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The Reinforcement Threshold for Nicotine as a Target for Tobacco Control

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Abstract

BACKGROUND—Cigarette smoking represents an enormous public health problem worldwide that leads to over 5 million deaths per year. The gradual reduction of the nicotine content of cigarettes below the threshold that is required to develop addiction is one strategy that might substantially reduce the number of addicted smokers and prevent adolescents from becoming addicted to nicotine (Benowitz and Henningfield 1994). While the potential public health benefits of this approach are enormous, the guiding concepts and relevant empirical evidence needed to support the implementation of a nicotine reduction policy require a critical examination.

METHODS—The purpose of this paper is to briefly review the current concepts and research regarding nicotine reduction while also discussing the utility of the addictive threshold for nicotine in this approach. The accurate determination of the nicotine addiction threshold presents some conceptual challenges as there is a lack of consensus on how to best measure nicotine addiction. This difficulty can impede the progress for developing a science-based tobacco control policy. As an alternative, the nicotine reinforcement threshold is a relatively clear concept, and well-accepted methods and criteria are available to measure nicotine reinforcement.

RESULTS—However, there are many gaps in our current knowledge concerning the nicotine reinforcement threshold in humans. The threshold for nicotine reinforcement remains to be determined in controlled settings using different populations of current or potential tobacco users. In addition, the value of the nicotine reinforcement threshold in predicting tobacco use in real-world settings needs to be examined. The results of such studies will determine the potential utility of the estimated threshold for nicotine reinforcement in developing science-based tobacco control policies.

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Conflict of Interest Dr. Sofuoglu serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline. Dr. LeSage has no conflicts to declare.

Keywords

nicotine; tobacco addiction; reinforcement; adolescent smoking

1. Introduction

Tobacco addiction remains the leading cause of preventable death and is responsible for over five million premature deaths annually worldwide (CDC, 2008). Of the 45 million current smokers in the U.S., 70% desire to quit; however, only approximately 5% will succeed per year (CDC, 2010). The currently available first-line medications used to treat tobacco addiction can increase the success rate of quitting smoking by 2- to 3-fold (Fiore et al., 2008; Herman and Sofuoglu, 2010). A combination of behavioral treatments with medications can further increase these success rates (Fiore et al., 2008). However, even with the most effective treatments available, a vast majority of smokers fail to quit. Because the efficacy of current smoking cessation therapies is limited and because most smokers are not actively attempting to quit despite their desire to, a significant reduction in the mortality and morbidity attributed to smoking will require effective tobacco control policies.

Although many factors contribute to the initiation and maintenance of tobacco use, nicotine is considered to be the main addictive ingredient in tobacco (Corrigall 1991; Harvey et al., 2004; Rose and Corrigall, 1997). Therefore, the nicotine content of tobacco products may serve as a logical target in the development of effective tobacco-control policies. Accordingly, the United States Food and Drug Administration (FDA) formally began considering approaches to control the levels of nicotine in tobacco products in 1994 (Kessler, 1994). Benowitz and Henningfield (1994) introduced an influential proposal that same year for a nicotine reduction strategy to prevent the initiation of smoking in adolescents, increase smoking cessation in adults, and, thus, reduce the overall public health burden of tobacco addiction. The recent approval of the United States Family Smoking Prevention and Tobacco Control Act (FSPTCA) (Lundeen, 2009; Waxman, 2007) provides an important framework for the implementation of a nicotine reduction policy. The FSPTCA gives the FDA the authority to regulate, but not eliminate, the nicotine content of tobacco products. While nicotine reduction policies might ultimately have a significant impact on public health (Tengs et al., 2005), there are many factors to consider in determining the viability and desirability of such approaches. As discussed in previous reviews (Parascandola 2011; Warner 2002), “reduced harm” products may provide a false sense of safety to consumers, serve as a gateway to more harmful nicotine products, and ultimately prevent individuals from quitting smoking. For example, “low-nicotine yield” or “light” cigarettes were promoted by tobacco companies as “safer” products and such claims were accepted by both consumers and government agencies (Parascandola, 2011). It is important to distinguish low-nicotine-yield cigarettes from low-nicotine-content cigarettes. The low-nicotine-content or “denicotinized” cigarettes are produced by either extracting nicotine from tobacco or using genetically engineered tobacco that has very low nicotine levels. In contrast, the low-nicotine-yield cigarettes contain as much nicotine as regular cigarettes but yield reduced nicotine delivery primarily through addition of ventilation holes to the filter. The low-nicotine-yield of these cigarettes, as measured by machine-smoking, has little bearing on nicotine intake and grossly underestimates the amount of nicotine delivered to smokers. In reality, smokers can easily increase their nicotine and tar intake by covering the ventilation holes or taking longer, deeper, and more frequent puffs. (Pollay et al., 2002; Scherer, 1999).

On the other hand, other authors note that the current tobacco control policies, including the prevention of smoking in workplaces and public areas and the increases in prices and taxes,

have had limited effectiveness, leading to a small reduction in smoking rates of 1 % per year, at best, in countries where smoking is common (Britton et al., 2008). Based on these figures, some authors argue for more drastic policies to reduce rates of smoking (Britton et al., 2008; Gartner and Hall, 2010).

Many recent reviews have discussed the scientific and political issues related to a nicotine reduction approach (Hatsukami et al., 2007; 2010). In these proposed strategies for reducing the nicotine content in tobacco products, the putative target has been the nicotine addiction threshold. Accordingly, reducing the nicotine content in tobacco products below this threshold would presumably curtail the initiation and maintenance of tobacco addiction as well as alleviate the harm associated with tobacco use. However, previous reviews have not critically examined the concept of a nicotine addiction threshold as a measurable outcome in nicotine reduction strategies. Given the growing interest in developing new science-based regulations for tobacco, it may be judicious to scrutinize the concept of an addiction threshold for nicotine in relation to a nicotine reduction approach, which is the main purpose of our review. We also discuss the reinforcement threshold, a related concept, as an alternative to the addiction threshold. We start with a brief summary of the nicotine reduction proposal (Benowitz and Henningfield, 1994), followed by a comparison of addiction and reinforcement thresholds as behavioral targets for nicotine reduction approaches; finally, we conclude with suggestions for future research. Our review will not address issues related to the rationale and potential adverse consequences of nicotine reduction policies, which are extensively discussed in other recent reviews (Gartner and Hall, 2010; Hatsukami et al. 2007; 2010; Parascandola, 2011).

2. The Nicotine Reduction Proposal

This section briefly describes the aspects of nicotine pharmacokinetics and metabolism that provide the basis for the nicotine reduction proposal as devised by Benowitz and Henningfield. Smoking a cigarette delivers approximately 1 to 1.5 mg of nicotine (Benowitz and Jacob, 1984). Smokers maintain plasma nicotine levels ranging from 10 to 50 ng/ml (Benowitz et al., 2009). Between 70 to 80% of the absorbed nicotine is converted into cotinine in the liver, mainly through the action of the CYP2A6 enzyme (Benowitz et al., 2009). The longer half-life of cotinine (16 to 20 hours) relative to nicotine (2 hours) makes it a useful biomarker for nicotine exposure. Smokers have average blood cotinine levels of 150 to 300 ng/ml (Fidler et al., 2008). Benowitz and Henningfield asserted that nicotine intake associated with plasma cotinine levels (the primary metabolite of nicotine) of over 50 to 70 ng/ml sustain nicotine addiction (Benowitz and Henningfield, 1994). This estimate was based on data from a group of non-addicted smokers, known as light and intermittent smokers (LITS) or chippers (Coggins et al., 2009; Shiffman, 1989; Shiffman and Paty, 2006). Typically, chippers smoke fewer than 5 cigarettes per day, have plasma cotinine levels of 50 ng/ml or lower, and show few or no signs of nicotine addiction as currently defined the by DSM-IV criteria (Coggins et al., 2009). Based on the nicotine intake of chippers, this threshold has been shown to roughly correspond to a daily intake of 5 mg nicotine (approximately 5 cigarettes/day). Assuming the daily nicotine intake (5 mg/day) in this population represents a mean threshold for addiction, Benowitz and Henningfield (1994) estimated that 0.17 mg nicotine per cigarette would be below the nicotine threshold level required to produce addiction. Accordingly, they proposed that the nicotine content of cigarettes should be gradually lowered over a 10–15 year period to an amount below the threshold necessary for the development and maintenance of tobacco addiction. This proposal (Benowitz and Henningfield, 1994) and its subsequent appraisal by the American Medical Association Council on Scientific Affairs (Henningfield et al., 1998) have provided the foundation for the current nicotine reduction approaches being considered for tobacco

control policies (Hatsukami et al., 2010). Since the passage of the FSPTCA, these approaches have gained increasing attention.

3. Addiction vs. Reinforcement Threshold

The concept of a nicotine addiction threshold implies that there is a minimum amount of nicotine intake required to initiate or maintain addiction to nicotine. As mentioned above, 5 mg/day (associated with plasma cotinine levels of approximately 50 ng/ml/day) has been proposed as an estimate of the addiction threshold for nicotine (Benowitz and Henningfield, 1994). Although Benowitz and Henningfield provided a clear and logical basis for this estimate, it is nonetheless preliminary, as this estimate was based on observational data in experienced smokers rather than empirical studies that manipulated nicotine exposure. While the original concept of a nicotine threshold for addiction was highly influential in the field of tobacco control, its utility as a measurable target for nicotine reduction strategies must be critically examined.

3.1 Measurement of Addiction

One of the key issues in determining the addiction threshold of nicotine is the accurate diagnosis of nicotine addiction. Although tobacco chippers or LITS were first described more than 30 years ago (Shiffman, 1989; Shiffman et al., 1990), there is still no consensus on how to best distinguish between nondependent and dependent smokers (Coggins et al., 2009). The two most commonly used tools to assess the presence or severity of nicotine dependence are the Fagerström Test for Nicotine Dependence (FTND) scale and the DSM-IV criteria (Piper et al., 2006). The DSM-IV criteria provide a categorical diagnosis across all addictions. Whether these same criteria can be applied across all types of addiction is debatable. As indicated by Hughes, the current DSM-IV criteria might not be suitable for the diagnosis of nicotine dependence (Hughes 2006). Hughes proposed that only a few of the DSM-IV criteria are relevant to nicotine addiction, including withdrawal, difficulty in controlling use, and continued use despite harmful effects (Hughes, 2006). The FTND scale is more commonly used than DSM-IV criteria in clinical and research settings. The FTND scale uses a scoring system that ranges from 0 to 10, and scores of 5 or above are considered to indicate a medium or high level of nicotine dependence (Heatherton et al., 1991). Both the DSM-IV criteria and FTND scale have been criticized for their psychometric properties, including their validity and factor structure (Baker et al., 2009). Moreover, the DSM-IV criteria and FTND scale do not correlate well with each other (Hendricks et al., 2008; Hughes et al., 1994; 2004; Moolchan et al., 2002), and neither the DSM-IV criteria nor FTND scale has consistently predicted other indices of smoking behavior or treatment outcomes of smokers. In a pooled sample of smokers from multiple clinical trials, the FTND score predicted short and long term success for smoking cessation but most of the predictive validity of the FTND could be attributed to its first item: time to smoke the first cigarette (Baker et al., 2007). Further, many studies employ the number of cigarettes smoked per day, a much simpler and cruder measurement of smoking, as a better predictor of treatment outcome than either of the previously mentioned measures (Dale et al., 2001; Franken et al., 2006; Piper et al. 2006). Although other scales have also been developed to overcome the limitations of the FTND scale and the DSM-IV criteria (Piper et al. 2006; Shiffman and Sayette, 2005; Smith et al., 2010), there is still no consensus on what represents the most reliable and valid method for assessing nicotine addiction.

The difficulties associated with the measurement of nicotine addiction may be partly due to the disconnection between contemporary theories of addiction and the current tools used to measure addiction (Tiffany et al., 2004). Although many contemporary theories of addiction favor a dimensional model of addiction, both the DSM-IV criteria and FTND scale favor a categorical classification of individuals as either dependent or non-dependent (Tiffany et al.,

2004). Furthermore, neither the DSM-IV criteria nor the FTND scale are based on a well-articulated theory of addiction; they may be especially insensitive to assessing smokers who are in the early stages of nicotine use, as these measures have been developed and validated in adult end-stage smokers (Colby et al., 2000; Rose and Dierker, 2010).

3.2 Measurement of Reinforcement

Another concept that is occasionally used interchangeably with the addiction threshold is the reinforcement threshold (Hatsukami et al., 2010). However, it is worth noting that addiction and reinforcement are not synonymous concepts. By definition, a drug is reinforcing if it increases and sustains behaviors (e.g., drug taking) that result in its presentation. Nicotine, similar to other drugs of abuse, acts as a reinforcing stimulus across multiple species (Rose and Corrigall, 1997). Accordingly, the reinforcement threshold for nicotine would be defined as the lowest nicotine dose that will increase or maintain nicotine self-administration behaviors (i.e., tobacco use; Corrigall, 1991). The nicotine reinforcement threshold differs from the nicotine addiction threshold in many ways as described below.

First, in contrast to nicotine dependence, reinforcement is less ambiguously defined. The gold standard behavioral measure for demonstrating nicotine reinforcement is self-administration (i.e., intravenous (IV) self-administration or cigarette smoking). A drug is considered to be reinforcing if it is self-administered to a greater extent than a vehicle or placebo (Audrain-McGovern et al., 2009). In general, there is a relatively well-accepted agreement on the experimental designs and data required to demonstrate reinforcement of self-administration behavior, as described in the numerous reviews of self-administration models (Ator and Griffiths, 2003; Balster, 1991; Carter and Griffiths, 2009; Comer et al., 2008; FDA 2010; Henningfield et al., 1991; O'Connor et al., 2011). Importantly, compared with the dichotomized models exemplified by the DSM-IV criteria or FTND scale, methods for assessing nicotine reinforcement can be based on broader models of addiction (e.g., operant, behavioral economics, and self-control), for an in depth discussion, see Glautier, 2004; Tiffany et al., 2004).

Second, because dependence does not occur if the substance is not reinforcing, the nicotine reinforcement threshold is likely to be lower than the nicotine addiction threshold (Audrain-McGovern et al., 2009; Glautier, 2004). Several studies have shown that substantial tobacco use can develop and be maintained without a progression to addiction. For instance, approximately 50 % of smokers do not fulfill the DSM-IV criteria for nicotine dependence (Hughes et al., 2006), and 38 % of smokers who smoke 10 or more cigarettes per day also fail to fulfill the DSM-IV criteria (Donny et al., 2007). Thus, the nicotine reinforcement threshold may be a more sensitive index for predicting tobacco use below the threshold for addiction.

Third, studies measuring the reinforcement threshold can be accomplished with short-term studies examining self-administration both in humans and non-humans (Comer et al., 2008; McKim, 2007; Schuster and Johanson, 1981). This approach allows for the examination of a broad range of factors that may influence the threshold for nicotine reinforcement. These factors may include individual differences (e.g., age, sex, and genetic factors), alternative reinforcers (e.g., money and food) and environmental factors (e.g., stress and the presence of peers). In contrast, even with the availability of valid and accurate measures of nicotine dependence, the determination of an addiction threshold will require, long-term, prospective follow-up studies of nondependent individuals for the development of addiction when their nicotine intake is controlled. These types of studies are difficult to conduct and fraught with many ethical and practical problems.

In summary, the lack of reliable and valid measures for nicotine addiction limits the utility of the nicotine addiction threshold as a target for tobacco regulation. Furthermore, the weak relationship between nicotine addiction and actual rates of tobacco use suggests that there could be significant scientific and legal debates about the predictive values of research on a nicotine addiction threshold, which could impede progress in developing and enforcing a science-based tobacco control policy. In contrast, the nicotine reinforcement threshold is more clearly defined and easier to measure in short-term studies than the addiction threshold and may be a more sensitive index for predicting tobacco use.

4. Reinforcement Threshold for Pure Nicotine

4.1 Human Studies

Because cigarette smoke contains many other compounds in addition to nicotine (Hoffmann and Wynder, 1986; Talhout et al., 2011) and the amount of nicotine delivered via smoking is difficult to control, dose-dependent nicotine effects are very difficult to characterize using tobacco products. Pure nicotine administration studies, especially via nasal spray and IV administration, have provided critical information on the reinforcing effects of nicotine in general and allow for preliminary estimates of a nicotine reinforcement threshold in current smokers (Rose and Corrigall, 1997). Although numerous studies have examined the self-administration of pure nicotine in humans, relatively few investigators have attempted to generate complete dose-response curves. This lack of dose-response data is a major knowledge gap that limits the current estimates of a nicotine reinforcement threshold.

Nasal spray—Nasal spray provides a faster delivery of nicotine compared to nicotine gum and patches or oral inhalers and the amount of nicotine delivered by nasal spray can be reasonably controlled (Perkins, 2009; Benowitz, 2006). However, nicotine nasal spray is not self-administered more than placebo (Perkins et al., 2001). This lack of reinforcement might be due to the adverse effects of nasal spray (e.g., local irritation and nasal burning) and the slower rate of nicotine delivery via spray compared to smoking. Because the speed of delivery partially determines nicotine reinforcement (Henningfield and Keenan, 1993), faster nicotine delivery systems might be better suited for determining the nicotine reinforcement threshold.

Intravenous Infusion—Although no pure nicotine administration method can fully simulate cigarette smoking, IV nicotine self-administration (NSA) has several advantages. First, the IV route produces a fast nicotine delivery with peak plasma levels reached in 20 sec, which is comparable to smoking (Matta et al., 2007; Rose et al., 2003; Zins et al., 1997). Second, IV nicotine provides accurate dosing by delivering nicotine directly into the circulation and bypassing absorption steps that show significant individual variation. Third, when administered rapidly (i.e., in less than 60 sec), IV nicotine elicits pleasurable subjective effects, such as “good drug effects” and “like the drug effects,” similar to those elicited by smoking and is self-administered by smokers (Harvey et al., 2004; Henningfield and Goldberg, 1983; Henningfield et al., 1983; Sofuoglu et al., 2008). As a limitation, nicotine delivered by an IV route does not produce the respiratory sensory cues that are typically associated with nicotine delivered by inhalation (Rose 2008).

Seminal studies of IV NSA by smokers were conducted by Henningfield and colleagues (Henningfield and Goldberg, 1983; Henningfield et al., 1983). Although nicotine responses tended to be more regularly spaced than responses to saline, the overall response rates for nicotine did not reliably exceed those for saline. Therefore, the evidence for nicotine serving as a reinforcer was not clear in these earlier studies (Henningfield and Goldberg, 1983; Henningfield et al., 1983). However, a more recent study (Harvey et al., 2004) has addressed some of the limitations of these early studies that might have obscured detecting the

reinforcing effects of nicotine (e.g., the minimal effort of only 5 responses needed to obtain infusions or alternating daily availability of nicotine and saline). In the Harvey et al. (2004) study, IV nicotine (75, 150, and 300 μg/injection) and saline were available concurrently for abstinent male cigarette smokers during 3-hour sessions. To receive the injections, smokers had to pull a lever according to a fixed-ratio requirement ranging from 10 to 1600. Smokers preferred nicotine injections compared with saline administration for all 3 nicotine doses. The nicotine doses used in this study were higher than the usual nicotine intake of a smoker, which is on average 1–2 cigarettes/hour or 1–4 mg nicotine/hour (Benowitz and Jacob, 1990). To address this limitation, a recent study examined the self-administration of nicotine using doses within the range of average intake by smokers (Sofuoglu et al., 2008). A choice procedure was used in which male and female smokers were able to choose between various IV nicotine doses (0.1, 0.4, or 0.7 mg/70 kg or 1.5, 6.0, or 10 μg/kg) or saline. Both the 6.0 and 10 μg/kg, but not the 1.5 μg/kg, doses were preferred over placebo. These findings were consistent with the threshold for nicotine discrimination (Perkins et al., 2001) and provided a preliminary estimate for the reinforcing threshold of nicotine as being between 1.5 and 6.0 μg/kg in smokers.

4.2 Animal Studies

Although one cannot extrapolate an absolute value for a nicotine reinforcement threshold for humans based on animal studies, animal research can complement and extend studies in humans by identifying a dose range that may contain the threshold, as well as the environmental and biological factors that support it (Matta et al., 2007). Although most animal studies have not examined a dose range broad enough to determine the reinforcement threshold for nicotine in animals (i.e., they did not include a dose that was not reinforcing), when viewed together they can provide a preliminary estimate. The maintenance of NSA in adult animals is dependent upon the unit dose. The peak of the unit dose-response curve typically lies at 10 to 30 μg/kg when the number of responses (e.g., lever presses) to produce each infusion is relatively small (e.g., 1–5 in rats) and the infusion is relatively rapid (e.g., 1 sec) (Matta et al., 2007). NSA in adult rats usually decreases below 10 μg/kg. Nonetheless, some studies have shown that unit doses as low as 3 μg/kg are still capable of maintaining response rates above that for saline when substituted for a higher training dose (e.g., 30 μg/kg), despite those rates being below the peak of the dose-response curve (Corrigall and Coen, 1989; Cox et al., 1984; Watkins et al., 1999). Whether this pattern was evident in individual rats or was an artifact of averaging data across rats was not reported.

These findings suggest that the nicotine reinforcement threshold for the maintenance of NSA in adult animals might be between 3 and 10 μg/kg nicotine. However, estimates based on existing data are limited because the number and range of the doses used has been small in many studies. Moreover, some studies have manipulated the doses between subjects, which is not analogous to the within-subject changes in doses that would occur following the implementation of a nicotine reduction policy. Finally, recent data suggest that slower infusions (e.g., 30 sec) of smaller (“puff-sized”) doses are more reinforcing than typical rapid infusions of higher (“cigarette-sized”) doses, indicating that infusion parameters can play a critical role in determining the threshold of reinforcing doses of nicotine in animal models (Sorge and Clarke, 2009).

4.3 Limitations of NSA studies and future directions

The self-administration studies with pure nicotine summarized above have many limitations, and important knowledge gaps remain in our understanding of the nicotine reinforcement threshold.

1) The IV route does not fully mimic nicotine delivery via smoking—The smell, taste, and respiratory cues associated with smoking may serve as conditioned reinforcers (Naqvi and Bechara, 2005). For example, nicotine delivered via smoking induces many sensory cues in the respiratory tract, including a harsh or irritating sensation in the mouth, throat, windpipe, and chest (Lee et al., 2007; Rose, 1988). These sensory cues likely contribute to the nicotine reinforcement threshold in cigarette smokers and could be examined using inhaler-type nicotine delivery systems. Currently available nicotine vapor inhaler does not effectively deliver nicotine to the lungs (Lunell et al., 2000) and most of the nicotine is absorbed through the buccal mucosa. A recently developed aerosol inhaler delivers nicotine to the lungs more effectively than the nicotine vapor inhaler and produces sensory cues in the respiratory tract similar to cigarette smoking (Caldwell et al., 2009). This type of rapid delivery inhaler may be useful for nicotine dose-response studies and helpful in determining the contribution of respiratory cues to the reinforcement threshold of nicotine.

2) Reinforcing effects of non-nicotine compounds in cigarette smoke— Although nicotine is considered to be the key ingredient responsible for tobacco addiction, increasing evidence suggests that other compounds in tobacco or smoke are either reinforcing in their own right or can enhance the reinforcing effects of nicotine. These compounds include acetaldehyde (Belluzzi et al., 2005; Karahanian et al., 2011), monoamine oxidase inhibitors such as harman and norharman (Baum et al., 1996; Rommelspacher et al., 2002), and minor alkaloids (e.g., nornicotine, anabasine, and anatabine; Clemens et al., 2009). The potential contribution of non-nicotine constituents to the reinforcement threshold of nicotine delivered by cigarette smoking requires further investigation.

3) Factors that may influence the nicotine reinforcement threshold—The nicotine reinforcement threshold may be influenced by many factors that need to be carefully examined. For example, individual differences due to age, sex, race, and genetic variation may modulate nicotine reinforcement levels between individuals and may potentially influence the reinforcement threshold (Benowitz 2008; Bierut 2009; Fowler et al., 2011; Perkins et al., 1999; Sofuoglu and Mooney, 2009). Such studies should include adolescent smokers because adolescence is associated with an increased sensitivity to nicotine (Adriani et al., 2002; Chen et al., 2007; Levin et al., 2003; 2011; McQuown et al., 2007; 2009) and because more than 80 % of smokers initiate smoking during adolescence (Marshall et al., 2006).

Another important consideration is whether the observed reinforcement effects of nicotine reflect nicotine's positive reinforcing effects or a reversal or prevention of abstaining from tobacco (i.e., negative reinforcement; Lerman et al., 2009). Evidence suggests that negative reinforcement may contribute to the escalation and maintenance of smoking even in the early phases of cigarette smoking (Eissenberg, 2004). A common approach to tease apart the direct effects from reversal of abstinence is to test smokers following brief periods of abstinence (e.g., overnight) or no abstinence. However, the duration of abstinence has to be considered in interpreting the findings related to the nicotine reinforcement threshold.

4) Predictive value of the reinforcing threshold for tobacco use—Once the reinforcing threshold dose of nicotine is determined in controlled settings, it will be important to demonstrate that this threshold predicts nicotine use in real-life settings. When self-administration cannot be directly measured, surrogate measures of self-administration (self-reported cigarettes smoked per day, breath CO levels, or nicotine and cotinine levels in bodily fluids) can be used (Benowitz et al., 2002). It is possible that the level of nicotine identified as non-reinforcing in controlled settings may lead to prolonged experimentation and use in real-life settings by the addition of other compounds that enhance the rewarding

or appealing effects of that product. In addition, these products may serve as gateways for other tobacco products with higher nicotine levels or lead to compensatory smoking, as shown for smokers that have switched to low nicotine yield cigarettes (Scherer, 1999). Studies in real-life settings may also help to determine vulnerability factors that predict escalating tobacco use that may inform science-based tobacco control policies.

5. Conclusions

A recent policy initiative that has given the FDA the authority to regulate tobacco products provides a unique opportunity to establish science-based tobacco control policies. As proposed by Benowitz and Henningfield, reducing the nicotine content of cigarettes below a threshold necessary for addiction is one method that may potentially reduce the rates of the initiation and maintenance of tobacco use. The measurement of a nicotine addiction threshold poses several challenges and may be difficult to assess. This may hamper the progress in the development of a science-based tobacco control policy. In contrast, the nicotine reinforcement threshold may be easier to determine using well-established methods in behavioral pharmacology under controlled settings. Extant studies using intravenous nicotine administration suggest that this reinforcement threshold for nicotine lies between 1.5 to 6.0 μg/kg in humans and 3 to 10 μg/kg in rats. However, these studies have many limitations, and important gaps remain in our knowledge concerning the nicotine reinforcement threshold. Future studies addressing these limitations may provide a more clear assessment of the reinforcement threshold for nicotine. Furthermore, the usefulness of the nicotine reinforcement threshold in predicting tobacco use must be determined in real-life settings. The results from such studies will determine if the estimated threshold for nicotine reinforcement and will be of value in developing science-based tobacco control policies.

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