Nicotine Dependence: Future Opportunities and Emerging Clinical Challenges

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Keywords: addiction; nicotine; smoking cessation; tobacco dependence; tobacco use treatment

Nicotine dependence is the manifestation of a chronic, compulsive brain disorder, characterized by repeated attempts to quit and high rates of relapse (1, 2). Pharmacotherapy, including nicotine replacement therapy (NRT), is safe (3), mitigates relapse, and increases the probability of cessation by a relative 50% to 70% (4). Physicians consistently affirm the value of tobacco use treatment but often fail to capitalize on their unique opportunity to engage in treatment interventions that maximize the potential for control of compulsion (5). Underestimation of the probability of success may limit physician engagement (6), as does their suspicion that a dogmatic approach to “cessation,” developed decades ago and focused primarily on amplifying the motivation to quit, may itself undermine effectiveness (7). Outdated treatment algorithms no longer align with our current understanding of the variations in dependence between individuals and across groups and provide inadequate guidance to clinicians routinely facing more nuanced, protracted challenges in practice.

In the face of such an obdurate and complex problem, treatment norms have begun to evolve. Well-done evidence reviews are providing guidance on some of the more subtle questions facing clinicians responsible for long-term management, such as what to do about concurrent smoking during treatment, safety of persistent use of NRT, and management of

relapse (8). Study designs have improved, better reflecting real-world experience by no longer limiting inclusion only to subjects currently interested in quitting or free of psychiatric and medical comorbidities (9, 10). The academic conversation has moved beyond the cessation focus and has begun to include careful consideration of long-term harm limitation in the case of continued use (11).

Most recently, the U.S. Food and Drug Administration (FDA) played a significant part in unsettling the status quo by announcing an approach to tobacco and nicotine regulation that places the biology of nicotine addiction at the center of their regulatory efforts, rather than focusing on the smoking behavior alone. “Because nicotine lives at the core of both the problem and the solution to the question of addiction, addressing the addictive levels of nicotine in combustible cigarettes must be part of the FDA’s strategy for addressing the devastating addiction crisis that is threatening American families,” said Commissioner Gottlieb in a news release explaining the agency’s position (12). The approach emphasizes reliance on a scientific evidence base to achieve integrated public health goals, such as reducing the number of children who become addicted to nicotine, improving probability of control among people already addicted, protecting those unable to achieve complete control by reducing the harmful effects of tobacco exposure, and preventing the potential

effects of unchecked nicotine on related disorders of motivational control. It is clear that frontline clinicians will face increasingly complex concepts of nicotine addiction that will likely challenge us to rethink the traditional foundations of our approach.

Nicotine Pharmacokinetics and the Concept of Addiction

Nicotine acts as an exogenous activator of cholinergic receptors in the survival centers of the brain, creating a powerful reinforcing safety signal. Though a weak primary reinforcer, with far fewer sensed or “hedonic” effects than other drugs of abuse, nicotine works by amplifying the “safety/threat” salience of otherwise irrelevant inputs from the outside world, hijacking instinctive survival mechanisms and persistently motivating compulsive behaviors in response to linked sensory cues (13, 14). In this manner, addictive compulsions become ineluctable, characterized by a subjective distress (i.e., threat) when routine behaviors are forgone. Nicotine’s effects are potentiated in proportion to the rapidity with which it reaches the brain (15). The cigarette is the perfect delivery device, engineered by the industry to optimize pharmacokinetic impact by maximizing absorption into the pulmonary venous circulation. When highly plastic neurons respond to nicotine’s “impact,” the reinforcing gratification effect

(Received in original form February 9, 2018; accepted in final form July 8, 2018)

Supported in part by National Institutes of Health grants P30 CA016520-41S4 and 1K12DA033012, as well as grants derived from Pennsylvania’s Master Settlement Agreement through the Pennsylvania Department of Health.

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Ann Am Thorac Soc Vol 15, No 10, pp 1127–1130, Oct 2018

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DOI: 10.1513/AnnalsATS.201802-099PS

Internet address: www.atsjournals.org

hardens the lifelong associations of addiction.

Implications of this insight are profound. For instance, the old model, wherein smoking is considered an antecedent to illness, gets replaced by a more comprehensive framework, wherein the behavioral manifestations of dependence are seen as the cardinal sign of the primary illness. The lungs and other organs become victims of disordered brain biology. In this new paradigm, clinicians faced with preventable disability and death will need better-developed cognitive management skills, not aimed at convincing people to stop but instead focused on resolving the ambivalence of addiction. We will be asked to realign both our management tactics and our therapeutic goals to include realistic expectations for a chronically relapsing and remitting condition.

Our current intellectual model of treatment frames pharmacotherapy simply as relief from withdrawal symptoms. However, this traditional view is incomplete. Evolving clinical models relate therapeutic goals to achieving control over compulsion. As our understanding of the biological basis of mind continues to improve, future strategies will aim to reset the distortions in allostasis, the processes used by the brain to return to homeostasis after a stressor, developed over a lifetime of nicotine exposure. Increasing attention to pharmacologic mechanism of action will improve the specificity of medication choices rather than approaching available options as therapeutically interchangeable.

III-Health Effects of Smoking as a Continuous Outcome

In much the same way we think about controlling asthma, future tobacco treatment prescriptions are likely to be based on clinical phenotypes that incorporate measures such as topography of smoke exposure, biomarker profile, or prior response to treatment, rather than on number of cigarettes consumed. And, like asthma, we will develop a broader set of effectiveness measures. For instance, pack-years remains the currently accepted measure of smoke exposure because of its demonstrated relationship to disease development (16). However, pack-years is conceptually based on outdated assumptions about average toxicant

exposure per unit cigarette. The measure remains notoriously imprecise and unresponsive to natural variations in smoking behavior (17). Markers of inflammation and oxidative stress are biologically derived measures of exposure and illuminate pathogenic mechanisms of obstructive lung disease, coronary artery disease, and diabetes (18). As intermediate metrics, these may be the earliest indicators of therapeutic effect, potentially identifying partial therapeutic responses or suggesting clinical targets for disease modification. As a consequence, population-based measures of effect are likely to be more stochastic, relating multiple covariates to probability of future illness. The compensatory behaviors used as the number of cigarettes consumed per day declines, or as users adopt the growing variety of alternative tobacco products, will be an important covariate in understanding the relative degree to which different nicotine delivery systems produce harm.

Treatment or Maintenance

A current priority in tobacco dependence treatment is identifying methods for improving the effectiveness of existing products, including the possibility of long-term pharmacologic maintenance with nicotine (19). Current FDA labeling for NRTs stipulates treatment duration of 8 to 12 weeks and recommends consultation with a healthcare provider if longer-term personal needs demand. Currently, 70% to 90% of smokers who use NRT do not exceed 8 to 12 weeks' duration (20). Two large randomized clinical trials showed that extending treatment with the nicotine patch to 26 weeks significantly increased relative cessation rates by 50% (21). Consistently, extending the use of NRT gum or patch to 6 months is safe and increases odds of cessation, but finding ways to bridge implementation gaps between what we know works, what clinicians can provide, and what patients will use remains a challenge (22).

Personalized Care

The 3-hydroxycotinine/cotinine ratio, a reliable and stable phenotypic measure of nicotine metabolism, can help clinicians improve treatment outcomes by identifying

the treatment strategy with the best efficacy-to-side effect balance (23). Biologic status accounts for variation in outcome independently from estrogen levels, alcohol use, body mass index, or menthol exposure and may represent an important step toward true personalization of treatment. Current availability and insurance coverage is variable, but the evidence supports the use of nicotine replacement therapy for slow metabolizers and nonnicotine treatments such as varenicline for normal metabolizers. Discarding outdated notions of therapeutic interchangeability will enable clinicians to improve treatment by maximizing efficacy and minimizing side effects; although practical strategies for office-based implementation exist, arbitrary variation in payor reimbursement policy currently limits their feasibility.

Complex life circumstances may also call for customization of approach. For instance, pregnancy may warrant dose adjustment, although the best direction of adjustment remains unclear. On the one hand, the efficacy of NRT may be reduced by higher rates of nicotine metabolism, potentially necessitating higher doses (24). On the other hand, although considered safe at recommended doses, fetal effects outside the expected dose range remain a concern (25, 26). Persistent FDA classification of nicotine patches as pregnancy category D likely continues to limit use by patients and healthcare providers, despite being inconsistent with current empirical evidence. Variations in social context, such as in-group identity and stigmatization, can exert complex influence over patients' treatment engagement and response to therapy (26). The burgeoning use of electronic cigarette products among adolescents and young adults may be a manifestation of this effect. How to best clinically position the use of future nicotine delivery devices and products within a therapeutic context is currently unknown, particularly in light of the inherent risk of paradoxically promoting nicotine dependence.

Other Indications for Nicotine

The potential therapeutic benefits of nicotine remain incompletely understood. Population-based observations of individuals who smoke suggest a protective effect for Parkinson and Alzheimer diseases

Table 1. Summary

Nicotine dependence is the manifestation of a chronic, compulsive brain disorder—the behavioral manifestations of dependence are the cardinal signs of the primary illness. Evolving clinical models will focus therapeutic goals on longitudinal control over compulsion, rather than on relief of withdrawal symptoms or cross-sectional abstinence rates. As in other complex illnesses, a broader set of meaningful effectiveness measures is required to identify partial therapeutic response and potential new targets for intervention. Control-based algorithms will help sort out appropriate indications for maintenance vs. episodic care and treatment personalization. A growing evidence base will help reduce practical barriers to implementation. The evolution in regulatory approach to the clinical nicotine dependence syndrome will require rethinking fundamental assumptions about the process for product label change, the possible therapeutic applications of nicotine, and the significant potential for underlying nicotine biology to impact overlapping motivational disorders such as substance abuse in unanticipated ways.

compared with never-smoking control subjects (27). Measurable improvements in cognitive performance, fine motor skills, and inflammatory bowel symptoms have also been noted. Exploration of biologic mechanisms, including possible protection from neuronal cell loss, provides insights into new treatment pathways. Clinicians may someday face the possibility of using nicotine as an adjunct in the treatment of dementia, attention-deficit hyperactivity disorder, mood disorders, schizophrenia, and obesity.

Product Label Change

The process for product label change is onerous and costly and is far outpaced by the rate of tobacco treatment innovation and discovery. Outdated instructions limiting use of effective combinations and based on antiquated notions of volitional control and

behavior change are unlikely to line up with evolving paradigms of dependence treatment and recovery and may in fact conspire to keep both clinicians and patients from engaging effectively. The implications of language choice are not subtle; phrases like “cessation attempt,” “quit,” and “success” explicitly assign accountability to the user, whereas concepts of “control,” “treatment,” and “recovery” reflect a shared responsibility for outcome and respect the complex longitudinal processes necessary for reversing maladaptive neural connections.

We can do more to address the epidemic of nicotine addiction. In 1996, the FDA allowed certain NRT preparations to become available over the counter. From then, it took nearly 20 years and a clinician-led petition to achieve a language change that accommodates the duration and

combination recommendations that had long before been shown safe and effective. Meanwhile, we were less effective than we could have been while the preventable death toll mounted. In 2009, the FDA Center for Tobacco Products was established to oversee implementation of the Family Smoking Prevention and Tobacco Control Act. Since then, regulatory requirements for new tobacco products and updated processes for evaluating safety and therapeutic claims for tobacco-derived products have the potential to substantially increase the pace of change in practice. As tobacco dependence treatment increasingly takes on the biologic specificity of other chronic diseases, clinicians open to these new ideas (Table 1) will be poised to make an enormous impact on the problem. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Childress AR, Hole AV, Ehrman RN, Robbins SJ, McLellan AT, O'Brien CP. Cue reactivity and cue reactivity interventions in drug dependence. *NIDA Res Monogr* 1993;137:73–95.
- Wray JM, Gass JC, Tiffany ST. A systematic review of the relationships between craving and smoking cessation. *Nicotine Tob Res* 2013;15:1167–1182.
- Lee PN, Fariss MW. A systematic review of possible serious adverse health effects of nicotine replacement therapy. *Arch Toxicol* 2017;91:1565–1594.
- Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, *et al*. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012;11:CD000146.
- An LC, Bernhardt TS, Bluhm J, Bland P, Center B, Ahluwalia JS, *et al*. Treatment of tobacco use as a chronic medical condition: primary care physicians' self-reported practice patterns. *Prev Med* 2004;38:574–585.
- Leone FT, Evers-Casey S, Graden S, Schnoll R. Behavioral economic insights into physician tobacco treatment decision-making. *Ann Am Thorac Soc* 2015;12:364–369.
- Dackis C, O'Brien C. Neurobiology of addiction: treatment and public policy ramifications. *Nat Neurosci* 2005;8:1431–1436.
- Zapawa LM, Hughes JR, Benowitz NL, Rigotti NA, Shiffman S. Cautions and warnings on the US OTC label for nicotine replacement: what's a doctor to do? *Addict Behav* 2011;36:327–332.
- Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, *et al*. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA* 2015;313:687–694.
- Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, *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;387:2507–2520.
- National Academies of Sciences Engineering Medicine. Public health consequences of e-cigarettes. Institute of Medicine. 2018 Jan 23. [accessed 2018 Feb 9]. Available from: <http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx>.
- U.S. Food and Drug Administration. Press announcements: FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death. 2017 Jul 28 [accessed 2018 Jan 24]. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm>.
- Leone FT, Evers-Casey S. Developing a rational approach to tobacco use treatment in pulmonary practice: a review of the biological basis of nicotine addiction. *Clin Pulm Med* 2012;19:53–61.
- Subramaniam M, Dani JA. Dopaminergic and cholinergic learning mechanisms in nicotine addiction. *Ann N Y Acad Sci* 2015;1349:46–63.
- Cooper DC. The significance of action potential bursting in the brain reward circuit. *Neurochem Int* 2002;41:333–340.

- 16 National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. 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 [accessed 2014 Apr 13]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK179276/>.
- 17 Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;55:651–656.
- 18 Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004;24:816–823.
- 19 Carpenter MJ, Jardin BF, Burris JL, Mathew AR, Schnoll RA, Rigotti NA, et al. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs* 2013;73:407–426.
- 20 Zhang B, Cohen JE, Bondy SJ, Selby P. Duration of nicotine replacement therapy use and smoking cessation: a population-based longitudinal study. *Am J Epidemiol* 2015;181:513–520.
- 21 Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med* 2015;175:504–511.
- 22 Schlam TR, Fiore MC, Smith SS, Fraser D, Bolt DM, Collins LM, et al. Comparative effectiveness of intervention components for producing long-term abstinence from smoking: a factorial screening experiment. *Addiction* 2016;111:142–155.
- 23 Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, et al.; PGRN-PNAT Research Group. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. *Lancet Respir Med* 2015;3:131–138.
- 24 Bar-Zeev Y, Lim LL, Bonevski B, Gruppetta M, Gould GS. Nicotine replacement therapy for smoking cessation during pregnancy. *Med J Aust* 2018;208:46–51.
- 25 Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. *Pediatrics* 2015;135:859–867.
- 26 Leone FT, Carlsen K-H, Folan P, Latzka K, Munzer A, Neptune E, et al.; ATS Tobacco Action Committee; American Thoracic Society. An official American Thoracic Society research statement: current understanding and future research needs in tobacco control and treatment. *Am J Respir Crit Care Med* 2015;192:e22–e41.
- 27 Picciotto MR, Zoli M. Neuroprotection via nAChRs: the role of nAChRs in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. *Front Biosci* 2008;13:492–504.