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Nicotine Reduction Revisited: Science and Future Directions

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Abstract

Regulation of nicotine levels in cigarettes and other tobacco products is now possible with the passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in 2009 giving the U.S. Food and Drug Administration authority to regulate tobacco products, and with Articles 9-11 of the World Health Organization Framework Convention on Tobacco Control.[1-2] Both regulatory approaches allow establishing product standards for tobacco constituents, including nicotine. The FSPTCA does not allow nicotine levels to be decreased to zero, although FDA has the authority to reduce nicotine yields to very low, presumably non-addicting levels. The proposal to reduce levels of nicotine to a level that is non-addicting was originally suggested in 1994.[3] Reduction of nicotine in tobacco products could potentially have a profound impact on reducing tobacco-related morbidity and mortality. To examine this issue, two meetings were convened in the United States with non-tobacco-industry scientists of varied disciplines, tobacco control policy-makers and representatives of government agencies. This article provides an overview of the current science in the area of reduced nicotine content cigarettes and key conclusions and

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OTHER DECLARATIONS

Dorothy Hatsukami has received grant funding from Nabi Biopharmaceuticals to conduct nicotine vaccine clinical trials. Jack Henningfield provides consulting support for GlaxoSmithKline Consumer Health through Pinney Associates on an exclusive basis on issues related to tobacco dependence treatment, has financial interest in a potential new oral nicotine replacement product, and serves as an expert witness in litigation against tobacco companies. Neal Benowitz serves as a consultant for Pfizer and as an expert witness in litigation against tobacco companies. Mitch Zeller provides consulting support to GlaxoSmithKline Consumer Health through Pinney Associates on an exclusive basis on issues related to tobacco dependence treatment. Kenneth Perkins has served as a consultant to Cypress Bioscience.

recommendations for research and policy that emerged from the deliberations of the meeting members.

Keywords

Nicotine reduction; nicotine addiction; tobacco performance standards

INTRODUCTION

The authority of the U.S. Food and Drug Administration (FDA) to regulate tobacco offers an opportunity to reduce cigarette smoking prevalence and tobacco-caused morbidity and mortality.[1, 4] Substantial reductions in smoking prevalence might be achieved by mandated reduction in the cigarette's addictiveness. The primary objectives of this reduction should be cessation, prevention of tobacco use and addiction (by delaying or eliminating progression from experimentation to addiction) and substantially reduced use among smokers who do not quit. Although many factors contribute to initiation of tobacco use, there is widespread agreement that nicotine addiction sustains tobacco use.[5-9] Thus, reducing the nicotine in cigarettes to a level that is non-addicting may have an impact on reducing morbidity and mortality and improving public health.

In 1994, Benowitz and Henningfield proposed gradually reducing nicotine levels of all cigarettes over 10-15 years.[3] Computer simulation modeling the effects of reducing nicotine in cigarettes to nonaddictive levels projected a decline in smoking prevalence from 23% to 5%.[10] However, few studies have addressed whether or not reducing nicotine in cigarettes is a viable public health policy measure.

Two meetings were held (in 2007 and 2009) in the United States to revisit this topic.[1] Using seminal articles [3, 11] as a starting point, these meetings sought to: 1) Present current science on topics related to nicotine reduction; 2) Based on this science, discuss the potential feasibility and approaches to reducing nicotine in tobacco products; and 3) Establish a research agenda to determine the viability and practicality of nicotine reduction as a policy measure. Topics for the scientific overview were determined by a steering committee. This paper provides an overview of the science on each of the topics presented at the meetings and an outline of the most pressing research questions proposed by participants. This paper is not intended to be a comprehensive review of the extant literature on all aspects of nicotine reduction. This paper is focused primarily on the contribution of nicotine per se to tobacco dependence and does not address other factors that may enhance the addiction potential or appeal of a tobacco product, such as cultural, social, physical and economic aspects associated with its use.

[1]Meetings were held in November 2007 and January 2009 with experts from different scientific disciplines, tobacco control policy advocates, and representatives of different federal government agencies (see Appendix 1). The meetings were sponsored by the National Cancer Institute's Tobacco Harm Reduction Network and the University of Minnesota Transdisciplinary Tobacco Use Research Center. The meetings were funded by the National Cancer Institute, National Institute on Drug Abuse and the American Legacy Foundation.

CURRENT SCIENCE

We review new science in two categories: a) human laboratory and clinical studies, and animal studies relevant to understanding the effects of a reduced nicotine policy, including studies that examine factors that may modulate nicotine reinforcement, and b) contributions of product design and non-nicotine constituents that may moderate the influence of low nicotine content on the addictiveness or abuse liability of a cigarette product.

Human research relevant to reduction in cigarette nicotine delivery

Reducing nicotine delivery in cigarettes would be aimed at preventing intake of nicotine that reaches the threshold dose for nicotine reinforcement (i.e., the level at which nicotine leads to persistent self-administration), which is believed essential for onset of addiction. The few human studies on reduced nicotine (or denicotinized) cigarettes [12-32,35-36,40] have examined: 1) positive and negative reinforcing effects of denicotinized cigarettes; 2) effects of reduced nicotine cigarettes on toxicant exposure and compensatory smoking (i.e. greater smoking in an effort to maintain a desired nicotine intake); and 3) use of reduced nicotine cigarettes as a cessation tool. In these studies, the nicotine delivery in most of the reduced nicotine or denicotinized cigarettes is relatively low because they contain smaller amounts of nicotine (5-10% of the yield of standard commercial brands) in the tobacco itself. (These are different from the widely-available, so-called “light” brands, which contain amounts of nicotine similar to standard brands but are engineered to dilute smoke intake with air.) There are also human studies describing the amount of smoking associated with onset of dependence symptoms. Although studies of the threshold for nicotine discrimination have been conducted, to date no systematic human study has examined the threshold dose for the development or maintenance of nicotine addiction nor directly examined the best approach for reducing levels of nicotine in cigarettes to maximize public health benefits.[2]

Laboratory and residential human studies—Laboratory studies show that denicotinized cigarettes produce acute subjective effects similar to those of nicotine cigarettes. For example, denicotinized cigarettes have been shown to reduce craving and negative affect due to withdrawal during short-term abstinence periods from usual brand cigarettes.[12-21] The acute withdrawal relieving effects are found not to be due to expectancies for nicotine or the simple motor aspects of smoking (e.g. handling), highlighting the importance of smoke inhalation per se.[22] Denicotinized cigarettes and standard nicotine cigarettes can produce similar self-reported liking and satisfaction in smokers [23, 24] although another study found results to the contrary [35], and can produce similar delays in the latency to smoke (i.e., the time to smoke a cigarette) or reductions in the amount of subsequent smoking of nicotine cigarettes.[17, 25] Denicotinized cigarettes may also be as acutely reinforcing as nicotine cigarettes in dependent smokers[26], suggesting that denicotinized cigarettes may serve as an effective short term substitute for nicotine-containing cigarettes when the latter are unavailable.[27-28]

[2]The tobacco industry itself conducted extensive research to determine the threshold for targeting nicotine dosing by cigarettes, concluding, for example that “to lower nicotine too much might end up destroying the nicotine habit in a large number of consumers and prevent it from ever being acquired by new smokers.” (U.S. Dept. Justice Ex 20,112, British American Tobacco Company, 1959, cf [34] However, the tobacco industry research appeared more focused on establishing the threshold dose that would r eadily sustain addiction and not necessarily the dose, below which addiction would be unlikely to occur.

Most of these studies were conducted in the laboratory and over a limited period of time (e.g. a few hours) and may not reflect outcomes observed over longer time periods. In an 11-day inpatient study, the reinforcing efficacy of denicotinized cigarettes decreased over time (as measured by number of cigarettes smoked and how hard subjects worked to earn puffs on the cigarette), but denicotinized cigarettes continued to effectively reduce craving from cessation of usual brand cigarettes [29], which is consistent with results from a similarly designed outpatient study.[36]

The responses observed with denicotinized cigarettes may be because non-nicotine sensory aspects have acquired reinforcing effects, non-nicotine constituents other than nicotine are reinforcing, or that low levels of nicotine are sufficient to maintain smoking behavior because these levels can produce effects of physiological significance, at least acutely. For example, recent brain imaging studies show that smoking a single very-low-nicotine cigarette results in significant (23%) occupancy of $\alpha 4\beta 2$ nicotinic receptors, which are considered the primary receptor subtype mediating nicotine's reinforcing and other behavioral effects.[37] Thus, the reinforcing and mood effects of very-low-nicotine cigarettes may be attributable, in part, to nicotine's pharmacological effects. Other evidence also suggests that very low-level nicotine exposure may have important pharmacological effects. This includes in vitro studies showing that significant nicotinic receptor desensitization, a potential contributor to nicotine addiction,[38] can occur with nicotine doses below a threshold for activating receptors, which mediates nicotine's acute reinforcing effects.[38-39]

In summary, abrupt switching to denicotinized cigarettes does not appear to result in significant withdrawal symptoms and may maintain similar levels of smoking reward and reinforcement in the short-term. Over more extended exposure, the positive reinforcing properties of denicotinized cigarettes appear to decrease. Longer-term clinical studies, presented next, address the time course of these effects while smoking reduced nicotine cigarettes, as well as their impact while smokers are in the natural environment.

Longer-term clinical studies: Gradual nicotine reduction effects—One of the major concerns regarding reduced nicotine cigarettes is whether they would lead to “compensatory” (i.e. increased) smoking behavior to maintain level of nicotine intake, which may result in greater exposure to toxic smoke emissions. In preparation for a series of clinical studies, Benowitz et al.[30] examined the acute effects of cigarettes containing five levels of nicotine (1 to 12 mg) on plasma nicotine and blood carboxyhemoglobin concentrations in a within-subject, cross-over study. Systemic nicotine intake was related linearly to the nicotine content of the cigarettes, and compensation after smoking a single low-nicotine content cigarette was relatively small. Carbon monoxide exposure was similar across the nicotine doses, further supporting the idea that compensation was minimal. Similar results were found when CO boost of an even lower, 0.05 mg nicotine yield cigarette was compared with preferred brand.[35]

A subsequent clinical study [31] examined the effects of reduced nicotine content cigarettes on nicotine and carcinogen exposure when smokers were asked to smoke progressively lower nicotine content cigarettes. Over the weeks of nicotine content tapering (5 levels of

nicotine from 12 mg to 1 mg, or 0.8mg to 0.1 mg nicotine based on machine determined yields; each level smoked for one week) plasma cotinine levels declined to 30% of that seen when subjects were smoking their usual cigarettes. There was little evidence of increased smoking (no change in number of cigarettes or CO), no change in cardiovascular risk factors (e.g., HDL cholesterol, c-reactive protein, fibrinogen, P-selectin), and a decrease in 4-(methlynitrosamino)-1-(3-pryridyl)-1-butanol and its glucuronides (or total NNAL), a metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen. Despite the sharp reduction in nicotine intake, there was no increase in craving and no change in self-reported depression. However, there was an increase in self-reported irritability and eating. At 4 weeks after the end of the study (when subjects were allowed to return to their usual brand cigarettes or to quit), 25% of the subjects attained abstinence, a surprisingly high rate given that these smokers did not enroll in the study in order to quit.

In a similarly designed study [32], researchers examined commercial low yield cigarettes engineered to increase smoke dilution to provide progressively lower yields, as assessed by smoking machine testing (0.9 mg to 0.1 mg based on machine determined yields). Little change was seen in plasma cotinine concentration from 0.9 to the 0.4 mg nicotine yield cigarettes, suggesting compensation in smoking behavior. However, significant decreases in this measure and carcinogen exposure biomarker levels (NNAL and metabolites of some polycyclic aromatic hydrocarbons) were observed when smokers were switched to 0.2 mg and/or to 0.1 mg nicotine yield cigarettes, most likely because of the extensive filter ventilation of these “ultralow yield” cigarettes, too much to be overcome by compensation. The 0.1 mg nicotine yield cigarette also produced non-significantly greater withdrawal. Two of 20 subjects quit smoking 4 weeks after tapering to the lowest yield cigarette. This study also suggests that substantial reduction in the nicotine yield of cigarettes may not lead to compensation, may reduce toxicant exposure, and may facilitate abstinence, if nicotine yields are sufficiently low.

Longer term clinical trials: Reduced nicotine cigarettes as a cessation tool— Recent clinical trials support the idea that low nicotine cigarettes may be useful as an aid for cessation. One study compared 6 weeks of use of 0.3 mg and 0.05 mg nicotine yield cigarettes with medicinal nicotine (lozenge) as methods for cessation. Seven-day point prevalence success rates at the end of 12 weeks were 14% with 0.3 mg cigarette, 36% with 0.05 mg cigarette, and 20% with nicotine lozenge [p= 0.02;40]. Number of cigarettes per day and level of carbon monoxide (CO) increased with 0.3 mg cigarette, but decreased with 0.05 mg cigarette; yet, in both conditions, there was significant reduction in biomarkers of carcinogen exposure, presumably because these cigarettes contain low nitrosamine levels [33].

Another relevant area of research includes examining methods that may maximize extinction of smoking behavior by separating nicotine intake from cigarette use. To date, four clinical trials have examined combined use of nicotine patch with denicotinized cigarettes over brief periods (2 weeks or less for denicotinized cigarettes).[36, 41-43] Findings suggest that the use of nicotine patch with denicotinized cigarettes, compared to nicotine patch or denicotinized cigarettes alone, may lead to greater satiation and craving relief.[42] On the other hand, another study showed no differences between denicotinized cigarettes with or

without the nicotine patch on cigarette satisfaction and liking, but a trend towards greater withdrawal relief.[36] This study also found addition of the patch reduced total puff volume, CO boost and number of denicotinized cigarettes smoked.[36] However, nicotine patch did not appear to facilitate the process of smoking extinction when observed under short term study conditions.[36]

These clinical studies suggest that reduced smoking behavior and increased cessation could occur with cigarettes of no more than 0.1 mg in nicotine yield. Addition of nicotine patch may promote smoking cessation, although the evidence is limited. Some study populations have consisted of smokers who wanted to quit, and quit motivation can strongly influence treatment effects.[44] In a 1940s study [45], “inveterate” smokers who were switched to a very low nicotine cigarette for about one month reported significant withdrawal symptoms. Therefore, research is needed on the impact of reduced nicotine cigarettes in a more representative population of smokers with varying levels of interest in quitting (i.e. the majority of smokers who would be confronted with a marketplace of low nicotine cigarettes).

Development of nicotine dependence—The dose of nicotine that will lead to extinction of smoking may not be the dose that is associated with the onset of dependence symptoms or nicotine addiction. Studies conducted with adolescent smokers [46-51] suggest that the potential threshold for onset of nicotine addiction is likely to be substantially lower than the 5 standard nicotine cigarettes per day suggested by earlier research.[3] Several cross-sectional and longitudinal studies have shown that youth smoking on a less than daily basis nevertheless report onset of dependence symptoms.[46-49] About half the youth smokers who reported one or more symptoms reflective of a loss of autonomy over smoking had smoked on average two cigarettes one day per week, and half of those who met ICD-10 defined dependence reported smoking 46 cigarettes a month, or 1-2 cigarettes per day. [50-51] That symptoms of dependence can develop with low rates of smoking is consistent with results from a small study of adults demonstrating about 50% occupancy of $\alpha 4\beta 2$ nAChRs for 3 hours after just 1-2 puffs on a 1.2-1.4 mg nicotine yield cigarette.[52] Similarly, other prolonged brain effects (long-term potentiation of the excitatory transmission to the brain reward centers) have been observed after brief application of low concentrations of nicotine [0.5-1.0 μM; 53].

Both human and animal studies have shown that the adolescent brain is more vulnerable and sensitive to nicotine's effects.[51] For example, adult smokers who initiated smoking during adolescence exhibit greater cigarette consumption, lower likelihood of trying to quit, and increased risk of relapse compared to those who started smoking later in life.[54-56] Adolescent rats and mice might also be more sensitive than adults to the rewarding and reinforcing effects of nicotine, as indexed by greater conditioned place preference (CPP), [57-62] faster acquisition of nicotine self-administration (NSA), and higher baseline NSA rates compared to adults [63-66; but see, 67-69]. What remains unknown are the effects of low dose nicotine cigarettes in adolescents and whether there is a dose that reduces the probability of sustained cigarette use.

Animal research

Given the similarity across species in intravenous nicotine doses that are self-administered[70-71], animal studies may be useful for identifying a range of doses that may encompass the nicotine reinforcement threshold in humans. Numerous studies have shown that acquisition and maintenance of intravenous NSA in adult animals (e.g., rats, monkeys) is dependent upon unit dose, with the peak of the dose-response curve at unit doses of 0.01 to 0.03 mg/kg under small fixed-ratio (FR, fixed number of lever presses for a dose of nicotine) schedules [see 70 for review]. While NSA in animals typically decreases at unit doses below 0.01 mg/kg, unit doses as low as 0.003 mg/kg have been shown to maintain NSA in rats above saline extinction levels when substituted for a higher training dose (e.g., 0.03 mg/kg), though variability between subjects is apparent [72-76; but see 77, 78]. No animal studies have specifically characterized the reinforcement threshold dose of nicotine during acquisition of NSA in adolescents or in the context of progressively reducing the unit nicotine dose during maintenance of NSA in adults.

Individual differences and environmental moderators

Animal or human data suggest that a variety of factors could modulate nicotine reinforcement thresholds. The same low dose of nicotine may or may not be reinforcing, depending on individual differences and environmental moderators of nicotine reinforcement (i.e. self-administration).

However, the focus of most research—differences between groups in their mean response to a fixed dose—is of uncertain utility in informing policy. Rather than a group's mean response at a particular low dose, the distribution of the minimum doses eliciting a response from the individuals within the group will be of greater relevance in identifying a nicotine dose below the threshold for nicotine reinforcement. Such a distribution identifies how many group members will be at risk at a given low dose below the group's mean threshold (e.g. if FDA set a maximum dose for cigarettes).

Although nicotine discrimination is not directly related to reinforcement, human studies of the threshold dose for nicotine discrimination provide an example of the potentially wide variability within groups of humans in reinforcement threshold doses. In a study involving nicotine nasal spray, the median threshold dose for discrimination from placebo was quite low and similar between 19 nonsmokers and 18 smokers, 0.002 mg/kg (approx. 0.14 mg for 70 kg human) and 0.003 mg/kg (approx. 0.21 mg/70 kg), respectively.[79] However, threshold doses in this study varied by over 100-fold within both smokers and nonsmokers, from 0.00013 mg/kg up to 0.020 mg/kg. Whether this within-group variability generalizes to nicotine via smoking would be important to determine. With these caveats in mind, the following brief overview of human research examines mean differences between groups in the reinforcing and rewarding effects of fixed nicotine doses.

Individual differences

Sex: A considerable body of research indicates that adult women smokers may be less sensitive than men to the reinforcing and rewarding effects of nicotine per se, but more sensitive to the reinforcing and rewarding effects of non-nicotine aspects of smoking, such

as cues.[80] This sex difference has also been observed among adult nonsmokers [81] suggesting an innate sex difference prior to onset of dependence.

However, adolescent girls are more likely than boys to report experiencing nicotine dependence symptoms[46-47, 49, 51] and experiencing the onset of nicotine dependence symptoms faster[51], although another study showed no difference in latency to dependence symptoms.[50] These results suggest a greater, rather than less, sensitivity to tobacco use in girls compared to boys, although the relative contributions of nicotine versus non-nicotine factors cannot be disentangled in this research. Animal studies also show greater sensitivity to nicotine in female rats compared to male rats.[82-83] However, these studies involved nicotine delivery accompanied by cues, and consistent with adult human differences [80], female rats also appear more sensitive to conditioned reinforcement from cues associated with nicotine intake.[84]

Comorbid disorders: Because smoking prevalence is much higher in those with other psychiatric or substance abuse disorders, nicotine may be more reinforcing in smokers with such comorbidities than in smokers without such disorders. These disorders include schizophrenia, major depression, attention deficit hyperactivity disorder, and alcohol, cocaine, opiate, and stimulant dependence.[86] Little research has directly examined this notion, but Hughes et al.[87] found that nicotine via gum was more reinforcing in smokers who were former alcoholics compared to smokers who had never been alcoholic. However, chronic alcohol exposure may lead to tolerance to many effects of nicotine,[88] suggesting reduced sensitivity to those effects and perhaps to nicotine threshold dose.

Individual differences: nicotine pharmacokinetics: Human studies have shown a relationship between nicotine pharmacokinetics and smoking. Populations with slower nicotine metabolism smoke on average fewer cigarettes per day than those with more rapid elimination,[89] and greater smoking and lower quit rates are associated with faster nicotine metabolism.[90] This relationship can be demonstrated within subjects, as inhibition of nicotine metabolism in smokers by methoxsalen is accompanied by smoking reduction.[91] While faster metabolism is associated with greater dependence in adult smokers, slower metabolism may be associated with a higher likelihood of developing dependence during smoking initiation ([92] but see[93]). In the context of initiation, slower metabolism may be associated with greater vulnerability to addiction, perhaps because it results in prolonged presence of higher brain nicotine concentrations, producing a higher magnitude (or longer duration) of reinforcement. For the same reason, slower metabolism could also enhance the reinforcing effects of smoking cigarettes with low nicotine content in both adults and adolescents. Slow metabolism could therefore lower the nicotine reinforcement threshold in smoking initiation and maintenance.

Ethnic/racial groups: Smoking prevalence and daily smoking rate vary by ethnicity, as does nicotine kinetics,[94] suggesting some possible influence of ethnicity/race on nicotine reinforcement. Some populations demonstrate slower nicotine metabolism (e.g. Asian Americans), which may account for their lower smoking rate compared to populations with more rapid elimination.[89] Few differences in pharmacodynamic effects of nicotine as a

function of ethnicity or racial identity have been shown, although little research has examined these differences.

Genetic factors: Genetic factors have been associated with risk of onset and persistence of nicotine dependence in clinical research,[95] but it is not clear that these associations are due to differences between genotypes in sensitivity to nicotine reinforcement, either prior to or after dependence onset. However, among nonsmokers in one study, nicotine choice (i.e. self-administration) via nasal spray was greater in those without the DRD4-7 allele compared to those with the 7 allele, but other dopamine-related genetic factors, including DRD2 and DAT, were not related to reinforcement.[96] Research with dependent smokers shows that presence of the G allele of OPRM1, the mu opioid receptor gene, is associated with reduced nicotine choice, but only in women and not men.[97] Together with the literature on genetic influences on nicotine metabolism,[90] the possible influence of genetic factors on nicotine reinforcement threshold dose remains likely, but more research is needed to clarify which factors are involved.

Other differences: Obese smokers may be less sensitive to nicotine reinforcement and reward,[98] suggesting that their threshold dose for nicotine reinforcement may be higher. Parental history of smoking is associated with greater risk of dependence in offspring, but greater sensitivity to nicotine reinforcement may not explain the association.[99] Impulsive personality factors are associated with greater risk of onset of dependence and may increase choice of nicotine nasal spray in nonsmokers, particularly in males,[100] suggesting that more impulsive individuals may be more sensitive to nicotine reinforcement threshold.

Environmental moderators—The reinforcing effects of nicotine are not an immutable property of the drug but may be acutely influenced by environmental factors. Environmental moderators of nicotine reinforcement may be numerous; only a few will be discussed.

Nicotine formulation (including expectancy and cues): Although differences between formulations in nicotine pharmacokinetics play a key role In abuse liability and possibly threshold dose for reinforcement,[101] differences in expectancy for effects and other stimuli accompanying nicotine intake may also be involved. Smokers have expectancies for pleasurable effects from smoking but usually little expectancy of positive effects from less familiar formulations.[102] Expectancy for nicotine can speed the latency to smoke and increase reward, especially in women.[103] Similarly, smoking-associated stimuli or cues enhance nicotine reinforcement and reward from smoking.[80] This suggests that the threshold dose for reinforcement in dependent adults may be lower with smoking than with other forms of nicotine.

Stress or mood: Acute stress and negative mood commonly increase risk of relapse in quitting smokers, and laboratory studies show that smoking reinforcement is greater under such conditions,[104-105] perhaps suggesting enhanced sensitivity to nicotine reinforcement threshold dose. Similar effects of stress have been reported with animal NSA models.[106] Older research suggests small changes in nicotine pharmacokinetics due to stress,[107] but this effect is unlikely to have a substantial influence by itself on threshold dose for reinforcement. One study of dependent smokers found greater acute smoking reinforcement

due to negative mood as a function of DRD4, DRD2 and DAT genotypes, but only DRD4 was associated with mood-induced increase in nicotine reinforcement per se.[108]

Acute alcohol intake and other drug use: Dependence on other drugs increases risk of smoking onset and persistence, and vice versa, but it is not clear that these associations are due to acute effects of those other drugs on sensitivity to nicotine reinforcement. Several, but not all, studies have shown increased acute smoking reinforcement following alcohol consumption [109] and stimulant use, such as methylphenidate[110] and cocaine.[111] Other research showed increased acute alcohol reinforcement following smoking, at least in men.[112] However, none of this research has clarified that the increases in smoking or other drug use are due to nicotine per se. Some animal studies have shown that caffeine and methylphenidate can increase NSA and nicotine discrimination in rats.[e.g., 113, 114]

Additional observations

In both the human and animal literature, there is a scarcity of data not only on the effects of reduced nicotine doses on smoking or nicotine intake but also on other responses. Even if a threshold reinforcing nicotine dose is identified and a non-addictive cigarette can be produced, it will be important to determine whether there are other adverse effects from the nicotine exposure that occurs in adolescents who nonetheless experiment with such cigarettes. The threshold for nicotine's reinforcing effects may be higher than the threshold for nicotine's other potentially adverse effects, including enhancing vulnerability to other drug use. In animal studies, very brief exposure to i.v. nicotine doses (only two infusions of 0.03 mg/kg daily for 4 days) in adolescent rats sensitized them to the reinforcing effects of cocaine, suggesting a potential adverse consequence of very limited nicotine exposure in adolescence.[115] This daily dose (0.06 mg/kg/day or 4.2 mg for a 70 kg smoker) is comparable in humans to the nicotine intake from 4 standard cigarettes. Therefore, low-level nicotine exposure in adolescents experimenting with cigarettes designed to prevent nicotine addiction could potentially produce risk of addiction to other drugs of abuse.

PRODUCT DESIGN AND CONSTITUENTS

Reducing dependence risk due to nicotine from tobacco use requires more than simply mandating lower amounts of nicotine in products. Although the addiction potential of a product is critically determined by its active pharmacological entities (e.g., nicotine), the real world risk of addiction is determined by many other aspects of the drug formulation (e.g., oral, nasal, smoked), which can influence the biological impact of a given drug dose. For example, oral smokeless tobacco products and cigars appear to carry a somewhat lower addiction risk than cigarettes,[116-118] and the risk of developing addiction to nicotine replacement medications appears to be very small [3, 5, 9, 119], even though the absolute nicotine delivery from these formulations may not differ much.

A variety of physical parameters, including amount of tobacco, its nicotine content, length and circumference of the tobacco column, filter length, filter ventilation, filter composition, and other ingredients, influence delivery of nicotine, nicotine-free dry particulate matter (NFDPM, commonly known as tar) and various gases.[6-7, 120] A wide range of chemical parameters (such as moisture content of tobacco, specific tobacco composition parameters,

specific additives in paper and tobacco) change the response of tobacco to heating under combustion or pyrolysis conditions. Interactions of physical and chemical characteristics of cigarettes may also change the size distribution of aerosol particles that determine deposition and absorption of nicotine and other constituents.[7]

The complexity of this issue is illustrated by a study that described how physical parameter differences of cigarette (e.g., non-filter cigarettes, cellulose acetate filter cigarette with and or without perforation, cellulose acetate filter cigarette with perforation and highly porous paper), despite the same tobacco composition, can dramatically alter the amount of machine-determined yields of nicotine and various other toxicants.[121] Formaldehyde varied among cigarettes from 21 μg to 36 μg, phenol from 62 μg to 161 μg, and acetaldehyde from 550 μg to 1290 μg. Nicotine delivery varied from 0.94 mg/cigarette to 1.5 mg/cigarette within the filter types. Changes in filtration, however, made very little difference for other toxicants such as the polycyclic aromatic hydrocarbons (e.g., benz(a)anthracene, benzo(a)pyrene), showing how limited and variable filtration can be in reducing some constituents.

Constituents within tobacco products also augment levels of free base nicotine and thereby may contribute to tobacco's reinforcing effects. For example, ammonia, diammonium phosphate, or urea have been identified in tobacco industry documents as capable of enhancing the bioavailability of nicotine by delivering increased levels of free-base nicotine in the smoke.[122-123] Pankow et al.[124-125] described changes that occur in the balance between nicotine in the particulate phase and the gas phase as chemical additives alter the pH of smoke. Since the rate of transfer of nicotine from product to smoke and from smoke to the nicotine-receptors in the back of the throat and lungs is driven by the fraction of free nicotine, addition of chemicals or design features altering either the pH of emissions or enhancing delivery from tobacco products might also contribute to the cigarette's high addiction potential.[34, 126]

Some of the more than 4,000 tobacco smoke constituents other than nicotine may also contribute to engendering and maintaining smoking behavior. For example, nornicotine, a minor alkaloid constituent of tobacco and a brain metabolite of nicotine,[127-128] accumulates in rat brain with repeated nicotine administration and exhibits a brain half-life three-times longer than nicotine,[129-130] evokes dopamine release in rat striatum in a mecamylamine-dependent manner,[131] elicits discriminative stimulus (i.e., subjective) effects similar to nicotine,[132] and produces reinforcing effects in its own right [i.e., is self-administered, 133].

Anabasine, another minor tobacco alkaloid, produces nicotine-like discriminative stimulus effects,[134-136] and the combination of nicotine with a smoke-relevant cocktail of minor alkaloids (anabasine, nornicotine, anatabine, cotinine, and myosmine) is more reinforcing than nicotine alone.[137] It is likely that other compounds in cigarette smoke contribute to addiction risk. For example, acetaldehyde, a combustion product, increases the firing rate of dopamine neurons in the ventral tegmental area,[138] potentiates the locomotor effects of nicotine,[139] is self administered in animals,[140-142] and increases acquisition of nicotine self-administration (NSA) in adolescent rats at unit nicotine doses that alone are not self-administered.[57]

Monoamine oxidase inhibitors (MAO) inhibitors, such as harman, are present in tobacco and tobacco smoke,[143-144] and the brains of smokers show 28% lower MAO-A and 40% lower MAO-B activity in PET-imaging studies.[145] Harman is also a condensation product of acetaldehyde.[143] MAO catalyses intraneuronal deamination of biogenic amines, such as dopamine, serotonin and noradrenaline. Consequently, MAO inhibition increases extracellular brain levels of these amines and may potentiate effects of nicotine, since nicotine stimulates amine release. Studies in rats show that the nonspecific MAO inhibitor tranylcypromine (TNCP) or various MAO-A selective drugs enhance nicotine-induced dopamine release in the nucleus accumbens,[146] locomotor sensitization to nicotine,[147] nicotine discrimination,[148] and nicotine self administration.[85, 146, 149] These findings provide evidence that non-nicotine tobacco constituents could play a role in moderating nicotine reinforcement thresholds.

In summary, product design, pH, and constituents other than nicotine may play a significant role in addictiveness of cigarettes.[150-151] Additives, such as menthol may also increase reinforcing efficacy by making tobacco more palatable, enhancing taste and smoothness, and facilitating self-administration.[152-153]

RESEARCH RECOMMENDATIONS

Based on the existing science, it appears reasonable to propose that a threshold dose for nicotine reinforcement will eventually be identified such that cigarettes containing doses below this threshold should not produce dependence in the majority of individuals. Identifying this threshold will require different lines of research, including assessment of smoking reinforcement in adult smokers as well as naïve adolescents as a function of lowering cigarette nicotine dose. Studies of nicotine threshold dose with naïve adolescents, however, will be particularly challenging and perhaps should be studied primarily in animal models.

The best approach to reduce nicotine in cigarettes is not certain, but two alternatives may be considered: 1) Over time, a mandated, stepped reduction of nicotine content in combustible products; or 2) Immediate, significant reduction of nicotine content in cigarettes to a dose where no significant compensatory smoking behavior would occur. The primary outcomes to be measured in clinical research would be: a) number of quit attempts; b) sustained cessation of tobacco use; c) toxicant exposure; and d) drop-out rate and other non-compliance measures, including uptake of other products. Attendant to this general research question are a number of specific research questions, listed in Table 1.

Unintended consequences may be particularly difficult to study.[11, 154] Among potential concerns are: 1) A switch to other drugs of abuse, particularly among populations smoking for social reinforcement, self-identity, or self-medication purposes; 2) Dual use of tobacco products, such as reduced nicotine cigarettes with oral tobacco or small cigars, which may lead to greater exposure to toxicants, especially if these other tobacco products continue to contain higher nicotine levels; 3) Use of reduced nicotine cigarettes as starter products. Just as low free-base nicotine smokeless tobacco products served as starter products for higher nicotine and more toxic smokeless tobacco products,[155] these reduced nicotine cigarettes

may lead to the use of other tobacco products with higher levels of nicotine, unless these other products also contain low nicotine levels; 4) Illicit cigarette marketing and smuggling[156] including through the internet and through territories that do not require reduced nicotine content of cigarettes; 5) Product tampering or manipulation (such as adding nicotine to the product); and 6) Industry manipulations (e.g., nicotine analogues, companion products to increase nicotinic effects).

Conclusions

Developing practical, scientifically-supported recommendations about nicotine levels in tobacco products involves filling gaps in knowledge in diverse areas including tobacco product design, content, and emissions; biomarkers of exposure; addiction; sensory perception; motivational factors; withdrawal and craving; animal studies; human clinical research; genetics; physiology, pharmacokinetics and metabolism; population studies; economics; and communications and messaging. Consequently, an organized and multidisciplinary effort should be established to set priorities and goals (the desired end results); engage appropriate scientific, research, and government communities/organizations; shape the direction of research; and ensure that efforts stay focused on the ultimate goal of understanding how nicotine reduction could impact the morbidity and mortality of tobacco use. Access to tobacco industry knowledge and research conducted in the areas of nicotine manipulation, nicotine analogues and abuse liability testing of tobacco products could advance the understanding of this issue.

If nicotine reduction is enacted, then large-scale surveillance is needed in order to understand the population-level impact of such changes. Marketplace monitoring and assessing unintended consequences (smuggling, nicotine spiking, new product introductions, etc) will also involve broad surveys.

We are in an unprecedented time in tobacco control where the possibilities of reducing tobacco-related morbidity and mortality by reducing nicotine in tobacco products could be a reality. Because this measure has the potential to have a profound impact on reducing smoking prevalence and thereby smoking-related death and disease, the sooner we are able to address the research questions described in this article, the sooner we can reduce the number of lives lost to tobacco.

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WHAT THIS PAPER ADDS

This paper provides a scientific exploration of the issue of reduction of nicotine content in cigarettes on tobacco addiction. This topic is of particular significance because of the Family Smoking Prevention and Tobacco Control Act, providing the U.S. Food and Drug Administration jurisdiction over the regulation of tobacco products, and Articles 9-11 of the World Health Organization Framework Convention on Tobacco Control. An updated overview of the scientific literature on reduced nicotine cigarettes is provided. In addition, recommendations for future directions and research agenda from tobacco control researchers, policymakers and representatives of governmental agencies developed at meetings convened in the U.S. are described.

Table 1

Nicotine Reduction Research Questions

Short-Term Needs
• What is the nicotine threshold dose(s) for addiction and the distribution of thresholds across subjects? What are the moderating influences?
• What are the effects of reduced nicotine cigarettes on the brain, both in adult smokers and in adolescents experimenting with these cigarettes? Are there changes in the receptor number or binding potential and do they change over time? Does receptor sensitization change over time?
• What is the extent of compensatory smoking across the two nicotine reduction approaches (immediate vs. gradual reductions in nicotine content) and what interventions can be used to minimize compensatory smoking, such as making nicotine available through less hazardous delivery systems (e.g, NRT) or through non-nicotine pharmacotherapies?
• What are the effects of reduced nicotine cigarettes in subpopulations (consumers who smoke for self-medication purposes such as those with co-morbidity or who are severely addicted to tobacco products) and how can negative consequences be mitigated?
• What product contents and design features affect product addictiveness (such as the identification and balance of acids and bases, the relationship between smoke chemistry and aerosol physics and respiratory tract deposition)? Should we be focusing more attention beyond nicotine to reduce addictiveness? What would be the effect be of merely banning ventilated filters or specific additives in cigarettes?
Long-Term Needs
• What would be the public's reaction to and perception of a marketplace containing only reduced nicotine cigarettes? How could we frame the message and educate the public about reduced nicotine cigarettes to produce the greatest public health benefit?
• What are the potential unintended consequences from reduced nicotine cigarettes, how can they be determined and monitored, and what needs to be done to mitigate against negative consequences?