Nicotine & Tobacco Research, 2022, 3–9
https://doi.org/10.1093/ntr/ntab148
Review
Received March 8, 2021; Editorial Decision July 11, 2021; Accepted July 14, 2021

Review

Reappraising Choice in Addiction: Novel Conceptualizations and Treatments for Tobacco Use Disorder

On Behalf of the Society for Research on Nicotine & Tobacco Treatment Network; Amanda M. Palmer, PhD[1,2], Benjamin A. Toll, PhD[1,3,4], Matthew J. Carpenter, PhD[1,3,4], Eric C. Donny, PhD[5], Dorothy K. Hatsukami, PhD[6], Alana M. Rojewski, PhD[1,4], Tracy T. Smith, PhD[3,4], Mehmet Sofuoglu, MD, PhD[7], Johannes Thrul, PhD[8,9], Neal L. Benowitz, MD[10,11]

[1]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA; [2]Department of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Medical University of South Carolina, Charleston, SC, USA; [3]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA; [4]Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA; [5]Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC, USA; [6]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [7]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; [8]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA; [9]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [10]Clinical Pharmacology Research Program, Division of Cardiology, Department of Medicine, University of California, San Francisco, CA, USA; [11]Center for Tobacco Control Research and Education, University of California, San Francisco, CA, USA

Corresponding Author: Benjamin A. Toll, PhD, Medical University of South Carolina, 135 Cannon Street, Ste 303C, Charleston, SC 29425-8350, USA; E-mail: toll@musc.edu; @bentollmusc

Abstract

The introduction of alternative nicotine and tobacco products (such as e-cigarettes, heat-not-burn devices, nicotine pouches) warrants an updated framework from which to conceptualize tobacco use disorder (TUD). The following review provides considerations for TUD within the context of novel products. Historically, the tobacco industry falsely claimed that cigarettes were not addictive or harmful and that those who smoked simply chose to do so. This generated an inaccurate lay perception that smoking is a free or informed choice. Research on nicotine pharmacology demonstrates the powerful addictive potential of nicotine, which is shaped by dose, speed of delivery, and other constituents generated. In addition, non-pharmacologic reinforcers motivate and maintain tobacco use behaviors for both traditional cigarettes and novel products. The negative consequences of combustible tobacco use are well known; however, these outcomes may differ for alternative products. Strategies used for combustible product cessation may be adapted for novel products, and treatment recommendations for TUD should be made within the context of a harm reduction framework wherein alternative product use may be the desired outcome. Providers must therefore be willing to modify their perceptions of products and treatment recommendations accordingly. Better public health outcomes are accomplished through promotion of abstinence from

combustible smoking. For those who cannot wean from nicotine entirely, switching to less risky modes of delivery might be a secondary goal, with an eventual aim of stopping use of the alternative product.

Implications: Given the advent of novel, alternative tobacco products, tobacco use disorder (TUD) must be conceptualized within a contemporary framework that includes harm reduction and alternative outcomes. The unique contributions of nicotine pharmacology, non-pharmacologic reinforcers, and consequences of use can be used to inform treatments for TUD with the ultimate goal of improving the health of individuals who use tobacco.

Introduction

Despite decades of treatment and regulatory advancements, tobacco use remains a leading cause of disease and mortality in the United States.[1] In 2018, 19.7% of adults (49.1 million) reported using tobacco products in the past 30 days, including 13.7% endorsing cigarette smoking.[2] Although some suggest that smoking is becoming increasingly difficult to treat (i.e., hardening hypothesis), reviews of historical data show that cessation has always been a challenging outcome to achieve.[3]

Healthcare providers frequently encounter negative consequences of Tobacco Use Disorder (TUD), which is defined and sustained by addiction to nicotine. Symptom criteria include impaired control over tobacco use, risky use, functional consequences, and physiological dependence (withdrawal and tolerance).[4] Smoking (i.e., combustible tobacco product use, most commonly cigarettes but includes cigars and pipes) represents a significant health concern warranting continuous monitoring and treatment. Despite the large body of evidence on the biology of nicotine addiction, a common perception of smoking is that individuals make an informed choice to smoke and are "unwilling" to stop smoking.[5,6] This approach may hinder the pursuit, delivery, and effectiveness of tobacco cessation treatment.[7,8]

The rapidly changing landscape of tobacco products presents an additional challenge for providers. E-cigarettes (e.g., vapes, such as JUUL®) are battery powered devices containing a heating element and liquid nicotine solution that are increasingly popular.[9] Heat-not-burn devices (e.g., IQOS) heat reconstituted tobacco at temperatures below combustion (i.e., 350°C vs. >600°C) to produce an inhalable aerosol. These products have gained significant interest in international market areas.[10] Oral products such as tobacco-free nicotine pouches (e.g., On!, ZYN) and snus are also increasing in international market popularity as alternatives to smoking.[11] The evolving availability and perceptions of new products calls for approaching TUD within an updated framework. One such example is tobacco harm reduction, which encourages substituting lower risk tobacco or nicotine products in high-risk product users who are unwilling or unable to quit.[12]

The present review represents a collaborative effort of the authors on behalf of the SRNT Treatment Network and was approved by the SRNT Board of Directors. This review provides a contemporary overview of TUD and the biology of nicotine addiction in the context of the continuum of risk of alternative products, to guide healthcare providers who are faced with decisions regarding treatment. Our perspective supports viewing tobacco use as a nuanced, complex addictive behavior, especially given the contemporary setting of novel nicotine and tobacco products. Considerations include the historical context of tobacco company disinformation, nicotine pharmacology, non-pharmacologic influences, outcomes and consequences of TUD, and a broad discussion of treatment options. We present an enhanced framework for conceptualizing TUD in individuals who use tobacco and nicotine-containing products, thus improving treatment decision-making for providers.

Historical Context

Tobacco companies have a long history of claiming (falsely and misleadingly) that cigarettes and nicotine are non-addictive[13] and tobacco use represents "free choice." Previously secret (but now publicly available) internal industry documents show that cigarette manufacturers knew that nicotine was addictive, and designed cigarettes to maximize nicotine delivery, thus ensuring sustained addiction.[14,15] For instance, a document entitled "Motives and Incentives in Cigarette Smoking"[16] stated "The majority of the conferees would go even further and accept the proposition that nicotine is the active constituent of cigarette smoke. Without nicotine, the argument goes, there would be no smoking. . . Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke" (p. 4).[16]

Similarly, the industry cast doubt on the association between the addictive behavior of smoking and lung cancer and other health problems, despite internal knowledge that smoking caused harm.[17] Tobacco industry representatives supported "scientific research to refute unfavorable findings or at a minimum to keep the scientific question open . . . [and conducting] information campaigns against claims by the antismoking lobby" (p. 1). By framing smoking as an individual choice for decades, alongside false scientific statements,[18] the tobacco industry slowed the progress of tobacco control policies.[13,19] Although tobacco companies have been forced, in recent years, to admit to the addictive potential and dangers of smoking, their original framing efforts contributed to and continue to maintain existing lay perceptions of choice in nicotine addiction, resulting in low empathy for challenges faced when trying to quit.[5] Due to this framing about nicotine addiction, some individuals may be hesitant to use or switch to alternative nicotine and tobacco products, despite the fact that these products are non-combustible. This might inhibit the potential for positive outcomes of alternative products.

Nicotine Pharmacology

Nicotine

At its core, TUD is driven by the pharmacologic effects of nicotine. When cigarette smoke is inhaled, aerosolized nicotine enters the lungs and is quickly delivered to the brain where it activates nicotinic cholinergic receptors (nAChRs).[20,21] Stimulation of nAChRs releases a variety of neurotransmitters in the brain, including dopamine, which is critical for the primary reinforcing effects of nicotine. Nicotine also releases neurotransmitters (e.g., norepinephrine, acetylcholine, serotonin) that produce stimulation, cognitive

enhancement, and changes in affect. The speed of nicotine delivery to the brain from cigarette smoking produces rapid reinforcement, and thus, is an important determinant of cigarettes' abuse liability.

With regular cigarette smoking, neuroadaptation occurs, and the brain changes its structure, normalizing function. Nicotinic receptors become less responsive to nicotine (i.e., desensitization) while at the same time the number of nAChR binding sites in the brain increases (i.e., upregulation). These processes underlie physical dependence; that is, the emergence of withdrawal symptoms (e.g., anxiety, irritability, craving) when regular nicotine intake is stopped. Once these neuroadaptations have occurred, nicotine (e.g., through continued smoking) is required to alleviate the craving and withdrawal (i.e., taking away craving and withdrawal or negative reinforcement).[19]

Nicotine Addiction Threshold

TUD (i.e., addiction) does not develop without nicotine. In 1994, Benowitz and Henningfield hypothesized that there may be a threshold nicotine dose below which addiction would not occur.[22] Over the past 2 decades, a number of trials have tested this theory using very low nicotine cigarettes (not to be confused with commercially available "light" cigarettes marketed by tobacco companies[23]). Double-blind clinical trials have shown reductions in smoking behavior when nicotine is cut from 10 to 15 mg nicotine/g tobacco in a regular cigarette to below 2.4 mg nicotine/g tobacco, with the largest effects seen at the lowest nicotine content (0.4 mg nicotine/g tobacco).[24–27] This effect has been observed with individuals trying to quit and also with those who are not interested in quitting smoking.[24,26] In these studies, when participants are not told that they are smoking low nicotine cigarettes and are not interested in stopping smoking, they smoke less and are more likely to quit when they receive cigarettes with very low nicotine content.[22,24] These findings suggest that the so-called "choice" to smoke tobacco cigarettes is constrained by the pharmacology of nicotine. Qualitative data obtained from participants in very low nicotine cigarette trials supports this, in that many reported feeling less dependent and more motivation to quit smoking.[28]

Considerations for Alternative Products

The pharmacokinetics of nicotine vary considerably depending on the delivery mechanism of the nicotine-containing product, which greatly influences the abuse liability. Nicotine delivered quickly into the arterial circulation, as occurs with cigarette smoking, will generate the greatest reinforcement and the greatest abuse liability. Rapid nicotine delivery may be desired and even required for reduced harm products, such as e-cigarettes, to facilitate product switching by people who smoke cigarettes. As device technology and constituents have advanced (e.g., pod systems with nicotine salts), nicotine delivery has improved compared to earlier products.[29] For example, pharmacokinetic studies of early versus later electronic devices show much greater efficiency, and by extension greater craving suppression among newer products.[30] Efficiency of nicotine delivery for any alternative product has direct implications on the degree to which that product can serve as a viable substitute for cigarette smoking, but it also has direct implications on abuse liability. That is, these same characteristics that affect substitutability among people who smoke may also affect initiation, and by extension, onset of addiction among those who never smoked.

With regard to new products, such as e-cigarettes and heat-not-burn, questions remain in determining how each product delivers nicotine relative to cigarettes, and the implication for onset and maintenance of TUD. Some e-cigarettes can deliver the same or nearly the same amount of nicotine at the same speed as traditional cigarettes,[31,32] and some nicotine pouches can deliver the same amount of nicotine as dip/chew.[33] However, we do not yet have a full understanding of the constituents that are present (e.g., fillers, flavoring), and their contribution to abuse liability of these products.

Non-Pharmacologic Influences

Associative Learning and Cue-Reactivity

Although nicotine is the primary addictive constituent in tobacco, non-pharmacologic factors, including environmental stimuli, play a critical role in establishing and maintaining tobacco use. Environmental stimuli paired with nicotine (e.g., smell of smoke) and subjective consequences of smoking (e.g., decrease in negative affect) can maintain smoking behavior through associative learning processes. This conditioning takes place hundreds of times per day, each day, for many years.[34] More distal cues (e.g., tobacco retailers) signal the availability of cigarettes, and come to act as discriminative stimuli, increasing the likelihood of smoking.[35]

In laboratory studies, individuals exposed to cigarette and smoking cues report high levels of cravings to smoke and initiate smoking more quickly when given the opportunity.[36,37] Contingent administration of smoking cues without delivering much nicotine (i.e., very low nicotine content cigarettes) reduces cravings to smoke.[38] These studies demonstrate that while nicotine is important in establishing and maintaining smoking behavior, cues also serve an important function in the maintenance of smoking behavior.

Environmental influences and cue-reactivity must also be considered in the context of alternative tobacco products. For each product, unique environmental stimuli develop as cues through conditioning processes, since use patterns may differ from combustible cigarettes. That is, individuals can use alternative products in environmental contexts that they cannot use combustible cigarettes (e.g., indoors). However, it is also likely that use patterns of novel products, especially by individuals with smoking experience, may be partially shaped by overlapping cues, leading to speculation that this may lend to easier substitution for smoking. The cue-reactivity mechanisms that drive e-cigarette use have only recently begun to be explored,[39] and this line of research should continue with emerging products (e.g., heat not burn/IQOS).[40]

Expectancies

Smoking expectancies refer to deeply engrained beliefs about the experience of smoking, outcomes of smoking, and quitting, which are developed even before tobacco use initiation.[41] Specifically, people who smoke hold expectancies regarding the impact of smoking on mood regulation (e.g., increasing positive mood, decreasing stress), appetite control, health, and cravings.[42] Balanced-placebo designs, in which nicotine content (nicotine or none) is crossed with instructional set (told nicotine or told no nicotine) have been used to demonstrate that the belief of receiving nicotine produces craving reductions, regardless of whether nicotine was administered. Early studies showed this effect with cigarettes[41] and nicotine gum.[43]

Research on the role of expectancies in use of non-cigarette tobacco products is still in its infancy. It might be assumed that expectancies for these products are less engrained (vs. those for cigarettes) due to their novelty, but whether this is true is unclear. Expectancies for e-cigarettes overlap with some, but not all, expectancies for smoking.[44,45] Much like with smoking, expectancies for novel

products shape non-pharmacologic effects on various outcomes, including quitting.[45] For instance, balanced-placebo studies suggest that e-cigarettes may function as smoking cessation aids through expectancy effects,[46,47] although this could be a result of other constituents in e-cigarettes or conditioned sensory effects. Therefore, use of novel and alternative products should be considered within the context of their relative expectancies. That is, these products may or may not be used for smoking cessation; which may be both a result of or result in differing sets of expectancies (for instance, higher expectancies for craving reduction among those trying to quit smoking).[48]

Outcomes and Consequences of TUD

Many individuals continue to smoke despite concerns for health, social relationships, finances, occupation, and other functional domains. Driven by pharmacologic and non-pharmacologic mechanisms, continued substance use despite negative consequences is a key hallmark of addiction.[49] Loss of control over one's substance use behaviors is a diagnostic symptom and consequence of addiction.

Health, Behavioral, and Social Consequences of Alternative Product Use

The advent of new tobacco products creates an enormous challenge to understand their health, behavioral, and social consequences along a spectrum of risk. While studies indicate that e-cigarette use is associated with substantially fewer acute health effects compared to cigarette smoking, it is not entirely harmless.[50,51] It may take years to fully understand the long term health consequences of e-cigarette use,[52] and the individual user may not experience negative health consequences of e-cigarette use in the short-term.

When considering TUD in the context of other alternative products, each manifests a specific set of health, social, and behavioral consequences that are shaped by sociocultural contexts of use. Importantly, users of alternative products may voice an objection to the term "addiction" because they are experiencing few negative consequences of using, and perhaps find more benefits to use compared to cigarettes. Therefore, the question remains as to whether the keystone symptom of addiction—continued use despite negative consequences—is applicable for the short-term use of these novel tobacco products.

Treatment Considerations

As tobacco use is a chronic, relapsing disorder, the various treatment methodologies described should be employed until the symptoms of TUD are managed.

Assessment of Tobacco Use

Clinical practice guidelines encourage providers to ask all patients about tobacco use, assess dependence and readiness to quit, advise patients to quit, assist via referrals to counseling and/or pharmacotherapy, and arrange follow-up (i.e., the 5 As).[53] One challenge faced by clinicians is measuring tobacco use. Whereas quantifying cigarettes is straightforward, alternative products vary from those challenging to quantify (e-cigarettes) to others easily measured (snus, nicotine pouches), rendering direct comparisons to smoking extremely difficult. Additionally, quantification of daily amounts used may not necessarily capture all aspects of dependence.

Validated clinical instruments can be useful for assessing the severity of tobacco dependence and in making treatment decisions. Although several scales exist for assessing dependence on cigarettes, less is known about assessing general nicotine addiction or dependence on novel tobacco products. Scales developed to assess e-cigarette dependence have largely utilized adaptations of measures for cigarettes in order to retain cross-product comparability.[54,55]

Interventions for Smoking Cessation

First line pharmacotherapies for TUD include nicotine replacement therapies (NRT), varenicline, and bupropion.[53] NRTs include long-acting (transdermal patch) and short-acting products (gum, lozenge, oral inhaler, and nasal spray), with higher efficacy for quitting when combining both. All NRTs alleviate tobacco withdrawal symptoms and craving by acting on nAChRs to reduce nicotine withdrawal symptoms and/or to desensitize nAChRs to reduce reward from nicotine.[56] Varenicline is a partial agonist of nAChRs that blocks the rewarding effects of smoking, and during abstinence, mitigates craving and withdrawal. Varenicline is well-tolerated by most users, and recent evidence demonstrates no increased risk of neuropsychiatric or cardiovascular adverse events[57] as was suggested by early observational studies. Bupropion, an anti-depressant, blocks neuronal reuptake of dopamine and norepinephrine and is a weak antagonist of nicotinic receptors antagonist which may contribute to its efficacy for smoking cessation.

Studies have found that behavioral support improves quit rates in individuals who are using pharmacotherapy.[58] This includes a broad range of interventions such as self-help materials, individual counseling by phone or in person, group counseling, and increasingly more common, support by text messaging, mobile, or web applications.[59] These interventions address smoking-related stimuli by providing skills training to reduce cue-induced urges, restructure the environment to make it most conducive to quitting, as well as challenge expectancies and beliefs about smoking.[60] In the United States, quitlines in all 50 states can be reached via a common toll-free telephone number (800-QUIT-NOW). National organizations, such as NCI, also provide accessible behavioral support.

Interventions for Alternative Product Cessation

Whereas some e-cigarette users are ambivalent about quitting,[61] especially if e-cigarettes were used to quit smoking, other surveys suggest that many are interested in quitting.[62–64] Despite this, clinical trials for e-cigarette cessation are extremely limited. In one of the only investigations (prospective, non-randomized cohort) to date in dual users of cigarettes and e-cigarettes, those who accepted varenicline showed superior rates of quitting both products.[65] Additionally behavioral and pharmacologic (specifically, nicotine lozenges and varenicline) interventions have demonstrated efficacy for smokeless tobacco cessation,[66] which shows promise for treatments for alternative products such as snus or nicotine pouches. Future trials that capitalize on pharmacological and behavioral strategies will elucidate the potential of such interventions.[67] Additionally, further investigation is needed for treatment of multiple tobacco product use.

Harm Reduction and Switching

Rather than stopping the use of tobacco or nicotine-containing products, some might find switching to a different (potentially less harmful) nicotine or tobacco product more acceptable or beneficial (e.g., use e-cigarettes to quit smoking combustible

cigarettes). Public health authorities in some countries such as the United Kingdom support this approach, while other countries such as the United States are less supportive. The most recent Clinical Guidelines by major US medical associations were released in 2018 by the American College of Cardiology (ACC) and in 2020 by the American Thoracic Society (ATS). The ACC Guidelines emphasize complete cessation of combustible products, use of FDA approved medication, and encourage evidence based discussions with patients about e-cigarettes, including complete switching (i.e., no combustible tobacco use) with a goal of eventual cessation of e-cigarette use.[68] The ATS Guideline suggest use of varenicline over the use of e-cigarettes.[69] Aligned with these Guidelines, people who smoke combustible products should be advised that reduction of exposure to harmful constituents will be most meaningful if they completely substitute smoking with the alternative product. A caveat to this approach that must be considered is the potential for dependence on the new, alternative product, which may warrant additional cessation efforts in the future.

Among alternative tobacco products, e-cigarettes have received the greatest attention based on their potential to help individuals to quit smoking.[70] In randomized clinical trials, e-cigarettes have demonstrated efficacy, with those assigned to e-cigarettes having greater abstinence rates than those assigned to NRT (estimated risk ratio = 1.69).[46] However, in the more recent trials showing efficacy for e-cigarettes, a significant number continued to use e-cigarettes after smoking cessation,[71,72] which has raised concerns as the long-term effects of e-cigarettes are unknown.[73]

Snus is a smokeless tobacco product that is used in packets or pouches held between the lip and gums and has demonstrated lower levels of carcinogens than other smokeless tobacco products. For this reason, it has been used as a harm reduction tool in Scandinavia (Norway, Sweden). In Sweden, a country with widespread snus use among men, a dramatic decrease in cigarette smoking and lung cancer has been observed[74] and currently Sweden has the lowest tobacco-related morbidity and mortality in the world.[75] Clinical trials of snus have demonstrated smoking cessation efficacy among those interested in quitting,[76] but less so among those ambivalent about changing smoking.[77]

Although not yet formally tested, other alternative products may have harm reduction potential due to reduced toxicity. Heat-not-burn products deliver fewer toxicants and carcinogens than cigarettes, but more than e-cigarettes.[78] Notably, these products have FDA authorization to be marketed with modified risk exposure claims.[79] Tobacco-free nicotine pouches have the least harmful constituents of all the other tobacco products.[11] Future clinical trials are needed to evaluate the risks and benefits of these products as smoking substitutes or potential cigarette cessation tools.

Conclusions

As the variety and availability of tobacco products broadens, so must the role of providers in preventing tobacco-related disease and mortality. A thorough understanding of nicotine pharmacology within each product is crucial for determining addictive liability and considering treatments. Additionally, there are unique non-pharmacologic reinforcers that develop alongside continued nicotine delivery from alternative products. Finally, both nicotine and non-nicotine influences of product use must be acknowledged in the context of recommendations for use or cessation. That is, the negative consequences that are hallmark features of addiction for combustible tobacco products may not apply (or be perceived) by those who use alternative products, especially among those who use them for cigarette cessation. Some users may acknowledge that these products are not entirely harmless, but may choose not to stop using them, given few proximal functional consequences.

The ultimate goal for medical providers should be to improve the health of their patients. With regard to tobacco treatment, this can be accomplished through promotion of abstinence from combustible smoking. For combustible tobacco product users who cannot quit nicotine entirely, switching to less risky modes of delivery might be an alternative goal, with an eventual aim of stopping use of the nicotine product. Despite some products lying lower on the continuum of risk, they are not completely harmless. Therefore, if patients wish to continue use of alternative products, they should be counseled about known and unknown long-term consequences, including the potential for dependence on a new product. For most individuals, quitting cigarettes is difficult due to nicotine addiction, and therefore, shifting to products lower along the continuum of risk might be a way to reduce risk and eventually lead to quitting nicotine altogether; although to date, evidence on how to achieve the latter outcome is less clear.

Cigarette smoking has historically been posed to the public as a free or informed choice,[5,8] essentially negating other pharmacologic and psychological factors that maintain smoking and which may hinder cessation efforts. Patients and/or clinicians may be unwilling to discuss smoking and smoking cessation, or clinicians may lack self-efficacy to promote behavioral changes whereas patients may lack self-efficacy to maintain behavioral changes towards abstinence. In light of the availability and use of alternative tobacco products, treatment for TUD should be reconsidered in a more contemporary context that includes harm reduction.

Future Directions

It is imperative that clinical science remains open to diverse outcomes. Importantly, shifting towards harm reduction for adult tobacco users need not impede on the progress of public health, such as prevention efforts aimed at youth and adolescent nicotine and tobacco use. To begin, research should explore means for revising assumptions and perceptions of the range of available tobacco products, including their associated risks, reasons for use, and dependence. Studies can also evaluate the efficacy of alternative products for cigarette cessation, as well as interventions for cessation of novel products and multiple-product use. This will help providers counsel patients on tobacco use within an informed, contemporary context. The foundation for modifying how addiction is conceptualized starts by acknowledging that tobacco use encompasses a broad spectrum of behaviors with varying levels of risk, driven at its core by the reinforcing effects of nicotine.

Funding

This research was supported by by National Institutes of Health Institutional Postdoctoral Training Grant NIH-T32-HL144470, National Institute on Drug Abuse grant K01DA047433 (Smith), and National Cancer Institute grant K07CA214839 (Rojewski), and the Hollings Cancer Center (P30 CA138313). The sponsor had no role in the design of the study or the preparation of the manuscript.

Declaration of Interests

Drs Benowitz, Carpenter, and Toll have consulted to Pfizer for an advisory board. Dr Benowitz is also a consultant to Achieve Life Sciences. Drs Benowitz and Toll testify as expert witnesses on behalf of plaintiffs who filed litigation

against the tobacco industry. Dr Carpenter received consulting honoraria from Frutarom Pharmaceuticals. Dr Thrul is a member of the Advisory Board of MindCotine Inc. All other authors have no financial disclosures.

Author Contributions

A.M.P., B.A.T., and N.L.B. were responsible for conception of the manuscript. All authors were responsible for drafting of the manuscript. We would also like to acknowledge the members of the SRNT Treatment Network and SRNT board (Jan Blalock, Andrea Weinberger, Billie Bonevski, and Suzanne Colby) who reviewed and provided feedback for this manuscript prior to submission.

References

1. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the surgeon general. In: *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
2. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *Morb Mortal Wkly Rep*. 2019;68(45):1013.
3. Hughes JR. An update on hardening: a qualitative review. *Nicotine Tob Res*. 2020;22(6):867–871.
4. Shmulewitz D, Greene ER, Hasin D. Commonalities and differences across substance use disorders: Phenomenological and epidemiological aspects. *Alcohol Clin Exp Res*. 2015;39(10):1878–1900.
5. Hoek J. Informed choice and the nanny state: learning from the tobacco industry. *Public Health*. 2015;129(8):1038–1045.
6. Harding G. Constructing addiction as a moral failing. *Sociol Health Illn*. 1986;8(1):75–85.
7. Morphett K, Carter A, Hall W, Gartner C. Framing tobacco dependence as a "Brain Disease": implications for policy and practice. *Nicotine Tob Res*. 2017;19(7):774–780.
8. Hoek J, Ball J, Gray R, Tautolo ES. Smoking as an 'informed choice': implications for endgame strategies. *Tob Control*. 2017;26(6):669–673.
9. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ*. 2017;358:j3262.
10. Ratajczak A, Jankowski P, Strus P, Feleszko W. Heat not burn tobacco product—a new global trend: impact of heat-not-burn tobacco products on public health, a systematic review. *Int J Environ Res Public Health*. 2020;17(2):409.
11. Robichaud MO, Seidenberg AB, Byron MJ. Tobacco companies introduce 'tobacco-free' nicotine pouches. *Tob Control*. 2020;29(e1):e145–e146.
12. Hatsukami DK, Carroll DM. Tobacco harm reduction: past history, current controversies and a proposed approach for the future. *Prev Med*. 2020;140:106099.
13. Slade J, Bero LA, Hanauer P, Barnes DE, Glantz SA. Nicotine and addiction. The Brown and Williamson documents. *JAMA*. 1995;274(3):225–233.
14. *Ammonia*. RJ Reynolds Records; Minnesota Documents; Master Settlement Agreement. 1982. https://www.industrydocuments.ucsf.edu/docs/khmv0094. Accessed July 19, 2021.
15. *Implications and Activities Arising from Correlation of Smoke pH with Nicotine Impact, Other Smoke Qualities, and Cigarette Sales*. RJ Reynolds Records; Minnesota Documents; Master Settlement Agreement; 1973. https://www.industrydocuments.ucsf.edu/docs/gsvh0083. Accessed July 19, 2021.
16. Morris P, Dunn WJ. *Motives and Incentives in Cigarette Smoking*; R107. Philip Morris Records; Master Settlement Agreement; 1972. https://www.industrydocuments.ucsf.edu/docs/jspf0085. Accessed July 19, 2021.
17. Jones SO, Hoover KH. *Chemical Engineering. Monthly Research Report*. 1957 (570000), No. 11. 1957 November 26. RJ Reynolds Records; Master Settlement Agreement. https://www.industrydocuments.ucsf.edu/docs/hgxb0099. Accessed July 19, 2021.
18. Friedman LC, Cheyne A, Givelber D, Gottlieb MA, Daynard RA. Tobacco industry use of personal responsibility rhetoric in public relations and litigation: disguising freedom to blame as freedom of choice. *Am J Public Health*. 2015;105(2):250–260.
19. Pepples EC. *Industry Response to Cigarette/Health Controversy*. Brown & Williamson Records; Master Settlement Agreement; Congressman Bliley Philip Morris Collection; 1976. https://www.industrydocuments.ucsf.edu/docs/jnxd0024. Accessed July 19, 2021.
20. Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362(24):2295–2303.
21. Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: nicotine addiction. *Sci Adv*. 2019;5(10):eaay9763.
22. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med*. 1994;331(2):123–125.
23. Zeller M, Hatsukami D; Strategic Dialogue on Tobacco Harm Reduction Group. The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the US. *Tob Control*. 2009;18(4):324–332.
24. Donny EC, Denlinger RL, Tidey JW, et al. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med*. 2015;373(14):1340–1349.
25. Smith TT, Koopmeiners JS, Tessier KM, et al. Randomized trial of low-nicotine cigarettes and transdermal nicotine. *Am J Prev Med*. 2019;57(4):515–524.
26. Shiffman S, Kurland BF, Scholl SM, Mao JM. Nondaily smokers' changes in cigarette consumption with very low-nicotine-content cigarettes: a randomized double-blind clinical trial. *JAMA Psychiatry*. 2018;75(10):995–1002.
27. Hatsukami DK, Luo X, Jensen JA, et al. Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. *JAMA*. 2018;320(9):880–891.
28. Denlinger-Apte RL, White CM, Donny EC, et al. "I actually finally feel like the cigarettes aren't controlling me." – interviews with participants smoking very low nicotine content cigarettes during a residential study. *Drug Alcohol Depend*. 2021;219:108465. doi:10.1016/j.drugalcdep.2020.108465.
29. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A, Przulj D. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*. 2020;115(6):1141–1148.
30. Stiles MF, Campbell LR, Graff DW, Jones BA, Fant RV, Henningfield JE. Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: implications for abuse liability. *Psychopharmacology*. 2017;234(17):2643–2655.
31. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res*. 2018;20(8):1004–1009.
32. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control*. 2017;26(e1):e23–e28.
33. Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic comparison of a novel non-tobacco-based nicotine pouch (ZYN) with conventional, tobacco-based Swedish Snus and American Moist Snuff. *Nicotine Tob Res*. 2020;22(10):1757–1763.
34. Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychol Rev*. 1990;97(2):147–168.
35. Rupprecht LE, Smith TT, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Behavioral mechanisms underlying nicotine reinforcement. In: *The Neuropharmacology of Nicotine Dependence*. Switzerland: Springer International Publishing; 2015:19–53.
36. Lazev AB, Herzog TA, Brandon TH. Classical conditions of environmental cues to cigarette smoking. *Exp Clin Psychopharmacol*. 1999;7(1):56–63.
37. Wertz JM, Sayette MA. A review of the effects of perceived drug use opportunity of self-reported urge. *Exp Clin Psychopharmacol*. 2001;9(1):3–13.

38. Rose JE, Behm FM, Westman EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacol Biochem Behav.* 2000;67(1):71–81.
39. Maloney EK, Cappella JN. Does vaping in e-cigarette advertisements affect tobacco smoking urge, intentions, and perceptions in daily, intermittent, and former smokers? *Health Commun.* 2016;31(1):129–138.
40. Maloney S, Eversole A, Crabtree M, Soule E, Eissenberg T, Breland A. Acute effects of JUUL and IQOS in cigarette smokers. *Tob Control.* 2021;30:449–452.
41. Brandon T, Juliano L, Copeland A. *How Expectancies Shape Experience.* Washington, DC, US: American Psychological Association; 1999.
42. Brandon TH, Baker TB. The Smoking Consequences Questionnaire: the subjective expected utility of smoking in college students. *Psychol Assess.* 1991;3(3):484.
43. Hughes JR, Gulliver SB, Amori G, Mireault GC, Fenwick JF. Effect of instructions and nicotine on smoking cessation, withdrawal symptoms and self-administration of nicotine gum. *Psychopharmacology.* 1989;99(4):486–491.
44. Morean ME, L'Insalata A. The short form vaping consequences questionnaire: psychometric properties of a measure of vaping expectancies for use with adult e-cigarette users. *Nicotine Tob Res.* 2017;19(2):215–221.
45. Harrell PT, Simmons VN, Piñeiro B, et al. E-cigarettes and expectancies: why do some users keep smoking? *Addiction.* 2015;110(11):1833–1843.
46. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2020;10:CD010216.
47. Palmer AM, Brandon TH. How do electronic cigarettes affect cravings to smoke or vape? Parsing the influences of nicotine and expectancies using the balanced-placebo design. *J Consult Clin Psychol.* 2018;86(5):486–491.
48. Adriaens K, Van Gucht D, Baeyens F. Differences between dual users and switchers center around vaping behavior and its experiences rather than beliefs and attitudes. *Int J Environ Res Pub Health.* 2017;15(1):12.
49. National Institute on Drug Abuse. *The Science of Drug Use and Addiction: The Basics.* Washington, DC: NIDA; 2020. https://www.drugabuse.gov/publications/media-guide/science-drug-use-addiction-basics. Accessed July 19, 2021.
50. Dinakar C, O'Connor GT. The health effects of electronic cigarettes. *N Engl J Med.* 2016;375(14):1372–1381.
51. Song MA, Reisinger SA, Freudenheim JL, et al. Effects of electronic cigarette constituents on the human lung: a pilot clinical trial. *Cancer Prev Res.* 2020;13(2):145–152.
52. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med.* 2017;52(2):e33–e66.
53. Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. 2008. https://www.ncbi.nlm.nih.gov/books/NBK63952/. Accessed July 19, 2021.
54. Morean ME, Krishnan-Sarin S, Sussman S, et al. Psychometric evaluation of the e-cigarette dependence scale. *Nicotine Tob Res.* 2019;21(11):1556–1564.
55. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res.* 2015;17(2):186–192.
56. Simmons SJ, Gould TJ. Involvement of neuronal β2 subunit-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal: implications for pharmacotherapies. *J Clin Pharm Ther.* 2014;39(5):457–467.
57. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387(10037):2507–2520.
58. Hartmann-Boyce J, Hong B, Livingstone-Banks J, Wheat H, Fanshawe TR. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev.* 2019;6:CD009670.
59. Health UDo, Services H. *Smoking Cessation: A Report of the Surgeon General.* Atlanta: US Department of Health and Human Services; 2020.
60. Abrams DB, Niaura R. *The Tobacco Dependence Treatment Handbook: A Guide To Best Practices.* New York, NY: Guilford Press; 2003.
61. Etter JF. Are long-term vapers interested in vaping cessation support? *Addiction.* 2019;114(8):1473–1477.
62. Rosen RL, Steinberg ML. Interest in quitting e-cigarettes among adults in the United States. *Nicotine Tob Res.* 2020;22(5):857–858.
63. Smith TT, Nahhas GJ, Carpenter MJ, et al. Intention to quit vaping among United States adolescents. *JAMA Pediatr.* 2021;175(1):97–99.
64. Palmer AM, Smith TT, Nahhas GJ, et al. Interest in quitting e-cigarettes among adult e-cigarette users with and without cigarette smoking history. *JAMA Netw Open.* 2021;4(4):e214146.
65. Hajek P, Peerbux S, Phillips-Waller A, Smith C, Pittaccio K, Przulj D. Are 'dual users' who smoke and use e-cigarettes interested in using varenicline to stop smoking altogether, and can they benefit from it? A cohort study of UK vapers. *BMJ Open.* 2019;9(3):e026642.
66. Nethan ST, Sinha DN, Chandan K, Mehrotra R. Smokeless tobacco cessation interventions: a systematic review. *Indian J Med Res.* 2018;148(4):396–410.
67. Graham AL, Jacobs MA, Amato MS, Cha S, Bottcher MM, Papandonatos GD. Effectiveness of a quit vaping text message program in promoting abstinence among young adult e-cigarette users: protocol for a randomized controlled trial. *JMIR Res Protoc.* 2020;9(5):e18327.
68. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2018;72(25):3332–3365.
69. Leone F, Zhang Y, Evers-Casey S, et al. Initiating pharmacologic treatment in tobacco-dependent adults: an Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2020;202(2):e5–e31.
70. Hajek P. Electronic cigarettes have a potential for huge public health benefit. *BMC Med.* 2014;12:225.
71. Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med.* 2020;8(1):54–64.
72. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019;380(7):629–637.
73. National Academies of Sciences E, Medicine. *Public Health Consequences of E-cigarettes.* Washington, DC: National Academies Press; 2018.
74. Foulds J, Ramstrom L, Burke M, Fagerström K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control.* 2003;12(4):349–359.
75. Ramström L, Borland R, Wikmans T. Patterns of smoking and snus use in Sweden: implications for public health. *Int J Environ Res Pub Health.* 2016;13(11):1110.
76. Hatsukami DK, Severson H, Anderson A, et al. Randomised clinical trial of snus versus medicinal nicotine among smokers interested in product switching. *Tob Control.* 2016;25(3):267–274.
77. Carpenter MJ, Wahlquist AE, Burris JL, et al. Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers. *Tob Control.* 2017;26(2):202–209.
78. Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-not-burn tobacco cigarettes: smoke by any other name. *JAMA Intern Med.* 2017;177(7):1050–1052.
79. Churchill V, Weaver SR, Spears CA, et al. IQOS debut in the USA: Philip Morris International's heated tobacco device introduced in Atlanta, Georgia. *Tob Control.* 2020;29(e1):e152–e154. doi:10.1136/tobaccocontrol-2019-055488.