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Review
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Review

Basic Science and Public Policy: Informed Regulation for Nicotine and Tobacco Products

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Abstract

Introduction: Scientific discoveries over the past few decades have provided significant insight into the abuse liability and negative health consequences associated with tobacco and nicotine-containing products. While many of these advances have led to the development of policies and laws that regulate access to and formulations of these products, further research is critical to guide future regulatory efforts, especially as novel nicotine-containing products are introduced and selectively marketed to vulnerable populations.

Discussion: In this narrative review, we provide an overview of the scientific findings that have impacted regulatory policy and discuss considerations for further translation of science into policy decisions. We propose that open, bidirectional communication between scientists and policy makers is essential to develop transformative preventive- and intervention-focused policies and programs to reduce appeal, abuse liability, and toxicity of the products.

Conclusions: Through these types of interactions, collaborative efforts to inform and modify policy have the potential to significantly decrease the use of tobacco and alternative nicotine products and thus enhance health outcomes for individuals.

Implications: This work addresses current topics in the nicotine and tobacco research field to emphasize the importance of basic science research and provide examples of how it can be utilized to inform public policy. In addition to relaying current thoughts on the topic from experts in the field, the article encourages continued efforts and communication between basic scientists and policy officials.

Introduction

Although tobacco smoking remains the leading cause of preventable disease and death in the United States and worldwide,[1] the prevalence of cigarette use has dramatically declined in both the United States (from 42.7% in 1964 to 16.8% in 2014)[2,3] and globally (28%–34% decrease from 1990 to 2015).[4] During this time, extensive efforts have been devoted to preclinical and clinical research on nicotine dependence, and findings from these types of studies have begun to contribute to regulatory and public health efforts (for instance, see[5–7]). The research findings from basic science continue to shape our current understanding of nicotine addiction through varying approaches,[8] including brain activity measurements with functional magnetic resonance imaging (fMRI) techniques, genetic studies of nicotine metabolism and use patterns, technologies and models for the study, prediction and understanding of toxicity, and many more. As these findings are translated into policy efforts, the potential relevance and limitations of research models (eg, in vitro cell culture, animal species, human populations, etc.) must be taken into consideration. For instance, a wealth of knowledge has emerged from animal models implicating subtypes of the neuronal nicotinic acetylcholine receptors (nAChR) in nicotine reward and reinforcement.[9–11] However, nAChR subtype distribution can vary across species,[12] which is an important issue to consider when examining the underlying neurobiological and behavioral mechanisms contributing to drug use in humans, as well as for the development of smoking cessation pharmacotherapies. Thus, bidirectional communication between basic scientists and policy makers is essential to maintain an accurate representation of science to guide policy decision making.

Although we are moving closer to the Healthy People 2020 goal of reducing cigarette smoking prevalence to ≤12.0%,[13] the decline in cigarette use has coincided with an increase in the use of other traditional and nontraditional nicotine-containing products, including hookah (waterpipe), cigars, smokeless tobacco, and electronic cigarettes (e-cigarettes).[14,15] Further, consuming two or more tobacco products, referred to as polytobacco use, has become more prevalent.[15–18] Moreover, in addition to the negative health impact on established users, developmental exposure (eg, in utero or via secondhand smoke exposure) and experimentation by adolescents remains a prominent concern (Box 1). In the United States alone, 10% of women smoke during pregnancy,[19] and each day 3800 people under the age of 18 smoke their first cigarette with 2100 of them going on to become everyday smokers.[20,21] As a smoking cessation strategy, pregnant mothers may be placed on nicotine replacement therapy to potentially reduce high levels of tobacco constituents and nicotine in fetal circulation[22]; however, nicotine exposure in utero has recently been associated with later neurobiological and behavioral consequences.[23,24]

In order to exert their regulatory authority in the context of this new tobacco/nicotine use landscape, governmental agencies need unbiased, evidence-based data on the impact of both tobacco cigarettes and other nicotine products on human health. For example, there is a need to understand the health consequences of long-term use of alternative nicotine products, as well as "characterizing flavors" (eg, candy, fruit) in these products. To address the current knowledge gaps in the United States, the FDA and National Institutes of Health have established a research portfolio directed to address tobacco regulatory science, and these efforts have resulted in the establishment of 14 Tobacco Centers of Regulatory Science programs across various academic institutions,[25] research development grant mechanisms, and FDA-funded research contracts and interagency agreements on targeted issues. In other countries, similar efforts have been initiated to utilize evidence-based regulation to promote public health.[26] For instance, the European Commission has incorporated various tobacco control measures, including the Tobacco Products Directive, approved in 2014, to address trade of tobacco products across borders, availability of products, and diverging national legislation.[27]

This narrative review was conceived to highlight the contributions that basic science can make to tobacco regulatory policies based on supporting evidence from the nicotine and tobacco research field. Given the multitude of research findings from the field, examples of basic science findings have been identified using a purposive approach to support our platform for evidence-based translation to public policy. As such, we acknowledge that other findings not reviewed herein may or may not necessarily support the same conclusions. Reciprocally, the contributions needed by policy makers to fuel constructive and informative research by basic scientists are discussed (Figure 1). As a point of initial clarification, we define basic science as "any field of study where data are collected and/or analyzed with the intent of understanding the etiology, mechanisms, or consequences of tobacco/nicotine use." This definition encompasses biological, pharmacological, behavioral, psychological, and population-based studies conducted in pre-clinical (eg, in vitro cell-based studies and in vivo animal model systems), clinical, and environmental settings. Further, the term "abuse liability" is defined as the likelihood to develop a behavioral disorder characteristic of dependence on a drug of abuse, such as nicotine.

Box 1: Key Evidence that Developmental Nicotine Exposure is Harmful

- Developmental nicotine exposure alters the behavioral response to nicotine in adolescent mice and rats.[275–278]
- Adolescent nicotine exposure results in reduced withdrawal symptoms compared to adult nicotine exposure and enhanced rewarding effects of nicotine in rats.[279,282]
- Altered ventral tegmental area dopaminergic function via enhanced NMDA receptor function occurs following developmental nicotine exposure.[280,281]
- Maternal smoking during pregnancy leads to greater risk of psychiatric morbidity in children.[291]
- Prenatal tobacco exposure increases risk for offspring nicotine dependence in humans.[274]

Summary: Developmental nicotine exposure leads to adverse health effects in offspring.

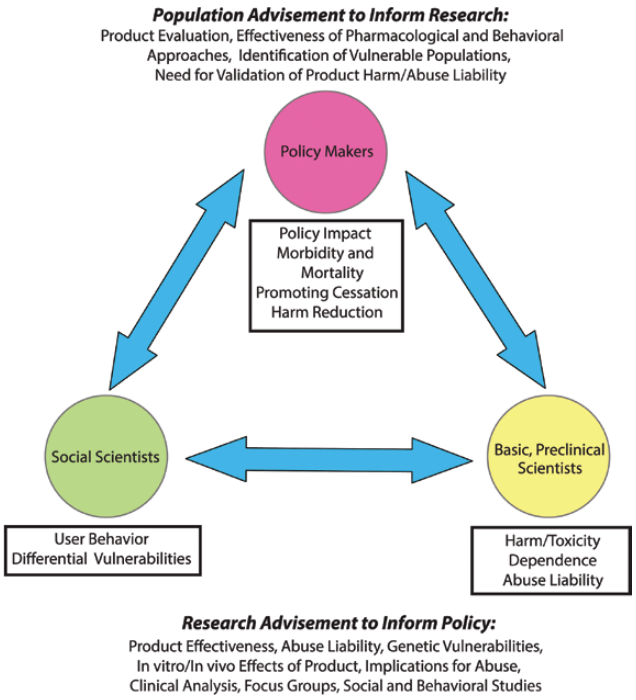

Figure 1. Bidirectional communication for informed regulatory policy. To enhance the incorporation of findings from basic science into policy, and to identify the needs of the public policy makers for understanding product actions/characteristics, information across varying levels should be relayed among policy, social and preclinical settings. Figure adapted with permission from Ashley, DL (2015, May). Scientific research to inform FDA regulatory actions on electronic nicotine delivery systems (ENDS). Presented in part at the annual meeting of the Tobacco Merchants Association, Williamsburg, VA.

We propose that increased communication between basic scientists and policy makers is required to bridge the current gaps in translation for more informed development and effective implementation of policy and law. Moreover, a common language and increased translational collaborations along the spectrum of basic scientists, from cell-based to animal models to human investigations, are needed to enhance our ability to critically evaluate and properly translate the relevance of basic science findings into advocacy and policy efforts.

Tobacco Cigarettes and Current Regulatory Policies

Although the issue of whether nicotine was in fact addictive remained a controversial issue as recently as 1992;[28] basic science contributed a great deal of evidence supporting the case that nicotine is addictive[29] (Table 1). Indeed, based on nicotine's actions on the mesolimbic dopaminergic pathway, as revealed from pioneering work in the field, nicotine is now recognized as a drug of abuse (Box 2). This contention was further supported with documentation of physical signs of dependence during nicotine withdrawal (Box 3). In the past few decades, basic scientists in close collaboration with epidemiologists and other researchers have provided comprehensive evidence linking tobacco use with a number of diseases. Specifically, the relationship between smoking and lung cancer is considered one of the most thoroughly investigated issues in biomedical research.[30,31] These research findings eventually encouraged government intervention to regulate the availability (eg, age of access, place of sale) of tobacco products. In the United States, federal regulation was prompted by the 1964 report of the Surgeon General,[32,33] which summarized findings from animal experiments, clinical studies, and population studies to conclude that cigarette smoking "is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."[34] Initially, this action involved informing the public of the dangers of cigarette smoking and subsequently led to bans on various types of marketing by the tobacco industry.[35,36] Globally, the World Health Organization (WHO) estimates that a comprehensive ban on tobacco marketing exists for 19 countries, which only accounts for approximately 6% of the world's population.[37,38]

Tobacco regulatory policies vary considerably depending on the country or geographical region, as evidenced by the systematic evaluation of key policies of the WHO Framework Convention on Tobacco Control (FCTC) in more than 25 countries.[39] Since 2002, the International Tobacco Control Policy Evaluation Project (ITC Project) has been gathering survey data in a growing number of countries to assess the impact and determinants of effective tobacco control policies across a variety of content areas (eg, health warning labels, smoke-free legislation, pricing and taxation of tobacco products). Notably, in the last 10 years, tobacco control policy has changed considerably in some countries. In the United States, there has been a push from the FDA Center for Tobacco Products (CTP) to facilitate basic science research in key areas such as addiction, toxicity/carcinogenicity, and relative risk of potential modifications to tobacco products, such as nicotine content reduction.[40] Most recently, the CTP finalized a rule that went into effect on August 8, 2016 to extend tobacco regulation to certain alternative nicotine delivery products such as e-cigarettes, waterpipes, and cigars.[41]

Effectiveness of Existing Tobacco Policies

Restrictions on tobacco advertising have been found to generally coincide with decreases in smoking prevalence.[42–44] However, the effects of these approaches are difficult to isolate from other societal and regulatory changes, which often co-occur with such restrictions. Thus, quantifying the impact of governmental regulations has proven to be difficult. The few studies attempting to do so generally find that such policies are secondary only to tobacco pricing in their impact on adult smoking.[45,46] Still, the complexity of the environments wherein these policies are implemented can result in counterintuitive findings. For example, an analysis of point-of-sale marketing restrictions in Australia found that stronger restrictions were associated with higher odds of past-month adolescent smoking. This finding was attributed to industry tactics to subvert regulation, most notably the introduction of larger pack displays with more brand variations.[47] Therefore, the difficulty of isolating the impact of regulations on smoking behavior necessitates the examination of intermediate outcomes and theoretical models of decision-making involving constructs such as marketing receptivity, outcome expectancies, and societal norms.[48–50] Additionally, fairly novel research methodologies, such as ecological momentary assessment and geospatial techniques, provide some promise in elucidating the complex relationships between marketing exposure and behavior.[51–53]

Similar to restrictions on advertising, enhanced understanding of the dangers of environmental tobacco smoke (ETS) has prompted

Table 1. Examples of Basic Science Research Contributions to Tobacco Policy Development

Mechanism discovered through basic science	Species	Translatability potential and/or past impact on policy	Citations
Dopamine release in mesolimbic system by nicotine	Rat, Human	Shared mechanism across addictive drug classes Contributes to policy on drugs of abuse	194–202
Serotonin release in various regions of the brain (eg, cortex, striatum) by nicotine (rat) Serotonin transporters/receptor genes implicated in nicotine addiction (human) Reduction in serotonergic signaling in the hippocampus in smokers	Rat, Human	Shared mechanisms underlying smoking, depression, and anxiety Contributes to comorbid treatment strategies	203–209; 292
Reinforcing and withdrawal-associated properties of nicotine mediated by nAChR subunits Allelic variations in CHRNA3-CHRNA5-CHRNAB4 gene cluster associated with tobacco addiction vulnerability	Rat, Mouse, Human	Rodent studies with face validity in relating to genetic findings in human smokers provide insight into mechanisms mediating dependence	9; 10; 210–214
Negative anhedonic state induced by nicotine withdrawal, which is mediated by nAChRs	Rat, Mouse	Evidence of the different aspects of nicotine withdrawal that can contribute to relapse	211; 215–219
Scientific evidence supporting nicotine as addictive	Rat, Mouse, Dogs, Monkeys, Humans	Nicotine was debated as being an addictive substance until ~1992 (see[28]; [220]; [221]) Data supports abuse liability of the drug	29; 147; 167; 222–225
Pairing nicotine with certain stimuli can lead to secondary reinforcement for the associated cue	Rat, Human	Examination of nicotine replacement therapy with relative safety Examination of underlying mechanisms driving cue effects	226–232
Some non-nicotine additives are psychoactive and may enhance nicotine's effects	Rat, Human	Support for regulation of non-nicotine additives in tobacco products	70–76; 79–81; 84; 85; 87; 233–235
Increased expression of nAChRs following nicotine or tobacco smoke	Mouse, Rat, Human	Common nicotine-induced neurobiological alteration from rodent to human Contributes to new pharmacotherapeutic avenues to promote smoking cessation Biomarker for dependence	208; 236–238
Different routes of nicotine administration can be studied to examine neurochemistry, neurophysiology, and behavior in nicotine reinforcement and withdrawal, as well as prenatal nicotine exposure	Mouse, Rat, Human	Evidence for the importance of delivery method in inducing fast action on nAChRs for abuse liability (inhalation, IV infusion), compared to sustained, long-term release with minimal abuse liability (nicotine patch) Contributes to policy decisions for efficacious treatment and prevention	23; 239–249
Delivery of nicotine/other chemicals in other products (eg, e-cigarettes)	Mouse, Rat, Human	Informs policy makers of potential harm of various nicotine delivery products, such as e-cigarettes, snus, waterpipe, etc.	119; 250–259
Behavioral economics as a model of nicotine "demand"	Rat, Human	Allows examination of neurobiological and behavioral components of nicotine motivation versus cost	137; 260–263
Nicotine reduction as an effective strategy to reduce nicotine dependence	Rat, Human	Examine if smokers will compensate smoke intake from low nicotine-content cigarettes. Inform policy makers on nicotine reduction as a viable strategy to promote cessation	107; 173; 260; 264–268
Menthol exerts reinforcing effects, both independently and through interactions with nicotine	Mouse, Rat, Human	Policy guidelines for menthol in tobacco products	91; 96; 98; 102–106; 269

restrictions on public use of tobacco. For most of the 20th century, tobacco smoking was allowed essentially anywhere and at any time.[54] Evidence began to accumulate that ETS significantly exposed non-smokers to tobacco particles and impaired pulmonary function.[55,56] Epidemiological evidence demonstrated that nonsmoking wives of smokers or ex-smokers were found to have significantly higher rates of lung cancer compared to non-smoking women married to nonsmokers.[57,58] Further, environmental analyses suggested that flight attendants exposed to ETS on airplanes experienced exposures similar to living with a pack-a-day smoker.[59] In 1998, California was the first state in the United States to require all workplaces, bars, and restaurants to be smoke-free. Most states in the

Box 2: Key Evidence that Nicotine Mediates Dopaminergic Signaling

- Cigarette smoking induces ventral striatal dopamine release in human smokers.[194–198]
- Similar to other drugs of abuse, nicotine enhances dopamine release in the nucleus accumbens.[194]
- Intra-accumbens nicotine infusions increase synaptic dopamine release in rats, which is blocked by the nicotinic antagonist mecamylamine.[195]
- Cigarette smoke inhalation stimulates dopaminergic neurons in rats.[200]
- Repeated exposure to nicotine results in an attenuation of dopamine release in the nucleus accumbens, which is potentially mediated by receptor desensitization.[201,202]

Summary: Based on nicotine's actions on the mesolimbic pathway, nicotine is now considered an addictive substance.

Box 3: Key Evidence that Nicotine Induces a Withdrawal Syndrome

- Tobacco withdrawal symptoms are alleviated by nicotine in human smokers.[216]
- Nicotinic acetylcholine receptors mediate the affective and somatic features of nicotine withdrawal.[214,219,284–287]
- Adolescent rats show decreased sensitivity to the somatic aspects of nicotine withdrawal, which may contribute to its reinforcing effects.[218]
- The habenula is a critical mediator of the aversive effects of nicotine, as well as nicotine withdrawal.[9,283,286]
- Mecamylamine, a nicotinic receptor antagonist, precipitates nicotine withdrawal.[288]

Summary: Nicotine withdrawal syndrome can be modeled preclinically and is mediated by specific neural mechanisms.

United States have followed suit with some form of smoking restriction,[33] although the comprehensiveness of smoking restriction policies is variable. Nonetheless, globally, 93% of the world's population lives in countries not covered by comprehensive smoke-free public health regulations.[60] Laws restricting ETS exposure are similar to marketing regulations in that causation can be difficult to determine. However, some evidence suggests that restrictions on ETS can reduce exposure to ETS, deter smoking relapse during abstinence, and reduce the probability of smoking initiation.[61–64]

Despite the potential power of tax increases, marketing, and ETS restrictions, continued cigarette smoking is almost certainly driven primarily by the pharmacological effects of nicotine. In 1995, David Kessler, Commissioner of the FDA at the time, determined that cigarettes and smokeless products were nicotine-delivery devices and therefore fell within the scope of the Federal Food, Drug, and Cosmetic Act.[65] This determination was contested by the Supreme Court,[32,33] but eventually resolved by the Family Smoking Prevention and Tobacco Control Act in 2009[66].

Non-nicotine Constituents in Tobacco and Nicotine Products

Many constituents in the smoke of commercial cigarettes exist at concentrations much lower than nicotine, and many of these substances are likely not reinforcing by themselves. However, a growing body of research suggests that some non-nicotine constituents have reinforcing potential and likely contribute to tobacco use behavior.[67–72] Importantly, non-nicotine constituents can magnify the reinforcing properties of nicotine, such as anatabine, anabasine, cotinine, and myosmine.[71,73] Further, non-nicotine tobacco smoke constituents such as cotinine, acetaldehyde, and nornicotine increase midbrain dopamine levels similar to psychostimulants such as cocaine.[74–76] Thus, the potential public health benefits of a proposed nicotine reduction policy could be undermined by strategic use of non-nicotine additives by cigarette manufacturers or consumers to reinforce and maintain smoking behavior. Of further importance, smokers may compensate and increase smoke intake/puff volume when smoking cigarettes with lower nicotine content,[77] which could resultantly increase levels of constituent exposure. To address the importance of non-nicotine constituents in the maintenance of smoking behavior, basic science has examined the reinforcing potential of non-nicotine constituents, alone and in combination with nicotine. For the purposes of this review, we briefly illustrate this point with evidence from two lines of research: tobacco components and menthol.

One potentially informative experimental approach has involved self-administration of tobacco smoke extract in animal models.[78,79] A recent study compared self-administration of an aqueous extract of cigarette smoke to that of pure nicotine in adult male rats and found that consumption was increased by the other components in the extract when nicotine concentrations were below the threshold that was considered reinforcing.[72,80] Further, among the classes of non-nicotine smoke constituents, acetaldehyde and several minor alkaloids are known to act as reinforcers.[81–83] However, their effects may only be induced when present at doses much higher than or equal to the dose of nicotine,[71,84–87] and thus these constituents may not enhance consumption in smokers given the relatively lower concentrations found in tobacco smoke. This example emphasizes the need for increased focus on the impact of interactions between nicotine and non-nicotine constituents on smoking behavior. Recent attention has also turned to the role of MAO inhibition on nicotine reinforcement. The β-carbolines, harman and norharman, are known to inhibit MAO and may potentiate nicotine reinforcement,[88] although at doses much higher than those delivered in cigarette smoke. Several studies have examined the influence of MAO inhibitors not present in cigarette smoke on nicotine reinforcement (such as tranylcypromine). Maximum inhibition of MAO results in potentiation of nicotine self-administration, especially at low nicotine doses.[85,88,89] It has also been demonstrated that low-dose nicotine self-administration is enhanced in rats with brain MAO activity levels only partially inhibited[90] but within the range seen in human smokers. Thus, future attention might focus on the identification of the non-nicotine constituents in cigarette smoke that result in the MAO inhibition observed in smokers, as this may be a critical determinant of smoking behavior.

Menthol, a common flavoring additive to cigarettes and e-cigarettes, may interact with nicotine to increase abuse liability. In cigarettes, menthol has been shown to affect a smoker's exposure to nicotine,[91,92] and smokers who use mentholated cigarettes have lower cessation rates in standardized treatment programs than

smokers who use non-menthol cigarettes.[93–95] The FDA, after reviewing the 2011 report by the Tobacco Products Scientific Advisory Committee and conducting its own literature review, concluded that the menthol in cigarettes is likely associated with increased dependence, and reduced success in smoking cessation, especially among African American menthol smokers.[96] In the European Union, a ban on cigarettes with characterizing flavors, including menthol, will be enforced beginning in 2020.[97] Although many factors have been implicated in the initiation and dependence to menthol cigarettes, earlier studies showed that menthol itself inhibits nicotine metabolism.[91] Menthol cigarette smoking may also lead to greater exhaled carbon monoxide levels and, perhaps, elevated serum levels of nicotine and cotinine.[92,98,99] By elevating nicotine levels, menthol may influence smoking dependence since nicotine mediates most of the pharmacological and addictive properties of tobacco. Other reports suggest that the sensory effects of menthol might also affect nicotine intake. For example, menthol significantly reduces the irritation and sensory perception induced by nicotine and cigarette smoke inhalation.[100–102] Menthol's ability to trigger the cold-sensitive transient receptor potential, melastatin, is thought to be a mechanism for the cooling sensation it provokes when inhaled, eaten, or applied to the skin. Indeed, recent animal studies suggest that the cooling sensation of menthol and similar cooling agents serves as a conditioned reinforcer for nicotine in rats.[103] More recently, menthol was shown to be an allosteric modulator of α7 nAChR subtypes[104] and to upregulate nAChR expression both in vivo and in vitro.[105,106]

Overall, the above examples suggest that more basic science work is needed to investigate the reinforcing potential of non-nicotine constituents as those data can inform efforts to develop nicotine reduction policy. Two avenues to reduce use of combustible tobacco products have been proposed and have shown promise to reduce nicotine use. Specifically, reducing nicotine content in nicotine and tobacco products has corresponded to reduced consumption in some cases (eg, such as when nicotine content is low enough to limit the user's ability to behaviorally titrate by increasing puff volume). The second avenue is to promote use of noncombustible tobacco products that deliver substantially lower levels of toxins than their combustible counterparts.[107] Support for policy to reduce nicotine content has become more prevalent in the United States and was recently submitted for consideration to the WHO Study Group on Tobacco Product Regulation, although it is worth noting that the impact of such policy does not appear to be uniformly recognized across countries.[107,108]

Beyond the Tobacco Cigarette: Alternative Nicotine Products

An increasing amount of basic science data is becoming available to guide future research directions and evidence-based public policy for alternative nicotine products, including e-cigarettes and waterpipes. E-cigarettes are battery-powered devices that deliver nicotine and other chemicals into an inhalable vapor (aerosol). Since their introduction in 2007, e-cigarettes have experienced a rapid surge in popularity worldwide. Importantly, a recent study found that a high proportion of individuals that use e-cigarettes alone (eg, no tobacco cigarette co-use) report feelings of being addicted (77.2%) and drug cravings (72.8%),[109] supporting the notion that nicotine by itself can support drug dependence in humans. Tobacco waterpipe (hookah) allows moassel tobacco, a high-moisture, fruit-flavored and scented formulation, to be heated with a lit charcoal, and the emissions are drawn by the smoker through a water chamber before inhalation. These unique features, including the low temperature of combustion and water "filtration", have prompted renewed popularity in this form of tobacco use across the eastern Mediterranean region, as well as among younger populations of tobacco users in other countries, including the United States. The increased use of these alternative products has prompted concerns about lowered perceptions of tobacco risk, encouraging use among those who would otherwise avoid tobacco products, and dual use with cigarettes among smokers.[110–114] Given the potential of these alternative nicotine products to appeal to youth and disrupt established tobacco control policies, scientific research across a number of levels is necessary to best inform policy reform; these levels need to include cell and animal toxicology, human exposure and health outcomes, nicotine delivery properties, vapor emissions and air quality monitoring, and trends in use.

Work on vapor/emissions constituent analyses has also begun to demonstrate the presence of toxicants in emerging products in isolation or compared to traditional cigarettes. Concerns have been raised about particulate matter, toxic and/or carcinogenic substances, including carbonyl compounds, acetone and ethylene glycol, all of which are emitted in e-cigarette vapor.[115–118] Tests of waterpipe emissions have yielded tar, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, nitric oxide and carbonyl compounds, among others.[119] Additional scientific inquiry is required to establish the health-related effects with long-term consumption of, or secondhand environmental exposure to, both products. For e-cigarettes, studies focusing on the effects of the hundreds of constituents in e-cigarette liquid (including flavoring additives), co-use with other substances of abuse, consequences of exposure during youth, and secondhand exposure to vapor/emissions are an urgent priority.

Recent research on waterpipes has addressed the challenge of adapting standard cigarette smoking protocols to that of waterpipe use, using human puffing parameters developed through measurement of waterpipe puff topography.[120] These innovations have produced critical findings showing that a single waterpipe session exposes users to approximately 76 liters of smoke emissions (compared with 0.6 liters for a cigarette), with corresponding implications for toxicant exposure.[119,121] Studies of waterpipe smoke have supported a cellular basis for chronic obstructive pulmonary disease (COPD) associated with waterpipe use[122] and the analysis of genotoxic effect on human lymphocytes using sister chromatid exchange suggests a potentially greater impact of waterpipe compared to tobacco cigarette smoking.[123] Other data on waterpipe health outcomes have shown associations with lung cancer, respiratory illness, low birth-weight, periodontal disease, and coronary arterial disease.[124,125] Critically, basic research has demonstrated that both e-cigarette and waterpipe use promotes nicotine dependence.[109,126] It should be noted, however, that other studies have shown a reduction in nicotine dependence with the use of e-cigarettes.[127,128] Of immediate importance, higher nicotine content e-cigarettes are rated as being more effective and thus preferred by smokers.[129] This has raised concerns regarding increased potential for dependence among initial users, including adolescents.

Unfortunately, industry promotion of emerging products has led to widespread public perceptions that those products are not harmful or addictive. After viewing television advertisements, adolescents and adults report increased positive attitudes toward e-cigarettes and greater desire for future use.[130,131] To counter these claims, rigorous

health communication and appropriate health warning labels are required.[132] The public appears to support efforts to restrict marketing and sale to adolescents, but not the restriction of flavors.[113,133] Given that flavors contribute to the desire to use e-cigarettes and thus might contribute to overdoses among youth,[134,135] as well as their direct contribution to toxicity,[136] restricting fruit, candy, and exotic flavors would be an important first step to decrease the initiation of use by adolescents. Recent evidence in rats suggests that nicotine enhances the reinforcing value of nonnutritive sweeteners, indicating that nicotine- and flavor-containing emerging products may increase abuse liability.[137] In addition, uniform adoption of comprehensive secondhand emission laws must be achieved to protect non-smokers from e-cigarette vapor and waterpipe emissions.[115,138]

One important consideration is that while alternative nicotine products have been promoted as a therapeutic harm-reduction treatment to minimize the deleterious effects of tobacco smoking,[139] and the FDA has approved pharmacological grade nicotine in the form of nicotine replacement therapy for smokers trying to stop smoking, nicotine is not risk free. Nicotine is associated with abuse liability, development and progression of smoking-related diseases, and altered neurocognitive function.[109,140–147] These effects may not only be mediated by nicotine's direct actions on nicotinic acetylcholine receptors but could also be due to modulation of other neurotransmitter systems, such as serotonin as one example (Box 4). Further, increasing evidence has demonstrated that nicotine enhances tumor maturation through increased cell proliferation, inhibition of apoptosis and angiogenesis, and metastasis of lung and pancreatic cancers.[148–150] It should be noted, however, that this science-based view does not yet appear to be uniformly accepted by policymakers.[151] In humans, developmental exposure to tobacco products has been associated with increased incidence of attention deficit hyperactivity disorder, depression, and drug abuse,[140–143] but it is admittedly difficult to determine whether tobacco use led to these behavioral changes or whether premorbid conditions contributed to drug consumption in humans. In addition, it is unclear what constituent components of these products may have directly contributed to these behavioral changes. However, given that adolescent nicotine exposure in rodents has been associated with long-term cognitive deficits,[152,153] changes in attention and impulsivity,[144] and altered anxiety and depression-associated behaviors,[145,146] one may infer that the aforementioned effects in humans could be due to the actions of nicotine (see also Box 1). Thus, studies are needed to specifically reveal the impact of nicotine and tobacco product constituents on health and abuse liability, especially as adolescents and young adults increasingly consume alternative nicotine products.

In the United States, the FDA is now beginning to support regulation of cigars, e-cigarettes and waterpipe tobacco products. Specifically, age restrictions on sale and scientific review of new tobacco products and manufacturers' claims are now required.[18] While taxation of tobacco cigarettes has been strategically employed to decrease consumption and provide funds for antismoking campaigns as well as research in certain states, similar efforts have not been universally imposed for e-cigarettes.[154] Although modest regulations on e-cigarette product standards have been introduced by the European Union, there have only been minimal recommendations for waterpipe products issued thus far[155] and a pending ban on flavored cigarette tobacco will exclude waterpipe tobacco.[156] Importantly, the WHO has proposed regulatory guidelines for e-cigarettes and waterpipe,[157,158] and the FCTC has far-reaching policy approaches that can be readily tailored based on new scientific evidence and potentially applied to emerging tobacco and nicotine products. Such approaches include provisions on price, contents and disclosures, health claims and warnings, advertising and promotion, and education.[159]

Box 4: Key Evidence that Tobacco Smoke and Nicotine Alters Brain Serotonin

- Acute and repeated nicotine decreases serotonin release in the brain.[203–205,289,290]
- Chronic exposure to tobacco smoke induces a brain subregion-selective reduction in serotonin, and increases receptor density in human hippocampus.[208,292]
- Serotonin transporter and receptor genes are implicated in human nicotine addiction and aspects of nicotine withdrawal, which may contribute to its reinforcing effects[206,207,218,270–272] aspects of nicotine withdrawal, which may contribute to its reinforcing effects.
- Polymorphisms of serotonin genes impact smoking habits, as well as chronic obstructive pulmonary disease.[270–273]

Summary: Nicotine and tobacco use impacts brain serotonin, and genetic variation in serotonin genes may increase nicotine addiction vulnerability.

Case in Point: Behavioral Economics to Inform Policy

As previously mentioned, basic research has contributed novel paradigms for the investigation of human nicotine and tobacco use, including studies on abuse liability and product perceptions to assist in the prediction of future patterns of product adoption and use. Behavioral economics is another basic research tool that may inform regulatory policy by examining motivation of choice. This analysis borrows from the field of microeconomics to characterize reinforcer consumption as a function of the unit price of that reinforcer.[160] Unit price is dependent upon the "cost" (monetary value, effort or time required to obtain the reinforcer) and the reinforcer magnitude. The amount an animal will work for nicotine may be thought of as the motivation to overcome an obstacle, such as cost, to obtain nicotine reinforcement. Rodents and non-human primates will self-administer nicotine in high effort schedules of reinforcement (ie, progressive ratio [PR] schedules),[161,162] with variability noted between species. Performance in PR schedules is indicative of the reinforcing efficacy of a broad range of stimuli, including cigarettes and nicotine, in humans and animals. When cigarettes serve as reinforcers, human PR performance is strongly associated with the desire to smoke.[163] Additionally, "breakpoint" (the measure of reinforcing efficacy, and is indicative of the slope of demand) has been associated with Pmax (the price at which the greatest amount of responding occurs) and elasticity (a reinforcer's sensitivity to price).[164,165] Importantly, this association illustrates that effort (measured via breakpoint) is translationally relevant to the amount of money humans will spend to obtain these reinforcers. It should be noted, however, that species may differ in their sensitivity to nicotine's reinforcing properties since rodents will expend more effort in PR schedules for other psychostimulants or food reinforcers than for nicotine[166–168] and choice for an alternative reinforcer increases with increasing effort required for cigarettes in humans.[169]

Research has demonstrated that some factors, such as prolonged nicotine exposure, impulsivity, or MAO inhibition increase self-administration of nicotine at higher break points or unit prices.[85,170,171] Taxation has been the most effective tobacco control approach to date in humans,[172] but many people continue to smoke despite economic burden. Recent work using rodent self-administration has demonstrated that nicotine consumption prior to a dose reduction may be predictive of elasticity of demand.[173] Findings from such studies may provide critical information regarding how smokers will respond to reductions in nicotine content in cigarettes, as demand curves describe changes in reinforcing efficacy and this information can be translated more easily across species.[67] Given that nicotine-seeking behaviors are complex and influenced by many factors, research aimed at understanding which factors modify nicotine-seeking using a behavioral economics framework can serve to inform tobacco product taxation policy, as some populations may be insensitive to increased cigarette/tobacco product taxation.

Traditionally, human behavioral economic studies allow participants to purchase (actual or hypothetical) cigarettes alone or alongside other products to determine how price and availability of varying products can impact purchasing behavior.[174–177] An important research area in this regard is the evaluation of the relative reinforcing value among alternative nicotine products as they relate to pricing structure and availability of different varieties of products.[175,178,179] For example, a recent study assessed smokers' behavior when participating in an online marketplace that allowed participants to view pictures, information, and prices for several nicotine-containing products (usual brand cigarette, Blu disposable e-cigarette, snus, dip, 4 mg nicotine gum, 4 mg nicotine lozenge, cigarillos).[175] Results revealed that as unit price of cigarettes increased, their consumption decreased (as predicted) and the absence or presence of cigarillos determined whether other nicotine products (e-cigarettes and snus) substituted for conventional cigarettes. As such, these findings provide a valuable insight into the relative reinforcing efficacy of key products on the marketplace and how pending policy regarding these products relative to each other could impact behavior. Future research fully exploring pricing structure with differing products in an experimental marketplace, such as that assessed in the above study, will be essential to guide policy in a way that benefits individual and population health.

Although behavioral economic approaches hold significant promise to guide policy reform, critical questions remain unanswered. For instance, research indicates that manipulations of instructional set (ie, what individuals are told about cigarette contents) can influence responses.[180,181] Double-blind trials offer numerous advantages, but cannot address how smokers will respond to a known reduction in nicotine content. Relatedly, how the instructions are conveyed could itself have a powerful influence on behavior.[182] Basic laboratory research is ideally suited to explore the impact of these factors and can directly inform policy. Ethical and pragmatic concerns preclude direct experimental examination of reduced nicotine cigarettes on smoking uptake. However, laboratory and imaging studies can identify thresholds below which nicotine is unlikely to produce psychoactive effects or result in the development of dependence.[183]

Conclusions

Concerns regarding the abuse liability, toxicity and other potential risks posed by cigarette and nicotine products have been raised since their development. In the field, debate remains regarding the early laboratory studies suggesting nicotine replacement had minimal abuse potential,[184–187] whereas more recent evidence indicates users can develop dependence on nicotine administering products, such as e-cigarettes.[109,126,129] Likewise, concerns about the safety of nicotine replacement therapy during periods of ongoing smoking appear to have been overstated.[188] Growing evidence also supports extending the course of treatment to improve cessation outcomes.[188–192] Finally, labeling requirements and recommendations for use of these products have the potential to positively impact public health by minimizing the use of these products, and the FDA through the Center for Drug Evaluation and Research (CDER) has recently revised labeling content in light of these concerns.

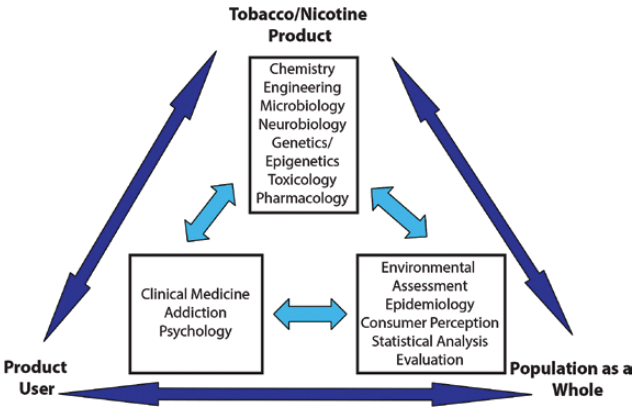

Figure 2. Varying Levels of Analysis and Expertise to Support Bidirectional Communication. The effects of tobacco/nicotine may be analyzed across varying levels with varying expertise. The level of analysis may include characteristics of the tobacco/nicotine product itself, biological/social impact on the product user, social/environmental effects on the population as a whole. Expertise may be derived from scientists specializing in varying realms (inner boxes) that provide insight supporting the varying levels of analysis. Figure adapted with permission from Ashley, DL (2015, May). Scientific research to inform FDA regulatory actions on electronic nicotine delivery systems (ENDS). Presented in part at the annual meeting of the Tobacco Merchants Association, Williamsburg, VA.

Looking forward, institutions and policy makers have an unprecedented ability to achieve significant advances to develop new and/or reform current policies, with the goal of promoting health through decreased drug consumption. Funding for basic science is essential to identify the key behavioral, neural, and associated factors fundamental to underlying use and dependence on tobacco and related nicotine products. In this regard, bidirectional communication between scientists and policy makers is crucial to guide science-based, informed decisions (for instance, see[193]; Figure 2). To facilitate constructive, bidirectional communication between basic scientists and policy makers, it would be helpful to begin the dialogue by understanding what questions policy makers have regarding the impact of nicotine and tobacco products at the behavioral and neurobiological levels, and the implications of these efforts on health outcomes. In this way, we can begin to address these questions through scientific advances that are relevant and informative. While significant advances have been made in these efforts over the last few years, much research is still needed to identify the neurobiological effects of emerging tobacco and non-tobacco products and their constituents during development and adulthood, along with the translation of these findings into policies that inform product standards, marketing, accessibility and sale for the protection of human health.

Supplementary Material

Supplementary data is available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

BAK is an employee of PinneyAssociates. PinneyAssociates works on smoking cessation and tobacco harm minimization (including nicotine replacement therapy and electronic vapor products) for Niconovum USA, Reynolds American Innovation, Inc., and RAI Services Company, all subsidiaries of Reynolds American Inc. However, we do not consult on conventional, combustible cigarettes. PinneyAssociates has also consulted to NJOY on electronic cigarettes in the past 3 years. All other authors declare no conflicts of interest.

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