Re-thinking nicotine and its effects

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In this paper, we broadly synthesize scientific evidence concerning use and effects of nicotine in human populations, and re-examine nicotine's role in promoting and potentially reducing tobacco-related harms. Tobacco- and nicotine-containing products have evolved considerably in terms of their modes of delivery and corresponding harm potential. When nicotine is delivered in combustible tobacco products (e.g., cigarettes, cigars), addiction and persistent use results in devastating consequences. Less clear are nicotine's effects when delivered in noncombustible tobacco products and, most recently, in forms that are increasingly separated from toxic tobacco and combustion byproducts. Can such products play a role in an overall tobacco harm reduction and control strategy?

Basic science studies of nicotine's effects on biology and behavior are voluminous. To avoid unnecessary granularity, we rely on authoritative summaries and reviews of the scientific literature to highlight consensus among leading scientists in each content area. We also focus on issues that could significantly affect the population of current tobacco product users, and non-users (especially youth), with respect to rapidly reducing the number of preventable tobacco-related harms (diseases and deaths). This is consistent with the FDA's public health mandate to determine the total societal benefits versus the harms of existing and new nicotine-containing products.

Scientific evidence is always subject to revision based on ongoing research. We therefore focus on what is currently known about nicotine that can then be used as a foundation to rethink the role of nicotine in society, and how this knowledge could inform policy making, regulation and further research.

Tobacco control's overarching goal is to save lives as rapidly and effectively as possible. This will require open minds to rethink harms of nicotine when it is decoupled from combustible tobacco. If nicotine cannot be totally banned and eradicated, then what kind of nicotine use is society willing to accept? What is the potential for unintended consequences of reduced-harm nicotine delivery products? What policies and regulations can ensure that harm from nicotine use are minimized while simultaneously moving the entire population away from deadly combustible tobacco products?

SUMMARY:

- Most of the physiological harm attributable to cigarette smoking derives from the toxicants in tobacco and combustion products. Preventable morbidity and mortality has overwhelmingly been related to combusted tobacco smoking, not to nicotine itself. Decoupled from combustion or other toxic modes of delivery, nicotine, by itself, is much less harmful.

- Nicotine is not known to cause cancer. Epidemiological evidence in human populations does not support the basic science concern from laboratory studies that nicotine promotes some cancer pathway activation. There is no evidence that nicotine, by itself, is a carcinogen. More research is required to demonstrate if, and to what degree, there may be a concern about nicotine's role as a cancer promoter.

- Nicotine may contribute to cardiovascular disease (CVD), but its impact is much less, compared to tobacco smoke.

- At very high doses, higher than those experienced by the vast majority of nicotine and tobacco product users, nicotine can cause serious acute toxicity.

- Nicotine is not generally safe to use in pregnancy and can harm fetal development. The U.S. Public Health Service Clinical Practice Guideline makes clear that smoking exposes the fetus to "numerous other chemicals that are injurious to the woman and fetus" (p. 172, 2008). However, many experts agree that nicotine replacement medications should be considered during pregnancy if smoking cessation cannot be achieved without the medications. The same treatment principle holds true for patients with CVD.

- Nicotine use causes neuroadaptive changes in the adult brain that may contribute to the risk of developing dependence, but many of these changes are largely reversible and not known to be harmful. Some animal model studies show that nicotine exposure in adolescence can induce neuroadaptive changes that persist into the adulthood of the animal. While animal models suggest possible concerns for humans, more research is required to demonstrate if, and at what dosage and duration of exposure, nicotine might have possible adverse effects during adolescent and young adult brain development.

- Nicotine is used for a number of reasons. In human studies, acute administration of nicotine can have positive effects on cognitive processes, such as improving attention, fine motor coordination, concentration, memory, speed of information processing, and alleviation of boredom or drowsiness. Some nicotine users benefit from self-medication effects for alleviation of stress, anxiety, depression, and other mental health and medical conditions, including schizophrenia and Parkinson's Disease. Nicotine also reverses cognitive deficits caused by withdrawal. It is not clear if chronic use of nicotine enhances cognitive function.

- Nicotine use is reinforcing and leads to varying degrees of dependence. The likelihood of dependence varies with the rate, amount, and pattern of nicotine delivery, as well as biopsychosocial differences between the users. When nicotine is delivered in the smoke from combusting tobacco, it is absorbed most efficiently and rapidly into the body and produces the highest level of appeal, addiction, and toxicity to human users.

- There are large differences in the response and degree of dependence to nicotine within a population. At the two extremes, some may find nicotine has little effect or may even be aversive, while others find it very appealing and become heavily dependent. The vast majority of effects are distributed between these two extremes. Some subgroups, such as those with an underlying vulnerability to mental health or medical conditions, may benefit, more or less, from the use of nicotine, when compared with the general population.

BACKGROUND

Cigarette smoking is the dominant mode of tobacco and nicotine use, and the death and disease from tobacco is overwhelmingly caused by cigarettes and other burned tobacco products (p. 7) (U.S. Department of Health and Human Services, 2014). Smoking involves the inhalation of combustion products, which are primarily responsible for its toxic effects. In the U.S., smoking kills 520,000 people per year (U.S. Department of Health and Human Services, 2010, 2014). Smoking prevalence has declined, largely due to decades of tobacco-control activities (e.g., smoke-free policies, age restrictions, taxation, counter-tobacco media and communications, provision of cessation services, litigation), but about 40 million smokers remain. Therefore, the 2014 Surgeon General's Report bluntly concluded: "The current rate of progress in tobacco control is not fast enough. More needs to be done." (p. 875) (U.S. Department of Health and Human Services, 2014). How can we, therefore, accelerate the decline in smoking combustible tobacco products, in particular cigarettes, which would improve the health of as many people as possible, as rapidly as possible (Frieden, 2015)? One approach to speeding the decline of smoking would be to encourage the use of Alternative Nicotine Delivery Systems (ANDS), which have gained traction in the marketplace but have just recently been placed into the U.S. Food and Drug Administration's (FDA) tobacco product regulatory framework (U.S. Food and Drug Administration, 2016a, 2016b). This will, however, require careful re-examination of the role that nicotine plays in sustaining toxic tobacco use and the role that it might play in reducing tobacco use if it can be delivered safely and separately from tobacco's toxic byproducts.

Clearly, our nation needs to maintain and strengthen current tobacco control efforts, including youth prevention, cessation interventions, and other best practices described by the CDC (Centers for Disease Control and Prevention, 2014). Other complementary tobacco control approaches, however, are now available. The Family Smoking Prevention and Tobacco Control Act (U.S. Food and Drug Administration, 2009), for the first time, gives the FDA authority to regulate the manufacture, distribution, and marketing of tobacco products, including non-therapeutic consumer nicotine products. The FDA has the power to regulate tobacco product ingredients, including reducing nicotine content (but not to zero). Reducing nicotine content of cigarettes, for example, has the potential to render them less addictive. This could prevent ever-users (e.g., youth) from progressing to persistent use (Hatsukami et al., 2010). It might also make it easier for current smokers to quit (Donny et al., 2015). The Tobacco Control Act also endorsed the principle of tobacco harm reduction through its requirement that the FDA provide a pathway for Modified Risk Tobacco Products (MRTPs) and encouragement of more flexible labeling for nicotine replacement medications. The Tobacco Control Act specifies that the FDA can evaluate and approve MRTPs that qualify as offering reduced exposure to toxic constituents.

By allowing smokers to transition to products that deliver nicotine without smoke's toxicity, MRTPs could reduce the population's exposure to the toxic combustion products inherent in smoking. The concept that "people smoke for nicotine but they die from the tar" has been widely accepted for decades (Russell, 1976), and was recently reinforced by the 2014 Surgeon General's Report, which noted the potential for noncombustible nicotine-delivery products to reduce morbidity and mortality (U.S. Department of Health and Human Services, 2014). Mitch Zeller, the current director of the FDA's Center for Tobacco Products, recognizing that "certain products pose more individual risk than others," has noted that the FDA's

regulatory authority has provided an "opportunity to create a comprehensive agency-wide nicotine regulatory policy." (U.S. Food and Drug Administration, 2013a). Reduction of nicotine levels in combustible tobacco products and introduction of MRTPs may have complementary effects on population harms. Reduced nicotine in combustible tobacco may drive smokers away from current toxic products so that they quit, and for those who cannot or will not quit, MRTPs can offer a safer alternative. However, the safety of MRTPs must be evaluated in light of what we know, and need to know, about the harms of nicotine.

As discussed below, a considerable body of evidence indicates that relatively little of the harm of smoking is due to nicotine, which, with some exceptions, is acceptably safe at dose levels within the range of those typically absorbed by tobacco users, and which may be obtained by over-the-counter nicotine replacement medications. A major strategy for potentially reducing population harm is to allow nicotine products (ANDS) that would substitute for smoking, enabling smokers to get nicotine without exposing them to deadly combustion products. This line of thinking raises the possibility that nicotine is not synonymous with tobacco and with tobacco-related harms, and that if nicotine could be decoupled from either tobacco or from the inhaled smoke of combusted tobacco, it could be freed from either all, or many, of tobacco's harmful effects. This, in fact, happened with the development of non-combustible tobacco products like low-nitrosamine Swedish snus and with tobacco-free nicotine replacement therapeutic products (NRTs) which are approved by the FDA and widely used as an aid to quitting smoking.

Conceptually, supporting the introduction and use of less harmful forms of nicotine for those who cannot, or do not wish to, completely abstain is not unlike advocating harm reduction in other areas involving undesirable or risky behaviors. For those who DO engage in the risky behaviors, harm reduction encourages consideration of approaches to reduce a risky behavior's most harmful consequences (e.g., using condoms when engaging in sex if one is unwilling to abstain; wearing helmets to reduce injury when riding a motorcycle or playing competitive football; needle exchange programs for injection-drug users). Harm reduction acknowledges that some behaviors deemed undesirable or enjoyable cannot be completely eliminated. It opens discussion of options to improve consumer-informed decision making by ensuring that accurate information is available about the consequences of risky behaviors and what actions can be taken to reduce the risks. Harm reduction approaches have often been resisted because of initial fears of unintended consequences, but then when carefully implemented, have dramatically contributed to reduced harm at the individual and population levels ("Harm reduction: An approach to reducing risky health behaviours in adolescents," 2008; U.S. Department of Health and Human Services, 2010; Vlahov, Robertson, & Strathdee, 2010; World Health Organization, 2016).

The questions raised here have widespread implications for how society more generally might re-think nicotine use in order to sharpen and inform approaches to tobacco control policy and public health practice, as well as for consumer education, advocacy, science, and regulation. These considerations raise the need for a reexamination of fundamental questions concerning nicotine itself: (1) When nicotine is delivered to the body via means other than inhalation of combusted tobacco smoke, to what extent does it remain biologically harmful; (2) How worrisome is its degree of addiction liability, and what are its behavioral or social consequences to individuals and society; and (3) From a public health

perspective, if nicotine can be used in substantially less harmful forms, would its widespread use have a positive or negative population impact on death and disease?

We begin by reviewing evidence to establish the effects of nicotine exposure, per se, on disease risk and addiction. For example, FDA-approved nicotine medications have been available at retail without a prescription for decades, and studies have documented their effects (U.S. Food and Drug Administration, 2013b). Some tobacco leaf oral products (Swedish snus) that are manufactured to reduce levels of nitrosamines are much less harmful than combustible tobacco, even though they deliver nicotine systemically (Royal College of Physicians, 2007; Royal College of Physicians, 2016; U.S. Food and Drug Administration, 2015). Devices that deliver aerosolized nicotine (vapor products) along with a few other ingredients (propylene glycol, vegetable glycerin, flavors) have recently become popular with consumers and pose much lower risks than nicotine delivered in inhaled smoke from combusted tobacco (McNeill et al., 2015).

As summarized below, the evidence indicates that nicotine itself, while not completely benign, carries substantially lower risks than smoking. This document briefly reviews the major findings from the evidence regarding the effects of nicotine itself, when divorced from smoking. It is meant to be a summary, rather than a detailed or comprehensive review, drawing heavily on existing authoritative reviews, such as the reports of the U.S. Surgeon General and the Royal College of Physicians (RCP) (Royal College of Physicians, 2016).

CANCER

Smoking is a major cause of cancer, and accounts for one out of every three cancer deaths in the U.S., and nine out of ten deaths from lung cancer (U.S. Department of Health and Human Services, 2014). Authoritative reviews of carcinogens in tobacco and tobacco smoke have not listed nicotine among the carcinogens. This includes recent reviews of evidence concerning carcinogens in smokeless tobacco by the WHO's International Agency on Research on Cancer (International Agency for Research on Cancer, 2007) and other tobacco products (International Agency for Research on Cancer, 2012), and the 2010 Surgeon General's Report (U.S. Department of Health and Human Services, 2010). In vitro and animal studies have raised concerns about whether nicotine might have cancer-promoting effects (Grando, 2014). Epidemiological data do not show that nicotine itself plays a role in promoting cancer, and multiple reviews have concluded that nicotine itself is not a carcinogen (Murray, Connett, & Zapawa, 2009; Shields, 2011).

IN VITRO STUDIES

In vitro studies demonstrate that nicotine is highly bioactive, and additional experimental studies are warranted in animals and humans. If nicotine in some way promotes cancer, the in vitro studies provide clues about how this happens, for example, by increasing cell proliferation or motility, impeding apoptosis and promoting angiogenesis (Dasgupta et al., 2006; Heeschen et al., 2001). However, the relevance of these studies to people is uncertain, and human epidemiological data so far do not suggest that nicotine causes cancer.

EXPERIMENTAL ANIMAL STUDIES

While there are some studies indicating that nicotine may promote cancers following exposure to tobacco carcinogens, more recent, better-designed studies do not. All of these studies, importantly, are experimental animal models of unclear relevance for extrapolation to humans, and serve only to indicate concerns and proof for a causal relationship for nicotine to cancer in humans. Nicotine does not act as a complete carcinogen on its own (U.S. Department of Health and Human Services, 2014).

HUMAN EPIDEMIOLOGY STUDIES

While in vitro and some experimental animal studies have raised concerns about the role of nicotine in cancer, these theoretical considerations are not corroborated by human epidemiological data. The RCP concluded that "there is no evidence that this theoretical risk, derived from animal studies, translates into an increase in cancer risk or tumor growth in humans." (p. 1260) (Royal College of Physicians, 2007). The potential effects of nicotine on cancer have been examined both in long-term users of nicotine medications (Murray et al., 2009), and in very long-term users of smokeless tobacco (who, of course, are also exposed to tobacco-specific carcinogens) (Lee, 2011, 2013; Lee & Hamling, 2009). These data sources suggest that nicotine itself does not cause or promote cancer, or if it does, its contribution is small.

There are no long-term studies that directly address the long-term use of nicotine, per se, on cancer risk, e.g., large population based studies with sufficient follow-up time to address the latency similar to that for smoking and lung cancer. Some short-term data are available from the Lung Health Study, which was a large prospective clinical trial in which smokers were urged to use nicotine gum for long periods. A 7.5-year follow-up of long-term users led to the conclusion that "nicotine replacement therapy does not cause cancer" (p. 1079) (Murray et al., 2009), although a longer follow-up period would be required to definitively confirm this statement. These results, in part, led to the FDA revising its guidance on use of NRTs to allow for longer-term use beyond that indicated on the product label (U.S. Food and Drug Administration, 2013b).

Risk can also be inferred from long-term cohort studies of smokeless tobacco users, as these indicate no increased cancer risks except for local effects in the oral cavity for conventional smokeless tobacco products and possibly for pancreatic cancer (Burkey et al., 2014; Rodu & Jansson, 2004). The reason for the latter is unclear, but not ascribed to nicotine. The best evidence comes from cohort studies in Sweden, where a low-nitrosamine snus product has been heavily used for more than 50 years. Several cohort studies have not identified increased cancer risks, except for in the pancreas (Lee, 2013). This is particularly reassuring because if nicotine promoted cancer generally, these studies would have identified oral cavity cancer risk. In the U.S. and elsewhere, use of higher-nitrosamine, oral smokeless tobacco products increased risk of oral cancer (U.S. Department of Health and Human Services, 1986), which is not surprising, given the exposure of oral tissues to the full range of tobacco carcinogens, including N-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK) (Rostron, Chang, van Bemmel, Xia, & Blount, 2015). Analyses of snus, which is lower in tobacco-specific nitrosamines, generally find no increased risk of oral cancer (Royal College of Physicians, 2007; Royal College of Physicians, 2016; U.S. Food and Drug Administration, 2015).
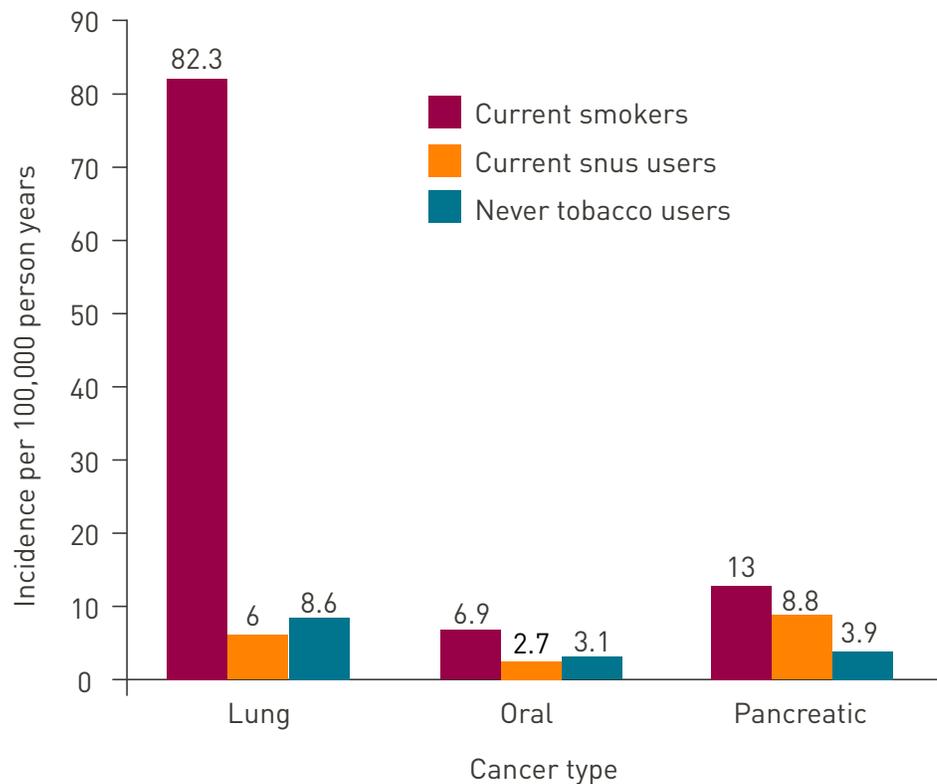
FIGURE 1. Incidence rate for three types of cancer (by 2004) as a function of tobacco use status in male Swedish construction workers at recruitment (1978-92). Adapted from data in Luo et al.

To consider the role of nicotine in cancers attributed to smokeless tobacco, one must consider that users of snus have nicotine circulating throughout their body at levels similar to those seen in smokers. Thus, if nicotine itself caused or promoted cancer, including lung cancer, one would expect snus use to be associated with increased risk of lung cancer and many other cancers. This is not seen in users of smokeless tobacco (Royal College of Physicians, 2007) who generally have much lower rates of all cancers than smokers do (Lee & Hamling, 2009). Indeed, Sweden, which has seen a migration of its male population from smoking to use of snus, has reported a dramatic decline in lung cancer, and now has the lowest rates among men in high-income countries (Organization for Economic Cooperation and Development, 2011). Based on these and other findings, the FDA recently issued a marketing authorization letter for eight Swedish snus products noting that there is sufficient evidence to demonstrate the product is appropriate for the protection of public health (U.S. Food and Drug Administration, 2015).

Overall, the data show that nicotine itself—to the extent that its effects can be separated from exposure to tobacco—does not measurably cause or promote cancer in humans. While there is some controversy regarding nicotine's role in promoting tumor growth once cancer has already occurred, this hypothesis has not been substantiated in human studies. The long-term data on Swedish snus (low nitrosamine) tobacco and on NRT use in former smokers is reassuring in that these forms of nicotine use do not appear to lead to excess cancer rates (see FIGURE 1). The role of nicotine as a cancer promoter is likely to be very small if there is any risk to humans at all.

CARDIOVASCULAR DISEASE (CVD)

Smoking is a leading cause of CVD, increasing the risk of heart attacks and stroke as much as five-fold. The 2014 U.S. Surgeon General's report concluded that combustion compounds in tobacco smoke, such as oxidizing chemicals, volatile organic chemicals, particulate and carbon monoxides, rather than nicotine, are the primary contributors to increased cardiovascular risk (U.S. Department of Health and Human Services, 2014).

The cardiovascular effects of nicotine need to be carefully considered, however, as nicotine releases stress hormones (e.g., catecholamines), and has potential hemodynamic effects, arrhythmogenic effects, adverse effects on lipids, and endothelial dysfunction (Morris et al., 2015; U.S. Department of Health and Human Services, 2010). Evidence from in vitro studies and animal models suggests that nicotine may inhibit apoptosis and enhance angiogenesis, and these effects raise some concern about the role of nicotine in promoting the acceleration of atherosclerotic disease (Heeschen et al., 2001; Morris et al., 2015; Nordskog, Blixt, Morgan, Fields, & Hellmann, 2003). Nicotine, per se, may contribute to CVD, but its impact is much less compared to tobacco smoke (Benowitz & Gourlay, 1997). Generally, NRT can be safely used by people with diabetes or high blood pressure and does not increase the risk of heart attacks (Patnode et al., 2015).

HUMAN LABORATORY STUDIES

Nicotine causes catecholamine release and cardiac acceleration, while also causing vasoconstriction and raising blood pressure, suggesting that it could play a role in CVD. However, administration of even very high doses of medicinal nicotine in smokers had little effect on cardiovascular function (Zevin, Jacob, & Benowitz, 1998). In one study, NRT use was associated with improved coronary perfusion in individuals with heart disease because it reduced cigarette smoking (Mahmarian et al., 1997).

HUMAN EPIDEMIOLOGY STUDIES

Data from the Lung Health Study on the natural history and safety of prolonged use of medicinal nicotine found no relationship between use of nicotine and cardiovascular disease (Murray et al., 1996). Some epidemiological studies of medicinal nicotine and smokeless tobacco use have suggested that such nicotine exposures may be associated with a modest risk of cardiovascular disease (Hatsukami, 2016). Even when an increased risk is reported, the risk is much lower than that associated with smoking (Benowitz & Gourlay, 1997). However, these studies often confound the effects of these non-combustible products with the effects of smoking. The RCP report (2007) notes that of six studies of risks of myocardial infarction in long-term Swedish snus users, only one found an increased risk, and five did not detect any increased risk over never-tobacco users, despite the fact that these snus users were typically absorbing high doses of nicotine over decades (Royal College of Physicians, 2007). In conclusion, nicotine, per se, may contribute to CVD, but its impact is much less than in tobacco smoke.

ACUTE TOXICITY

At high doses, nicotine can cause acute toxicity, particularly in non-tolerant individuals. At the lower doses typically seen in cigarettes and nicotine medications, nicotine can cause temporary discomfort (e.g., nausea and vomiting) in non-tolerant individuals, but is not associated with clinically significant toxicity (Niaura, 2013). This has allowed FDA-approved sale of nicotine products over-the-counter without any significant number of adverse effects. At higher doses, nicotine can induce toxicity. This was first observed among tobacco agricultural workers, who sometimes presented with 'green tobacco sickness' due to absorbing nicotine by handling wet tobacco leaves. Even at high doses, these syndromes generally resolve safely without lasting effects (McBride, Altman, Klein, & White, 1998).

The advent of e-cigarette "tank" systems and the availability of bottles of "e-liquids" containing nicotine have increased the risk of toxic exposures. Recent reports of young children who have ingested nicotine e-liquids confirm that large nicotine doses in non-tolerant individuals can be toxic. Most reported cases resolved without lasting effects (Alaska Department of Health and Social Services, 2015), but there have been fatalities (ABC News, 2014). Ingestion of very high doses (at least 500 mg (Mayer, 2014)) by adults can be life-threatening. Thus, the acute toxicity of nicotine depends heavily on the dose.

There has been extensive evaluation of nicotine safety and toxicity (U.S. Department of Health and Human Services, 1988, 2010; Zevin et al., 1998). Thousands of reports of tobacco and nicotine exposures are submitted to the Poison Control Centers each year, but deaths by those exposed at any age are rare, generally none or one per year (Mowry, Spyker, Brooks, McMillan, & Schauben, 2015). With the increasing availability of nicotine liquids ("e-liquid") for filling ENDS, exposures in children have risen in recent years and presently represent approximately 25 percent of all nicotine poisonings, with one infant death attributed to an e-liquid (Connolly et al., 2010; Mowry, Spyker, Cantilena, McMillan, & Ford, 2014; Novotny et al., 2011).

NEURODEVELOPMENTAL EFFECTS FROM NICOTINE EXPOSURE

Nicotine acts on the central nervous system (CNS) by mimicking the effects of the neurotransmitter acetylcholine. In animal studies, the acute reinforcing effects of nicotine appear to be dependent on dopamine release in the brain. However, nicotine induced dopamine release is markedly curtailed, or even disappears, when animals are chronically exposed to the drug (p. 233) (Royal College of Physicians, 2007). As with any CNS agonist, exposure to nicotine invokes adaptive responses (neuroadaptations), which may be reflected in changes in the configuration of neurotransmitter systems. Exposure in utero, during critical periods of fetal development, may affect the function of certain neural systems in the long run (Ross, Graham, Money, & Stanwood, 2015). Recent science suggests that some brain development continues through adolescence, and findings in rodents that nicotine exposure during adolescence affects these developmental processes have raised concerns about adverse effects on adolescent neurodevelopment (Slotkin et al.,

2015; Smith, McDonald, Bergstrom, Ehlinger, & Brielmaier, 2015). The functional implications of the experimental rodent models for humans are not currently clear, particularly as human studies are also suggestive of some cognitive and affective benefits.

Nicotine use in adulthood is associated with what appear to be reversible neuroadaptations, characteristic of drug exposures. Sophisticated evaluations of nicotine effects on brain function and treatment of cognitive disorders began in the 1990s and have revealed much about the extent and mechanisms of nicotine's potential beneficial behavioral, psychological and cognitive benefits (Balfour & Fagerstrom, 1996; Heishman, Kleykamp, & Singleton, 2010; U.S. Department of Health and Human Services, 2010). There is also evidence that certain subgroups of individuals that are experiencing cognitive decrements (e.g., individuals diagnosed with ADHD, older adults with mild cognitive impairment) might be most sensitive to nicotine-related cognitive enhancement (Besson & Forget, 2016).

ANIMAL STUDIES

Animal studies demonstrate that exposure to nicotine in utero – divorced from the other exposures that characterize smoking – leads to CNS changes (i.e., delayed maturation) that are associated with poor CNS control of respiration, and impaired response to oxygen deprivation. This may contribute to increased incidence of Sudden Infant Death Syndrome (SIDS) in human babies born to mothers who smoked during pregnancy (U.S. Department of Health and Human Services, 2014).

HUMAN EPIDEMIOLOGY STUDIES

Women who continue to smoke during pregnancy expose the fetal brain to nicotine (and thousands of other chemicals) throughout gestation, while also reducing the oxygen available to the fetus (carbon monoxide reduces the blood's capacity to carry oxygen). Children born to mothers who smoked during pregnancy show subtle developmental deficits (Abbott & Winzer-Serhan, 2012). They are more susceptible to Sudden Infant Death Syndrome (SIDS), which is thought to be due to poor regulation of respiration by CNS mechanisms. Such children also suffer from behavioral dysregulation later in life (Cornelius & Day, 2009; Zhu et al., 2014), although some of this may be due to genetic and social transmission, and potential effects of sidestream smoke exposure after birth. Initiating smoking early in adolescence is associated with more severe dependence later in life (Darville & Hahn, 2014).

REPRODUCTIVE EFFECTS

Smoking is associated with reduced fertility and with adverse outcomes of pregnancy. Women who smoke during pregnancy are more likely to deliver prematurely, to have low-birthweight babies who suffer increased perinatal mortality (U.S. Department of Health and Human Services, 2014). Although smoking, per se, contributes to these risks (for example, carbon monoxide reduces the blood's ability to carry oxygen to the fetus), some of these effects may be due to nicotine.

HUMAN EPIDEMIOLOGY STUDIES

Limited data on women who use NRT during pregnancy to quit or reduce smoking have generally shown few adverse effects. However, women who use smokeless tobacco show, at a reduced level, some of the effects seen in smokers. For example, mean birth weight is reduced by 39g in snus users compared to 190g in smokers (England et al., 2003). Pregnancies among users of smokeless tobacco are more likely to result in stillbirths compared to non-tobacco exposed pregnancies, and smokeless tobacco is associated with a greater incidence of pre-eclampsia (England et al., 2003; Wikstrom, Cnattingius, & Stephansson, 2010; Wikstrom, Stephansson, & Cnattingius, 2010). The data suggest that nicotine is not safe to use in pregnancy, although its effects are less than those of smoking. Thus, nicotine replacement is not contraindicated during pregnancy and, in fact, is often recommended during pregnancy if smoking cessation is not achieved without NRT. However, pregnant women are generally counselled to consult a pharmacist or doctor before using NRT.

There is also evidence that nicotine may affect the neural development of the fetus; these effects are discussed under 'neurodevelopmental effects.'

HEALTH ISSUES RELATED TO DELIVERY OF NICOTINE IN LIQUID AND AEROSOL FORMS

Some additional concerns arise when nicotine is delivered via alternative media (e.g., liquid solutions, aerosols, dissolvable oral compounds) versus via smoking combustible tobacco. For example, when nicotine is delivered in aerosolized form in electronic nicotine delivery devices, it is typically dissolved in a mixture of propylene glycol, vegetable glycerin, and flavorings. It is unclear whether these chemical compounds pose significant health risks when inhaled, especially with heavy use over long periods of time. Risks could result because of direct exposure to these compounds, exposure to contaminants, or exposure to chemical byproducts related to heating the liquid (e.g., acrolein and aldehydes, metals and fine particulate matter). The evidence available so far suggests that levels of biomarkers of exposure to toxicants related to use of these devices is significantly lower than for smoked cigarettes (Callahan-Lyon, 2014; Goniewicz et al., 2016).

Aerosolized nicotine delivery devices also typically contain flavors, and flavored product use is common (Corey, Ambrose, Apelberg, & King, 2015). Little is known, however, about how flavors might interact with nicotine to reinforce continued use. Flavors can be appealing on their own; they may also alter the taste and sensory characteristics of nicotine, making nicotine easier to ingest and/or more enjoyable. This applies to inhaled and oral nicotine delivery products (e.g., tablets, lozenges, gums, films).

It is not currently known whether inhalation of aerosolized nicotine produces unique and persistent health risks compared to nicotine that is delivered by other routes of administration (oral, mucous membrane, skin).

NICOTINE DEPENDENCE / ADDICTION

The nicotine molecule resembles acetylcholine, a native neurotransmitter chemical active in the brain. Nicotine activates cholinergic systems, and chronic administration leads to development of a new homeostatic equilibrium in the brain, which is disturbed when nicotine is withdrawn, leading to the emergence of withdrawal symptoms that motivate continued nicotine use (U.S. Department of Health and Human Services, 2010). Nicotine also has direct, positive effects that help sustain its use. The general pharmacological profile of nicotine is more stimulant than sedative. Thus, it is classified along with prototypic stimulants such amphetamine, cocaine, or methylphenidate, either pharmacologically or by diagnostic frameworks for assessing dependence or substance use disorder (e.g., Goodman and Gilman; APA DSM, WHO ICD10). It is not considered a hallucinogenic chemical. Intoxication can occur during acute nicotine overdose, but this is sufficiently rare that the American Psychological Association (APA) Diagnostic Statistical Manual (DSM) IV and V do not list intoxication among nicotine/tobacco use disorders.

Smoking can be highly addictive for some smokers, and its addictive potential is attributed primarily to nicotine (Benowitz, 2010; U.S. Department of Health and Human Services, 1988). However, as with many drugs, the dependence potential of nicotine varies considerably according to how rapidly it is delivered into the blood stream and to the brain. Thus, degree of dependence varies with the delivery system. For example, nicotine patches show no abuse potential (Pickworth, Bunker, & Henningfield, 1994), and addiction to NRT is rare (Fagerstrom & Eissenberg, 2012). The FDA has also recently acknowledged that "although any nicotine-containing product is potentially addictive, decades of research and use have shown that NRT products sold over-the-counter do not appear to have significant potential for abuse or dependence" (U.S. Food and Drug Administration, 2013b).

Susceptibility to nicotine dependence is not universal, and also varies with characteristics of the individual (e.g. genetic, epigenetic, psychosocial and/or cultural). Only a minority of individuals who are initially exposed to the most addictive form of nicotine (nicotine inhaled in tobacco smoke) actually progress to further use or to lifetime regular use, and only some portion of those regular smokers become dependent to varying degrees (about one in five past-year adult smokers are dependent, according to formal psychiatric diagnostic criteria) (American Psychiatric Association, 2013; Chou et al., 2016). In 1977, when there was widespread exposure to nicotine from smoking among adolescents, 75.7 percent of 12th graders had ever smoked, but only 38.8 percent smoked in the prior 30 days; and 28.8 percent smoked daily and 19.4 percent smoked a half a pack per day. In 2014 these numbers were 34.4 percent, 13.6 percent, 6.7 percent, and 2.6 percent (Kozlowski & Giovino, 2014; Warner, 2015) indicating large drops in intensity of use.

Individual characteristics that influence susceptibility to nicotine dependence include one's genetic profile, mental health, personality, and social characteristics. Many of these susceptibility factors are common across other risky behaviors, including use of other drugs. For example, studies show that the majority of adolescents trying a variety of smoking and smokeless tobacco and alternative nicotine delivery systems (ANDS—e.g., vaping of electronic or e-cigarettes) are also experimenting with alcohol and marijuana and are engaging in other risk-taking and sensation-seeking activities

(Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). Consistent with a "common liability" model, these risk-taking susceptibility factors and risky behaviors tend to travel together (Vanyukov et al., 2012; Vanyukov et al., 2003). Therefore, it has proven difficult, if not impossible, to demonstrate that there are unique factors that predispose toward nicotine dependence, or that nicotine use itself is an isolated cause of other risky behaviors.

IN VITRO STUDIES

In vitro studies demonstrate that nicotine effectively functions as a cholinergic agonist (i.e., it directly stimulates acetycholinergic receptors that occur throughout the brain and body). For example, nicotine stimulates acetylcholine receptors that cause contraction of skeletal muscles and release of catecholamines (stress hormones) from the adrenal gland (Nees, 2015).

ANIMAL STUDIES

The potential for dependence on nicotine has been demonstrated in animal studies showing that rodents will self-administer nicotine (Henningfield & Goldberg, 1983b; Shoaib, Schindler, & Goldberg, 1997), although they do so under a more narrow range of conditions than drugs such as cocaine and morphine (Goldberg & Spealman, 1982; Risner & Goldberg, 1983). Nicotine-dependent animals demonstrate withdrawal symptoms when nicotine is withdrawn. Neurobiological studies demonstrate that chronic nicotine use leads to proliferation of nicotine receptors in the brain; these effects are reversible when nicotine is discontinued.

HUMAN LABORATORY STUDIES

Laboratory studies demonstrate that nicotine is reinforcing to smokers (Henningfield & Goldberg, 1983a; Henningfield, Miyasato, & Jasinski, 1983), show abuse liability among smokers (Henningfield, Miyasato, & Jasinski, 1985; U.S. Department of Health and Human Services, 1988), and show that stimuli associated with smoking provoke craving (Conklin & Tiffany, 2001; Droungas, Ehrman, Childress, & O'Brien, 1995). Nicotine also appears to have some beneficial effects, particularly on mood and cognitive function (Robinson & Pritchard, 1992; US DHHS, 1988), which may also help motivate smoking. Human experiments suggest, consistent with animal data, that sensory cues and stimuli associated with smoking also play a major role in maintaining use behavior (Niaura, Abrams, Demuth, Pinto, & Monti, 1989; Shiffman et al., 2014).

HUMAN EPIDEMIOLOGY STUDIES

A robust body of evidence shows that nicotine effects and nicotine dependence are major drivers of smoking (Stolerman, 1999). Perhaps the most important manifestation of nicotine dependence is the difficulty smokers have stopping smoking (U.S. Department of Health and Human Services, 1988). The degree of nicotine dependence varies across smokers (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Killen, Fortmann, Kraemer, Varady, & Newman, 1992), but it is thought that a mix of direct reinforcing effects and dependence jointly motivate smoking, with the balance of the two varying across the population (Baker, Brandon, & Chassin, 2004; Stolerman, 1991, 1999). Different tobacco and nicotine products appear to induce different degrees of dependence, with NRT having very little dependence potential and cigarette smoking having the highest potential (Fant, Buchhalter, Buchman, & Henningfield, 2009; West et al., 2000). It is not yet known what degree of dependence might be associated with newer alternative nicotine-delivery systems (ANDS), partly because the products are evolving in their ability to deliver nicotine effectively. Some degree of effective nicotine delivery and reinforcement may be necessary if smokers are to switch from smoking cigarettes to using ANDS.

SYNTHESIS AND PUBLIC HEALTH IMPLICATIONS

Based on the evidence summarized above, we suggest the following: (1) Inhaled smoke from the combustible cigarette remains the single biggest threat to public health; it is widely used, highly addictive, and extremely toxic. (2) There is a continuum of harm among combustible and noncombustible, nicotine-containing products. (3) Good public health policy must recognize this continuum and leverage this knowledge to move continuing smokers, as rapidly as possible, toward less harmful nicotine delivery products while (4) simultaneously preventing the adoption of all nicotine containing or tobacco products among youth.

We offer the following framework to help organize thinking about nicotine and its individual and population effects. In considering how to re-think nicotine and its use with the aim of maximizing population benefit and minimizing population harm, one must consider three dimensions of nicotine products: (1) harmfulness, (2) appeal, and (3) degree of addiction potential (see FIGURE 2).

FIGURE 2

COMBUSTED TOBACCO: CIGARETTES, CIGARS, PIPE, HOOKAH...

Addiction Liability — Nicotine

NO USE AT ALL

Toxicity — Harmfulness

Appeal — Satisfaction

Nicotine products differ substantially in their toxicity and potential for medical/biological harm. Inhalation of smoke from combustible products represents the most harmful use. Use of medicinal nicotine products is least harmful, and other products (e.g., smokeless tobacco, e-cigarettes) fall somewhere in between. Nicotine or tobacco products also differ in their appeal, which contributes to the likelihood that the product will be adopted and its use sustained. Appeal is a complex function of attractiveness, sensory characteristics (including nicotine), cost, accessibility, and marketing practices. A product with minimal appeal will not be adopted or used extensively. Ideally, to displace smoking, less harmful products would have to be as, or more, appealing. Addiction liability refers to the potential for the product to induce addiction, which is a function both of its pharmacological and its chemosensory properties. Cigarettes are the most appealing, most addictive, and most toxic of all nicotine delivery products, and thus dominate population use and impose massive population harms. They are the perfect storm, and therefore are located at the highest level on all three dimensions of FIGURE 2.

One challenge is to identify products that move the largest proportion of the population that uses nicotine to a place along these three dimensions that minimizes net harm. Regulations and policy initiatives should be aligned so that less harmful products are able to compete and replace smoking as the way to obtain and use nicotine. Different tobacco and nicotine products can be ordered in this 3-D space for determining total population impact (for users and non-users, especially youth). Products can be compared to one another, and classes of products (e.g., combustible vs. noncombustible; high vs. low nitrosamine; fast vs. slow delivery; flavored vs. nonflavored) can be evaluated for comparative safety.

POLICY IMPLICATIONS

Assuming the framework described above reasonably represents the nicotine and tobacco product space, what are the policy implications of adopting such a model?

For non-users (especially youth), it is clear that prevention is warranted to keep individuals from entering the nicotine and tobacco product space altogether.

For early-stage users (experimenters) and those who have not been using nicotine and tobacco products for very long, the overall goal would still be to move to no use at all—what we refer to as prevention of escalation. Most late adolescent and young adult tobacco/nicotine users would fall into this category.

For tobacco/nicotine users who are further along the lifetime tobacco use trajectory and/or who are already dependent, one goal would still be to move to no use at all, but here is where other options can be considered. These options should be made available to tobacco users who are unable or unwilling to quit and would be directed by the goal of moving users away from the most addictive, appealing and toxic combustible products to less harmful alternatives—ideally FDA-approved MRTPs. By moving to MRTPs, the goal is to reduce harm of prolonged tobacco use, and make it easier for MRTP users to quit nicotine use altogether. This should be easier to do if the MRTPs are sufficiently appealing compared to existing combustible products. MRTPs, however, cannot be so unappealing such that very few people would ever use them.

The challenge for policy makers and regulators is to imagine how policy levers, regulations, and other tobacco control activities can be used in tandem to optimize population health: Preventing youth initiation and escalation, while helping 40 million smokers move to less harmful products and making it easier for them to quit and stay quit.

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