gain) overlap with symptoms of other psychiatric disorders. Treatment of nicotine withdrawal combines pharmacotherapy and behavioral strategies (e.g. physical activity, deep breathing). Failure to treat nicotine withdrawal, especially in patients hospitalized on smoke-free units, may lead to misattributions of withdrawal symptoms to a worsened psychiatric disorder with suboptimal care. In a study of psychiatric inpatients, failure to offer nicotine replacement was associated with a twofold

greater likelihood of against medical advice (AMA) discharge relative to smokers offered nicotine replacement, who had AMA discharge rates comparable to nonsmokers [17].

1.1.3. Suicidal behavior and tobacco use—Studies in young people and adults, with cross-sectional and prospective study designs, have found current smoking to be significantly associated with suicidal behavior, independent of depressive symptoms, prior suicidal acts, and other substance use [18,19]. The most recent study found that longer lifetime smoking (>40 years versus 10 years) was associated with a twofold higher odds of suicide [20]. Quitting smoking appears to mitigate the risk [21]. As a signal of self-harm and potentially suicidal behavior, tobacco use warrants attention in psychiatry.

1.1.4. Social impacts of tobacco—Tobacco use is costly, in one study, accounting for 27% of patients fixed incomes [22]. Among those with mental health concerns, smokers report greater disability in work functioning, greater family dysfunction, and poorer social functioning relative to nonsmokers [23]. With increasing public restrictions on secondhand smoke exposure, tobacco use also can be isolating, marginalizing, and stigmatizing [24]. In a study in California with smokers with serious mental illness, 75% reported smoking most or all of their cigarettes while alone [25]. Smoking also reduces housing options and is associated with greater difficulty securing employment [26,27].

1.1.5. Secondhand smoke—Secondhand smoke exposure is harmful to health, causing nearly 34,000 heart disease deaths annually among adult nonsmokers in the US [16]. Further, the effects of secondhand smoke go beyond respiratory and cardiac health, with evidence that secondhand smoke exposure is related to the development of depression, generalized anxiety disorders, attention-deficit/hyper-activity disorder, and conduct disorder [28,29].

In the early 1990s, hospitals went smoke-free via a Joint Commission ban; however, psychiatric units were exempted from the ban and remain exempt two decades later, although many psychiatric hospitals have opted for a voluntary ban. Several studies have reported secondhand smoke exposure to be higher among individuals with mental illness and addictive disorders and among those who are homeless [25,30,31]. Despite knowing that secondhand smoke is harmful, there remains resistance to ban smoking in psychiatric settings [32].

1.2. Reduced access to tobacco cessation treatment

Despite the known harms of smoking, there has been a historic reluctance to treat tobacco use among smokers with mental illness or addictive disorders due to concerns that mental health functioning or sobriety may be compromised. In a 2007 survey of more than 3000 physicians, psychiatrists were the least likely specialty to address tobacco; 47% of psychiatrists felt patients had more immediate problems to address, and 22% believed quitting smoking heightened other symptoms [33]. A review of 26 studies on smoking bans found that psychiatric staff believed tobacco is important for self-medication and smoking bans in psychiatric units would worsen symptoms and increase behavioral problems [34].

'Self-medication' beliefs (i.e. that cigarettes reduce psychiatric symptoms) also adversely affect treatment practices and quit attempts among people with mental illness. The tobacco industry furthered the self-medication hypothesis in targeted marketing and funding of research [35]. Cigarettes reduce nicotine withdrawal symptoms, which can mimic psychiatric symptoms, and cigarette smoke can reduce the blood levels (potency) of a number of psychiatric medications, thereby reducing medication-induced sedation and amotivation. Hence, it is not so much that smoking treats psychiatric illness, but rather that smoking reverses nicotine withdrawal and mitigates psychiatric medication side effects.

Further, counter to the self-medication hypothesis, research has demonstrated that clinical symptoms of unipolar depression, bipolar disorder, PTSD, and schizophrenia can improve with tobacco treatment [36]. Treatment of tobacco during a psychiatric hospitalization is associated with a decreased likelihood of rehospitalization and an increased likelihood of sobriety among smokers in treatment for addictive disorders [14,37,38]. Further, individuals with mental illness or addictive disorders are just as motivated to quit smoking as the general population. Among hospitalized smokers with mental illness, 65% were interested in quitting [39].

2. Medication treatment approaches to tobacco use disorders

2.1. First-line US FDA-approved cessation medications

Evidence-based tobacco treatments are effective for people with mental illness and substance use disorders. There are seven FDA-approved medications for smoking cessation in the US: varenicline (Chantix), bupropion (Zyban), and five nicotine replacement therapies (NRTs).

An oral medication, varenicline is a partial agonist at the $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor; as a partial agonist, it relieves craving and withdrawal, but reduces the reinforcing effects of nicotine by blocking dopaminergic stimulation (less smoking reinforcement/reward). In EAGLES, the largest tobacco cessation clinical trial conducted to date, varenicline was more effective for quitting smoking than placebo, nicotine patch, and bupropion; bupropion and nicotine patch were more effective than placebo and were comparable to each other [40]. The randomized trial was triple-blinded and enrolled 8144 daily smokers about half of whom had active or past history of psychiatric disorder. In the psychiatric cohort, continuous abstinence rates at 6-months follow-up were 18.3% for varenicline, 13.7% for bupropion, 13.0% for NRT, and 8.3% for placebo. In the analysis of neuropsychiatric safety, the frequency of moderate-to-severe events was under 3% in the nonpsychiatric cohort and under 7% in the psychiatric cohort, with no significant difference by medication condition [40]. The most frequently reported symptom was agitation, a known feature of nicotine withdrawal. In December 2016, the FDA announced removal of the box warning on varenicline for serious neuropsychiatric adverse events.

The other oral medication is bupropion, acting on dopamine, norepinephrine, and nicotinic-cholinergic receptors, thereby decreasing cravings and withdrawal symptoms. In EAGLES, bupropion outperformed placebo and was well-tolerated among smokers with current or past psychiatric disorders [40]. Among patients with schizophrenia stabilized on an adequate

antipsychotic regime, two meta-analyses concluded that bupropion for quitting smoking was well tolerated and more than doubled the likelihood of abstinence at end of treatment and 6-months follow-up [41,42].

NRT was the first FDA-approved treatment for tobacco use disorders. NRT patch, gum, and lozenge are available over-the-counter, while NRT inhaler and nasal spray are available by prescription. Nicotine when delivered via a smoked cigarette reaches the brain in under 10 s. In contrast, NRTs offer slower and more steady delivery of nicotine, thereby satisfying receptors without reinforcing addiction. In addition to slower delivery, only 30–75% of nicotine in NRT is absorbed compared to smoking. NRT, by alleviating some of the discomfort of nicotine withdrawal, allows the smoker to focus on behavioral aspects of tobacco cessation. A large number of randomized controlled trials have been conducted on NRT in the general population, and meta-analyses have found that all NRT forms significantly improve abstinence rates when compared to placebo; NRT approximately doubles long-term quit rates relative to placebo; and the strongest evidence is for combination NRT, which adds to the long-acting patch one of the short-acting NRT forms (gum, lozenge, nasal spray, or inhaler) [43–45]. While the patch is easy to use and conceal and provides a slow steady delivery of NRT, the other NRTs can be added to provide symptomatic relief as needed for cravings and trigger situations. Far fewer studies have tested NRT in psychiatric samples. As mentioned, EAGLES, the most recent, largest, and only placebo-controlled randomized trial of NRT in a sample with current or past psychiatric disorders, found that the NRT patch was comparable to bupropion and both outperformed placebo [40].

The U.S. Public Health Service Clinical Practice Guideline for Treating Tobacco Use and Dependence and the American Psychiatric Association recommend the use of cessation medications with all smokers interested in quitting, with few contra-indications [44,46]. All of the cessation medications double quit rates compared to placebo, and varenicline and combination NRT appear to be the most effective, followed by bupropion and single form NRTs [47]. NRT also can be combined with bupropion. Factors to consider in selecting a medication include previous quit history, potential medication interactions, patient input and adherence, cost and severity of dependence/withdrawal and breakthrough symptoms.

2.2. Medications with evidence but not FDA approval for treating tobacco

Three older medications have demonstrated efficacy for smoking cessation, but are not FDA-approved. They are clonidine, an alpha2 adrenergic receptor agonist; nortriptyline, a tricyclic antidepressant and weak antagonist of nicotine receptors; and cytosine, a naturally occurring plant alkaloid (as is nicotine) that functions similarly to varenicline with strong binding affinity for the nicotinic acetylcholine receptor. Cytosine is considered first-line in many European countries, and recent research and reviews have supported its use [43,48]. We are unaware of any studies in psychiatric samples.

2.3. Medication targets under study

Other targets and pharmacologic treatment approaches are being researched. Nicotine is metabolized by cytochrome CYP2A6, so potentially an inhibitor may be useful for

prolonging effects of NRT [49]. Another target may be in opiate receptor pharmacology; it is proposed that chronic nicotine exposure enhances kappa opiate receptor activity which produces worse nicotine withdrawal. Therefore, kappa antagonists may reduce some of the kappa-mediated anxiety and withdrawal [50]. Research also is ongoing with phase I and II clinical trials for nicotine vaccines, which produce antibodies that bind to nicotine to prevent nicotine from acting on receptors [51]. We are unaware of any studies in psychiatric samples.

2.4. Genetic testing and treatment tailoring

Genome-wide association studies help identify new targets for treatment of tobacco use and addiction such as single nucleotide polymorphisms on specific genes that are implicated in tobacco dependence [52]. *CHRNA5* was the first gene of interest identified in 2007; the *CHRNA5-CHRNA3-CHRNA4* gene cluster on chromosome 15 encodes for most of the receptor subunits of interest in nicotine dependence and changes in specific amino acids of these genes lead to varying levels of nicotine response. This can lead to varying responses to NRT with implications for precision medicine applications in tobacco cessation [53]. However, given that medications such as NRT are underutilized, improving access to these medications, regardless of allele, is also imperative. We are unaware of any studies in psychiatric samples.

3. Psychosocial treatment approaches to tobacco use disorders

3.1. The 5-As framework

Success with quitting smoking is strongest for combined psychosocial and pharmacological approaches [44,46]. The U.S. Public Health Service Clinical Practice Guideline for Treating Tobacco Use and Dependence and the American Psychiatric Association recommend the Five As as a model for clinicians to organize tobacco cessation treatment: Ask, Advise, Assess, Assist, and Arrange follow-up [4,45]. At all clinical encounters, providers should *ask* about tobacco use. Patients who use tobacco should be *advised* to quit, with a personal, nonjudgmental message, and then *assessed* for interest in quitting. For those not ready to quit, a foundation of rapport should be developed with a focus on building motivation. For those ready to quit, *assistance* should be provided with goals of setting a quit date and developing a quit plan, considering cessation medications to address withdrawal, identifying triggers, buffering social support, and referring to community resources. Finally, *arrange* follow-up to continue the conversation.

3.2. Smoke-free treatment settings

Establishing smoke-free buildings and grounds helps promote a culture for smoking cessation, and smoke-free psychiatric hospitalization (people admitted for acute psychiatric and substance related disorders like depression, bipolar disorder, schizophrenia, and so on) is a key time for intervention. Nicotine withdrawal symptoms peak in 1–3 days and then resolve over 2–4 weeks. Enduring those symptoms in a safe environment, ideally with cessation medication provided to alleviate withdrawal, can help support cessation [54]. Research has demonstrated that a technology-supported intervention combined with NRT, initiated during a smoke-free hospitalization, tailored to patients' motivation to quit, and

providing follow-up treatment post discharge was effective for achieving abstinence out to 12 months [37,55].

3.3. Psychosocial approaches with evidence

Strategies for assisting patients with quitting smoking include individual and group counseling, phone counseling (quitlines), and digital health interventions. Brief counseling and motivational interviewing in health settings also are both effective, and longer engagement increases success rates further [42,56–60].

3.3.1. Behavioral therapy—Delivered by a variety of health professionals, an extensive literature supports behavioral therapy (BT) approaches [44,45,61]. BT targets learning processes and contextual factors that have been sustaining the problem behavior. Typically delivered weekly over a number of weeks, BT attends to the physiological, psychological, social, and environmental aspects of smoking and nicotine addiction. BT teaches strategies to identify, avoid and cope with triggers; manage craving; reduce withdrawal symptoms; and engage social support. BT encourages treatment adherence and continued engagement and attends to associated health issues (e.g. stress, mood, weight gain, substance use) [45].

3.3.2. Acceptance and commitment therapy—Acceptance and commitment therapy (ACT) is a form of contextual BT where the emphasis is on mindfulness and acceptance, rather than cognitive restructuring of difficult feelings [62]. A recent review of ACT versus treatment as usual for treating smoking in five studies, with nearly 1000 patients, found a small to medium significant effect size favoring ACT [63]. Notably, effects were stronger over time, attributed to the ‘sleeper’ effect of ACT, whereby psychological flexibility improves over time even after the intervention has ended. ACT has demonstrated efficacy for treating major depression, anxiety disorders, borderline personality disorder, and substance abuse [64,65]. The potential for integrating tobacco cessation treatment within ACT-based interventions with psychiatric populations warrants further study [66,67].

3.3.3. Contingency management—Contingency management (CM) is an approach that pairs positive reinforcement (the possibility of acquiring material or financial incentives) to a desired behavior (participation in cessation treatment) or outcome (confirmed not smoking with a carbon monoxide breath sample). Used in substance use treatment, CM has had encouraging effects for treating tobacco, especially in those with comorbid substance use disorders [68,69]. The effects, however, are difficult to maintain once the incentives cease [70].

3.3.4. Quitlines—Quitlines are evidence-based psychosocial interventions that have been in the community for over 25 years, provide individual coaching over the phone and sometimes free NRT; the 1–800-quit-now number links callers to the quit smoking program in their state [71,72]. Recent national promotional efforts by the Centers for Disease Control and Prevention (TIPS) directed at smokers, health care providers, and family members have repeatedly demonstrated effectiveness in driving callers to quitline cessation services [73]. The 2016 TIPS campaign featured a woman with a history of depression successful with quitting smoking: <https://www.cdc.gov/tobacco/campaign/tips/stories/rebecca.html>. A study

conducted in six Veterans Affairs Medical Center compared the standard state quitline to a specialized telephone smoking-cessation intervention developed for mental health patients. While control group patients were referred to their state quitline with a warm transfer, the special intervention patients received proactive multisession counseling from a study counselor who followed a manualized protocol developed for the study, integrating motivational interviewing, problem-solving therapy, and cognitive BT approaches. They addressed behavioral, cognitive, affective, and health education domains of quitting. The counselors also integrated the mental health providers in treatment communication. At 6 months, participants randomized to the specialized counseling arm were significantly more likely to report 30-day abstinence (26% vs. 18%) and were more satisfied with the treatment [74]. Increasingly, states have added program supports or specially trained counselors or pharmacists for callers with mental illness [75].

3.3.5. Digital health—As people increasingly use technology for health, interest is growing in programs, applications, and forums for quitting smoking. Most (93%) smokers report owning a mobile phone with 76% owning a smartphone [76]. A 2013 Cochrane review ($N = 28$ studies) concluded that web-programs that are interactive and individually tailored show evidence of assisting smokers with quitting out to 6 months or longer [77]. One of the most popular quit smoking websites, used by over 3 million smokers in 2013, is the National Cancer Institute's evidence-based Smokefree.gov. Smokefree.gov includes five websites (smokefree.gov, smokefree.gov/veterans, women.smokefree.gov, Espanol.smokefree.gov, and teen.smokefree.gov), seven text message programs, five smartphone apps, and multiple social media platforms. For a clinician, it is easy to use, has printable info-sheets and educational modules. Smokefree.gov offers SmokefreeTXT services for free with self-reported quit rates of 9.46% 6 months after the 8 week program [78]. To register, patients can go online (smokefree.gov/SmokefreeTXT) or send a text message with the word QUIT to 47,848. A Cochrane review of 13 studies of texting interventions reported a significant 36% improvement in quit rates and similar outcomes to quitline services [79].

Smartphone apps are numerous; in 2013, there were over 400 smoking cessation apps with over 3 million downloads in the US [80,81]. Examples include QuitGuide, MyQuit, SmartQuit, and Craving to Quit [82,83]. Technology is expanding quickly and evaluations are needed. A study that identified 252 smoking-cessation apps for iPhone and 148 for Android found the most popular apps scored low on adherence to the Clinical Practice Guidelines, and the publicly available apps failed to recommend cessation medications or the tobacco quitline [84]. Digital gaming is another popular medium. Video games for quitting smoking include *Nicot*, where users crush virtual cigarettes; *Lit 2 Quit*, which guides users through breathing exercises; and *QuitIt*, based on Social Cognitive theory, with users practicing strategies for coping with smoking urges and maintaining abstinence by going through episodic stories [85–87].

Social media also is exceedingly popularity with potential applications for treating tobacco use. Facebook has nearly 1.9 billion monthly users, and a mixed methods survey of 570 young adult Facebook users found nearly one in three smokers were interested in using Facebook for quitting smoking [88]. Facebook page *Crush the Crave* boasted 34,690 likes

and a total reach of 7282 people in 2013; UbiQUITous is based on the US Public Health Service '5As' model [89]. Twitter also shows promise. *Tweet2Quit*, a hybrid social media intervention, with daily, automated communications sent to small, private, self-help groups to encourage high-quality, online, peer-to-peer discussions doubled sustained abstinence out to 60 days follow-up [90].

To date, digital health interventions have received limited investigation among smokers with mental illness. Testing these strategies as adjuncts in psychiatric and substance use settings is needed.

4. Approaches to tobacco harm reduction

4.1. The rise of e-cigarettes

While cigarettes represent about 90% of tobacco/nicotine use, the market for e-cigarettes is growing. E-cigarettes are battery-powered devices that generate an inhaled aerosol. E-cigarettes typically consist of a metal tube resembling a normal cigarette, a battery, an atomizer, and a replaceable cartridge that contains liquid nicotine, propylene glycol, glycerin, flavoring, and other chemicals. Tank or open system e-cigarettes allow users to fill the device with their substance of choice. (In an anonymous survey of high school students [$n = 7,000$], nearly one in five e-cigarette users reported using the device to smoke cannabis oil [91].) Developed and commercialized in China in 2003, e-cigarettes entered the US market in 2006, though tobacco companies such as Philip Morris have been researching precursors to e-cigarettes since 1990 [92].

Over the past decade, advertising and sales of e-cigarettes have increased exponentially year over year, and the major tobacco retailers are now dominating the cigalike market (products resembling cigarettes) [93]. Unlike traditional cigarettes, where advertising has been banned from television and radio since 1970, e-cigarettes are promoted widely on TV and radio as well as on the Internet and in social media. Similarly, access has proliferated with purchase available online, in convenience stores, and in neighborhood vape shops. Another concern with e-cigarettes is their youth-friendly flavors (e.g. cotton candy, Katy Perry cherry, unicorn-vomit). Among high school students, past-month e-cigarette use nearly tripled from 2013 to 2014 (4.5–13.4%), surpassing all other tobacco use [94]. Among people with mental illness, 15% have tried e-cigarettes compared to 7% of the general population [95]. In a study with 956 cigarette smokers hospitalized for mental illness, trial use of e-cigarettes went from 0% in 2009 to 25% in 2013; use was unrelated to success with quitting combustible cigarettes [96].

E-cigarettes use has the potential of reducing harm for smokers able to switch completely from traditional cigarettes to e-cigarettes, where there is no combustion, and therefore, no carbon monoxide and smoke exposure. (Study is needed, however, of the safety and harms of chronic, repeated vapor inhalation [97].) Dual use (smoking combustible cigarettes and e-cigarette) also is common with possibly greater nicotine exposure; many 'nicotine-free' e-cigarette products, inaccurately labeled, contain nicotine [98,99]. The FDA recently exerted its regulatory authority over e-cigarettes. Product safety has yet to be established.

Only two randomized controlled trials have evaluated early forms of e-cigarettes as a method for quitting conventional cigarettes using early forms of the devices; in a review, the quality of evidence was judged to be low grade, and in both trials, e-cigarettes with nicotine were equal to placebo (nicotine-free) e-cigarettes in efficacy for quitting smoking [100]. Both studies were conducted with smokers without mental illness or addictive disorders. The American Heart Association's (AHA) policy statement is the most recent expert guideline regarding e-cigarettes. The AHA guideline does not recommend e-cigarette use. If a patient has tried and failed evidence-based tobacco cessation methods or is unwilling to try them, the AHA guideline recommends no dual use of traditional cigarettes with e-cigarettes and that a quit date be set for the e-cigarette [101].

4.2. Very low nicotine content cigarettes

Very low nicotine content (VLNC) cigarettes (not to be confused with tobacco company marketing of light and ultralight cigarettes, which do not actually reduce nicotine content) are being researched for harm reduction. It is proposed that reducing nicotine content to 0.5 mg in a cigarette or less (half of a standard cigarette) can reduce addiction potential [102]. A seven-group, double-blind, randomized trial conducted with 840 participants at 10 sites compared control cigarettes (regular cigarettes) to reduced nicotine cigarettes that had 2–33% of the nicotine of the control cigarettes. Participants using cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking, without significantly increasing the expired carbon monoxide level or total puff volume, suggesting minimal compensation. Regardless of baseline depressive symptoms, participants randomized to VLNC cigarettes had lower smoking rates, nicotine intake, nicotine dependence, and craving at week 6 post-randomization than those assigned to normal-nicotine cigarettes. In those with higher baseline depressive symptoms, VLNC cigarettes were associated with lower week 6 depressive symptoms than those assigned to normal-nicotine cigarettes [103]. There are a few smaller studies also supporting use of VLNC cigarettes for reducing exposure and harm [104,105], and a protocol has been published for evaluation specifically in smokers with mood and/or anxiety disorders [106].

With VLNC cigarettes, there are concerns that smokers may compensate for the reduction in nicotine by smoking or inhaling more strongly. A small within-subject, counterbalanced lab-based study examined the smoking topography (e.g. total puffs, puff intervals, number of cigarettes) of smokers with and without schizophrenia who smoked their usual brand versus VLNC cigarettes. Relative to the standard cigarettes, for both smokers with and without schizophrenia, when smoking the VLNC, their puff duration increased, while the time between puffs decreased as did total puffs and total cigarette volume. The authors concluded that acute VLNC cigarette use did not increase smoking in those with schizophrenia [103]. A 2010 randomized semi-blinded study examined whether varying lower nicotine content cigarettes were associated with compensatory smoking behavior and found that they do not. Furthermore, 0.05-mg nicotine yield cigarettes were associated with more withdrawal relieved and similar rates of cessation as nicotine lozenges. A larger randomized double-blind study ($n = 840$) found that individuals who used lower nicotine cigarettes did not have increased CO expiration or puff volume, suggesting that there was minimal compensation

observed. They conclude that the study that reduced cigarettes can reduce nicotine exposure and dependence [107,108].

4.3. Heat-not-burn tobacco cigarettes

Heat-not-burn (HNB) tobacco products heat tobacco sticks, soaked in a solvent like propylene glycol, to around 300°C (whereas traditional cigarettes burn to above 800°C) in a device so that a vapor is inhaled [109]. HNB products are currently being evaluated by the FDA for sales in the US. Tobacco companies are marketing HNB products as more appealing than e-cigarettes (because they contain tobacco) while producing less smoke than traditional cigarettes. The smoke that is released from heating has the same harmful constituents of conventional tobacco cigarette smoke. Preliminary research indicates that HNB tobacco products provide more nicotine than e-cigarettes but less than traditional cigarettes [110]. More research on these devices is needed.

5. Expert commentary

This review summarizes the ongoing need to address tobacco use in people with mental illness and addictive disorders, groups that have a high prevalence of tobacco use and tobacco-related health harms. Smoke-free treatment settings and residential environments are important, and treatment approaches that are matched to patients readiness to quit, combine cessation medication with behavioral counseling, and use technology have evidence. Treating tobacco use in those with mental illness will yield major benefits by improving healthcare outcomes and reducing morbidity and health-care costs. A 2025 Healthy People goal is to reduce US adult tobacco use to 12%, with attention to all subgroups, including smokers with mental illness [111].

6. Five-year view

Cigarette smoking is deadly and addictive. Over the next 5 years, we anticipate a continued shift in mind-set and practice so that tobacco use disorders are identified, documented, and treated in those with mental illness and other addictive disorders. Training curricula have been developed and disseminated, available for download at <http://rxforchange.ucsf.edu> and with demonstrated effects on clinician knowledge, attitudes, and counseling behaviors [112].

The research will continue to expand to fill gaps in the evidence base, with a particular focus on informing best treatment practices. A recent analysis of the literature on tobacco and mental illness documented a steady increase in research publications comparing the 2-year periods of 1993–1995 ($n = 65$), 2003–2005 ($n = 153$), and 2013–2015 ($n = 329$) [113]. More than 8 in 10 publications, however, were descriptive with less than 13% experimental in design (i.e. testing cessation interventions), and this pattern was consistent over time. Exclusion of smokers with psychiatric or addictive disorders from tobacco treatment trials has been recognized as a disservice to the field and to the population [114]. We anticipate greater integration over time.

In August 2016, e-cigarettes came under the regulatory authority of the FDA, and research is certain to expand. This will occur via observational studies of e-cigarette use in the

population, as well as in trials testing e-cigarettes as cessation aids. The last FDA-approved medication for smoking cessation was varenicline in 2006. Continued investigation into novel targets to treat tobacco addiction is needed with the potential for new drug discoveries. Already existing medications, however, are underutilized, and strategies to maximize their use will remain an important part of services research.

With hope and optimism, we anticipate that the next 5 years will yield advances in research, training, and practice that will serve to reduce the great disparities in tobacco use and tobacco-related disease burden among smokers with mental illness and addictive disorders. Change is needed.

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Key issues

- Tobacco is the leading preventable cause of death in the US and worldwide, disproportionately affecting people with mental illness and addictive disorders.
- Traditionally, mental health settings have been reluctant to treat tobacco use out of unfounded concerns that doing so can adversely affect mental health and sobriety outcomes.
- Treating tobacco is efficacious and does not worsen, and may even help, mental health and sobriety.
- At present, the benefits and harms of e-cigarettes are largely unknown; though less harmful than traditional cigarettes, they may still pose an addiction and health risk.
- There are evidence-based strategies for treating tobacco in those with mental illness and addictive disorders including medications and psychosocial approaches.
- Technology, new medications, and alternate nicotine methods may be promising for tobacco cessation.
- Services research can help guide how to increase utilization of existing treatments.