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How Intravenous Nicotine Administration in Smokers Can Inform Tobacco Regulatory Science

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Abstract

Reducing the negative health effects caused by tobacco products continues to be a public health priority. The Family Smoking Prevention and Tobacco Control Act of 2009 gives the Food Drug Administration authority to pursue several new strategies, including regulating levels of nicotine and other ingredients in tobacco products. A nicotine reduction strategy proposed by Benowitz and Henningfield aims to reduce the nicotine content of tobacco products to an amount below a threshold that supports neither the development nor maintenance of addiction. Many factors must be considered to determine the viability and efficacy of this approach. For example, the policy should be based on precise information on the dose-dependent effects of nicotine on reinforcement and factors that contribute to individual differences in these effects. However, there have been few studies on these topics in humans. Here, we briefly review nicotine pharmacology and reinforcement then present several studies illustrating the application of intravenous (IV) nicotine delivery to study nicotine reinforcement in humans. We discuss how nicotine delivery by IV infusion may be uniquely suited for studying nicotine's dose-dependent effects, and how this can inform tobacco regulatory science to facilitate the development of effective tobacco control policies.

Keywords

nicotine; intravenous; abuse liability; nicotine reduction; regulatory science

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Human Subjects Statements

This work did not involve any human subjects research.

Conflict of Interest Statement

Dr. Sofuoglu has served as an expert witness on behalf of Pfizer in lawsuits related to varenicline. All other authors declare no conflict of interest.

INTRODUCTION

Tobacco use causes or contributes to the mortality of multiple diseases, and it is the leading cause of preventable death worldwide.^{1, 2} Nicotine is an addictive substance that plays a key role in initiating and maintaining tobacco use.^{3–5} The Family Smoking Prevention and Tobacco Control Act of 2009 (FSPTCA) gave the United States Food and Drug Administration (FDA) authority to regulate the content of tobacco products, including the nicotine content, to reduce the abuse potential and negative health effects associated with their use. The FSPTCA permits the FDA to reduce, but not eliminate, nicotine in tobacco products. The tobacco control policies currently under consideration have their genesis in an influential article by Benowitz and Henningfield.⁶ This article proposed a gradual reduction in the amount of nicotine in a cigarette to below a threshold that would support neither the development nor maintenance of addiction.⁶ With the Benowitz and Henningfield proposal on the nicotine content of cigarettes as a foundation, several research priorities and studies have been proposed to facilitate the development of an effective nicotine reduction strategy.⁷ To reach this goal, an important initial step is to determine a threshold dose value for nicotine's addictive effects. A second key step is to characterize individual differences in nicotine's addictive threshold. As suggested by Henningfield et al., the addictive threshold may likely vary based on age, gender, genetic differences, and presence of comorbid mental health problems.⁸

For clarity, it is important to distinguish 3 terms: abuse potential, addiction threshold and reinforcement threshold. As we reviewed recently, abuse potential refers to the intrinsic pharmacological effect of a drug that is reported as “liked” by users or induces positive subjective effects (eg, drug liking, good drug effects, high, want more drugs) that are concomitant with behavioral reinforcement (ie, self-administration).⁹ With prolonged use, these subjective effects are thought to facilitate the development of addiction,^{10, 11} although in some cases subjective effects may be disassociated from the reinforcing effects of a drug.^{12, 13}

The reinforcement threshold is the lowest nicotine dose that will initiate or maintain self-administration behaviors (ie, tobacco product use).¹⁴ The nicotine addiction threshold is the minimum amount of nicotine intake required to initiate or maintain behaviors that meet a clinical criterion for addiction (eg, DSM 5 criteria for tobacco use disorder or Fagerstrom Test for Nicotine Dependence score ≥ 5). As we commented previously,⁹ an addiction threshold is difficult to operationalize partly due to lack of consensus on the criteria for nicotine addiction and the weak relationship between nicotine addiction and actual rates of tobacco use.⁹ In contrast, the nicotine reinforcement threshold is easier to operationalize using established methods of human behavioral pharmacology. It is important to acknowledge that identifying the nicotine reinforcement threshold will be one of the critical steps in determining the addictive threshold for nicotine in tobacco products.⁹

Among numerous compounds in tobacco, nicotine is considered an important ingredient that facilitates reinforcement and the development of addiction.^{3, 15} However, others have questioned the role of nicotine in initiation and maintenance of tobacco addiction.¹⁶ Support for nicotine's addictive effects has accumulated from studies on pure nicotine self-

administration in animal models and human laboratory studies^{17–26} and studies on the neurobiological effects of nicotine on reward pathways within the brain.^{27–30} It is also noteworthy that naturally occurring genetic variation within the genes encoding nicotinic acetylcholine receptors (nAChRs) and nicotine metabolizing enzymes are known sources of individual differences in risk for developing tobacco use disorder. Specifically, genetic variation at the $\alpha 3$, $\alpha 5$, $\beta 4$ nicotinic receptor subunit gene cluster, the $\alpha 4$ nicotinic receptor subunit gene and variation proximal to the *CYP2A6* gene are among the most strongly supported by genomewide association studies for an association with tobacco use phenotypes.^{31–36} These human genetic association studies, which were based on a hypothesis-free approach (ie, all possible genes were considered), converge on findings where the genes that encode proteins that interact directly with nicotine and mediate nicotine's biological effects are among the most strongly supported for association with TUD. Additional support for the role of nicotine in tobacco addiction comes from the use of medications that target nicotinic receptors to treat smoking (eg, nicotine replacement therapy).³⁷ Because these findings highlight nicotine as central to the development of tobacco use disorders, additional studies on the reinforcing effects of nicotine in humans are warranted.

There are many unanswered questions regarding the dose-dependent effects of nicotine on reinforcement in humans. Studies on nicotine reinforcement in animal models have been informative, but it is unclear how this information will translate into regulatory policy for tobacco control in humans. Nicotine's effects in humans can be studied using a variety of nicotine delivery systems. However, precise, reproducible dosing necessary to observe dose-dependent effects of nicotine on reinforcement has been a challenge. Here we will provide an overview of intravenous (IV) nicotine administration studies on nicotine reinforcement and will make the case for this method's potential unique utility in informing tobacco regulatory science. To reach this goal, we review nicotine pharmacology and reinforcement, nicotine delivery systems to study nicotine reinforcement in humans followed by how nicotine delivery by IV infusion can be used to inform regulatory science, such as inform guidelines for an effective nicotine reduction strategy.

Nicotine Pharmacology and Reinforcement

Nicotine's pharmacological effects in the central nervous system (CNS) are mediated by nAChRs. nAChRs are ligand-gated ion channels, which consist of pentameric combinations of subunits ($\alpha 2$ – $\alpha 10$ and $\beta 2$ – $\beta 4$) that are encoded by different genes. The reinforcing effects of nicotine, similar to other drugs of abuse (eg cocaine), are likely mediated by dose-dependent stimulation of dopamine (DA) neurons in the ventral tegmental area (VTA) and the resultant DA release in the nucleus accumbens.^{30, 38} Nicotine stimulates DA release in the nucleus accumbens via activating nAChRs that include, $\alpha 4$, $\beta 2$, $\alpha 5$, $\alpha 6$ and $\beta 4$ subunits.³⁸ There are significant differences in agonist affinity and desensitization thresholds among nAChRs based on subunit composition, and there is significant diversity in subunit expression throughout the CNS.^{39, 40} Considering the dose-dependent effects of nicotine on specific nAChRs is important because high doses of nicotine have pronounced aversive effects that oppose reinforcement.⁴¹ The "aversive", reinforcement-opposing effects of nicotine are mediated, in part, by specific activation of $\alpha 5$ -containing nAChRs expressed in

neurons of the medial habenula interpeduncular tract. The reinforcing effects of high-doses of nicotine are markedly different for $\alpha 5$ knockout (KO) mice compared to wild-type animals.⁴² At high-doses of nicotine, the reinforcing effects of nicotine are attenuated for wild-type mice relative to $\alpha 5$ KO mice.⁴² These dose-dependent effects of nicotine on nAChR activity and reinforcing versus reinforcement-inhibiting processes are relevant to the development of tobacco use disorders, given that genetic variation within the genes encoding nAChR subunits, including $\alpha 5$, are well-established sources for individual differences in vulnerability to indicators of heavy cigarette use.^{31–36} Cumulating evidence from human studies suggests that sensitivity to the aversive subjective effects of nicotine may prevent initiation of tobacco product use and affect the amount of nicotine intake in established tobacco users.⁴³ Among teenagers experimenting with cigarettes, sensitivity to aversive effects of nicotine (eg, unpleasant sensations, nausea, coughing, difficulty inhaling, or heart pounding) was associated with a low likelihood of becoming a daily smoker.^{44, 45} Moreover, flavors like menthol may facilitate addiction by reducing the aversive effects of nicotine.⁴⁶

Nicotine Delivery Systems

Cigarettes and electronic cigarettes—Among nicotine delivery systems in humans, cigarette smoking produces the most rapid delivery of nicotine to the brain. Nicotine from inhaled tobacco cigarette smoke is rapidly absorbed across the lungs and reaches the brain within 10 to 20 sec.⁴⁷ Peak nicotine levels are reached within the brain in about 2 minutes. Peak venous plasma nicotine concentrations (10 to 50 ng/ml) are reached immediately following smoking and decline rapidly within the next 20 minutes due to tissue distribution. Because cigarette smoke contains many other compounds in addition to nicotine,^{15, 48} and the precise dose of nicotine delivered via smoking cannot be reliably controlled, cigarette smoking is not suitable for examining nicotine dose-dependent effects on reinforcement. However, it is important to note that non-nicotine compounds in cigarette smoke may influence smoking behavior by modulating the reinforcing effects of nicotine.^{49–52} In addition, the primary reinforcing effects of nicotine delivered via tobacco cigarettes are difficult to assess in the presence of sensory cues (eg, taste, olfactory or visual stimuli) that are paired with smoking a cigarette. Although these effects are important for reinforcement, they are not directly related to nicotine dose.^{53, 54}

Electronic cigarettes (EC) deliver nicotine slower than cigarette smoking but faster than most other delivery products; but delivery rates vary greatly between different types of EC and between different users.^{55, 56} As commented on by Shihadeh and Eissenberg, differences in nicotine delivery kinetics might affect nicotine intake rate and the level of reinforcement for different EC products.⁵⁷ The pharmacokinetics of nicotine delivered by various types of EC devices was characterized in a recent study.⁵⁶ In this study the mean peak nicotine concentration in blood, ~8 ng/ml, was approximately 12 minutes after the initiation of 15 puffs, with one puff every 30 sec.⁵⁶ The mean peak nicotine concentration in blood was lower than the level achieved by smoking for all but a few subjects. There was great variability in nicotine delivery, retention and pharmacokinetics, which could be attributed to the individual user or the different brands of EC used in experiment. Absorption of nicotine via EC may be slower than tobacco cigarettes because a significant amount of the nicotine contained within the EC vapor is absorbed by tissue outside the lung.⁵⁶ Similar to

cigarette smoke, EC vapor may contain many compounds and thus, ECs are not a pure nicotine delivery system.^{58–60} Moreover, delivery of precise doses of nicotine by EC puffing cannot be reliably controlled in an experimental setting,⁶¹ thus ECs are not optimal tools for examining dose-dependent effects of nicotine on reinforcement. Similar to cigarette smoking, the primary reinforcing effects of nicotine when delivered via EC are difficult to assess in the presence of sensory stimuli (eg, taste, olfactory or visual stimuli) that are paired with the EC, but not directly related to nicotine dose.

Nicotine replacement therapies—In addition to tobacco or EC, nicotine gum, lozenge or nasal spray can be used as nicotine delivery systems. Nicotine delivery by nasal spray produces peak plasma nicotine concentrations in 25 to 30 min, or about 10 fold slower than tobacco cigarette smoking.⁶² In human laboratory studies, these delivery products generally do not elicit “drug liking” subjective effects that are indicative of reinforcement; in fact, some of these products may provoke aversive subjective effects.^{63, 64} These methods alleviate symptoms related to nicotine withdrawal in individuals who are dependent upon nicotine, but do not have strong positive reinforcing effects.

IV nicotine—IV self-administration is considered the “gold standard” for assessing dose-dependent effects of drugs on reinforcement, partly because precise, reproducible dosing can be achieved with this method.²² Nicotine reinforcement in animal models has been studied extensively using IV self-administration. In animal models the dose-response function for nicotine reinforcement has been explored with interesting results. At high and low end of the nicotine dose range, there are dose-dependent changes in nicotine reinforcement while among the mid-range doses, reinforcement is relatively uniform.^{17–21}

Nicotine can be safely administered to human subjects by IV infusion. Typically, in these studies pure nicotine is diluted in saline solution and administered at a precise dose and rate to a subject via a catheter inserted in a forearm vein. IV infusion of nicotine can be carefully modulated to resemble the kinetics of nicotine intake from tobacco smoking or other tobacco products, as described in section 3.2.3. Several studies have demonstrated the reinforcing effects of IV nicotine (ie, self-administration) in dependent adult smokers.^{5, 22, 23, 25, 26} Although critical for determining a threshold dose for nicotine reinforcement, and central to the nicotine reduction strategy for tobacco product regulation, there have been very few studies on the IV nicotine dose-response curve for reinforcement in humans. A study by Jensen and colleagues that investigated dose-dependent effects on reinforcement within a limited range that included low to moderate doses is described in section 4.1.⁶⁵

Smoking versus IV administration—While nicotine delivered via the IV route does not fully mimic nicotine delivered via inhalation by tobacco smoking, the pharmacokinetics and subjective effects of inhaled and IV nicotine can be controlled so that they are very similar in many respects. For example, Rose et al. compared the venous and arterial concentrations of nicotine following cigarette smoking to IV nicotine administration.⁶⁶ In the Rose et al. study, the amount of nicotine exposure from smoking was first determined for each subject and then the same dose of nicotine was delivered intravenously to the same subject over a similar time course as smoking. This study demonstrated that IV infusion can produce arterial (20.5 ng/ml) and venous (6.9 ng/ml) plasma concentrations of nicotine that are

similar to the arterial (20.4 ng/ml) and venous (7.8 ng/ml) concentrations that occur from smoking.⁶⁶ The rapid time to peak arterial nicotine concentrations following smoking can also be observed for IV infusion.⁶⁶ In this study, the time to reach peak arterial nicotine concentrations following smoking and IV infusion were 20 sec and 30 sec, respectively.

Smoked and IV nicotine produce similar subjective drug effects. In a study by Mello et al., IV nicotine (1 or 1.5 mg) infused over 60 sec produced “good” subjective drug effects and a subjective “high” that was similar to the effects induced by low- and high-nicotine cigarettes, respectively.²⁶ Multiple studies have demonstrated that rapid IV nicotine infusion (ie, less than 60 seconds) elicits positive subjective drug effects (eg, “good effects” and “drug liking”) similar to smoking, and reinforcing effects (ie, self-administration) in dependent adult smokers.^{5, 22, 23, 25, 26} Thus, in addition to its ability to mimic the rate of delivery and induce subjective effects similar to that of smoked nicotine, IV nicotine delivery allows for an accurate control over the dose and rate of nicotine infusion. These features are crucial for systematically examining the relationship between nicotine dose and nicotine’s pharmacological and reinforcing effects in humans.

Potential Utility of IV Nicotine for Tobacco Regulatory Science

Effective nicotine reduction policies to reduce the harm caused by tobacco smoking need to be empirically supported by carefully controlled studies on nicotine’s pharmacological effects, including dose-dependent effects on reinforcement in humans. Several procedures and nicotine delivery systems exist to study the potential effects of nicotine in humans; however, IV administration is among the few pure nicotine delivery systems that can achieve the precise, reproducible dosing that is crucial for evaluating dose-dependent effects. Importantly, IV administration can uncouple the effects of nicotine from other potential effects that are associated with the use of a tobacco product but not directly related to nicotine dose. IV nicotine administration studies on 1) nicotine reinforcement threshold, 2) nicotine aversion as a risk factor for initiation and maintenance of smoking and 3) sex and menstrual cycle effects on nicotine sensitivity, highlight the potential utility of IV nicotine for tobacco regulatory science.

Nicotine reinforcement threshold—Recently, we utilized an IV administration protocol to characterize the dose-response curve for the reinforcing effects of low to moderate doses of IV nicotine in male (N = 12) and female (N = 14) tobacco smokers.⁶⁵ In this study, all subjects participated in an experimental session that started the morning following overnight smoking abstinence that was verified by measuring breath carbon monoxide levels. Four doses of IV nicotine (0.1, 0.2, 0.3 and 0.4 mg) were tested relative to saline in 4 separate experimental sessions (one nicotine dose versus saline at each session). Doses were selected to approximate the nicotine intake from inhaling 1 to 4 puffs of tobacco cigarette.⁶⁷ At each session the nicotine dose and saline were randomly labeled as “A” or “B” and administered in a double-blind fashion. For each nicotine dose condition, subjects first received in random order one sample dose each of saline and nicotine. Following the sample infusions there were 6 forced-choice trials where the subject chose to receive IV infusions of nicotine or saline while the subject remained blinded. Sex effects were tested in all analysis because of prior evidence supporting sex differences in nicotine’s

pharmacological effects.⁶⁸ During the experimental session, subjects were monitored for changes in heart rate and blood pressure, and they recorded their subjective effects using a Drug Effects Questionnaire (DEQ) at several time points after the infusion of the sample doses of saline and nicotine. Figure 1 shows the outcome of the force-choice trials for male and females. At the 0.1 mg dose, but not at the other doses, males had more nicotine self-administrations compared to females. There was a significant negative linear relationship between self-administration choices and nicotine dose among males. Males chose to self-administer nicotine more often at 0.1 mg and 0.2 mg doses compared to the 0.4 mg dose. In contrast, among females there were no differences in choice preference for nicotine (over saline) between nicotine doses. There was no choice preference for nicotine over saline at any dose condition. Interestingly, all nicotine doses were rated as more pleasurable than saline for males and females, indicating abuse potential for all tested doses including 0.1 mg, the lowest tested dose.

The sex differences are consistent with prior work from several studies by Perkins and colleagues which concluded that females had less nicotine dose-sensitivity than males, in part due to poorer ability to discriminate nicotine doses and less tendency to self-titrate across nicotine doses to achieve a total target dose compared to men. Perkins concluded that female's smoking behavior may be reinforced more by smoking-related cues and less by the nicotine itself, compared with men's smoking behavior.⁶⁹ In the Jensen et al study, sex differences were dose-dependent, ie, they manifested at low doses but not high doses. The careful dosing procedure revealed how males and female smokers may react differently to nicotine reduction strategies. It will be interesting to see if these dose-sensitive sex differences in the reinforcing effects of low to moderate doses of IV nicotine correspond to sex differences in the dose for discrimination of nicotine via cigarette smoking. A recent study by Perkins et al. investigated the nicotine threshold for discriminating ultralow nicotine content cigarettes from cigarettes with higher nicotine content, however there were too few females in this study to test for potential sex differences.⁷⁰ Males may be more likely than females to modify their tobacco use behavior to compensate for nicotine reduction.

Reduced nicotine aversion as a risk factor for initiation and maintenance of smoking—In a separate study, we utilized an IV nicotine infusion protocol to test how individual differences in genetic vulnerability to heavy cigarette smoking affected the acute response to nicotine among smokers.⁷¹ We applied an IV nicotine protocol to a sample of smokers, stratified by a common functional SNP, rs16969968, encoded in the nAChR $\alpha 5$ subunit gene, *CHRNA5*. SNPs in *CHRNA5*, including rs16969968, have strong statistical support for an association to the amount of cigarettes smoked per day.^{32–35} Subjects in this study were adult male and female smokers that had abstained from smoking for ~10 h (overnight). The average age was 36 years (SD = 8.9) and all subjects were daily smokers (~10–20 cigarettes per day with average blood cotinine level ~150 ng/ml). Subjects received infusions of saline and doses of nicotine at 0.5 and 1.0 mg (per 70 kg body weight) in uniform order with each infusion lasting 60 seconds. The total amount of nicotine delivered by these infusions approximated the dose of nicotine delivered by smoking 1 to 1.5 tobacco cigarettes.⁷² Subjective drug effects were assessed at several time points after each infusion.

Figure 2 shows the marked difference in subjective ratings of aversive effects for subjects stratified by rs16969968. In rodent models, $\alpha 5$ containing nAChRs mediate the aversive effects of nicotine and function as reward-inhibiting signals to reduce nicotine's reward-enhancing effects, and *in vitro* functional studies indicate that rs16969968 affects *CHRNA5* function.^{41, 42, 73–77} The differential response to nicotine's aversive effects via rs16969968 is one hypothesized mechanism for the observed association of rs16969968 with risk for heavy smoking. Consistent with this hypothesis, we observed that the heavy smoking risk allele (rs16969968*A; frequency=28% in European American subjects and 6% in African American subjects) was associated with lower ratings of aversive subjective effects in response to nicotine ($p < 5 \times 10^{-8}$). The measure of aversive subjective effects was an average of 3 highly correlated responses, "I feel anxious", "I feel bad", and "I feel down". Notably, the effect of rs16969968 was specific to the aversive subjective effects; responses for pleasurable and stimulatory subjective effects did not differ by rs16969968 genotype.

Evidence is accumulating from animal models and human studies suggesting that individual differences in sensitivity to the aversive effects of nicotine, including individual differences based on genetics, are important factors for the initiation of regular tobacco product use and the amount of nicotine intake in established tobacco users.^{31–36, 43} Sensitivity to the aversive subjective effects of nicotine may be particularly important among adolescents given epidemiological studies that have linked the initial subjective response to smoking to later life tobacco dependence.^{44, 45, 78, 79} As evidenced by genetic variation within *CHRNA5*, sensitivity to the aversive effects of nicotine is a source of individual differences in susceptibility to developing nicotine addiction. The IV nicotine administration procedure utilized in this study demonstrates how sensitivity to the aversive effects of different nicotine doses can be studied in humans.

Sex and menstrual cycle effects on nicotine sensitivity—Sex differences in the effects of nicotine may contribute to individual differences in tobacco use behavior. However, findings on this topic have been inconsistent, potentially due to differences in study designs and the difficulty in accurately assessing the dose-dependent effects of nicotine with many of the commonly used nicotine delivery systems (eg, EC or cigarettes).^{68, 80, 81} DeVito et al. used an IV nicotine administration procedure to investigate how sex and menstrual phase influenced sensitivity to precisely delivered doses of nicotine.⁸⁰ In this study there were 115 male and 45 female daily cigarette smokers (> 10 cig/day) that were not seeking treatment. All subjects abstained from smoking overnight prior to the IV nicotine session. Following baseline assessments, participants received IV saline and 2 escalating weight-adjusted doses of nicotine (0.5 mg and 1.0 mg nicotine per 70 kg body weight) in uniform order. Females were stratified by menstrual phase based on serum levels of progesterone (N = 29 in follicular phase, progesterone < 2 ng/ml; N = 16 luteal phase, progesterone $\geq$ 2 ng/ml). The effects of sex and phase were analyzed for outcomes relevant to the acute effects of nicotine, including the subjective drug effects. There were no significant sex differences on baseline measures related to tobacco smoking severity; however, several interesting findings emerged for assessments on the acute response to IV doses of nicotine. As shown in Figure 3, there were dose-sensitive effects of both sex and menstrual phase on subjective drug effects. Men reported greater dose-related

increases in positive subjective drug effects (eg, “stimulated”, “feel good”) while women distinguished between nicotine and saline for these positive subjective ratings, but did not dissociate between the lower and higher nicotine doses. However, on some measures women were more nicotine-responsive than men. For example, a sex by dose interaction for subjective anxiety showed a greater effect of nicotine doses in females compared with males, and a sex by dose interaction for heart rate showed greater nicotine dose-related increases in females than males. When looking in more detail at the menstrual phase effects, the general pattern with subjective ratings showed that the sex differences in subjective ratings may have arisen more from the females in the luteal phase because females in the follicular phase showed more similarities with male subjective ratings. For example, within females, those in the luteal phase reported diminished positive effects (eg, ‘I feel good’, ‘I feel high’), in response to IV nicotine at 0.5 and 1.0 mg per 70 kg body weight doses compared to follicular phase females. Furthermore, luteal-phase females, relative to those in follicular-phase, showed less abstinence-related cognitive decrements (ie, better cognitive performance) on a measure of sustained attention.

The findings of the DeVito et al study contribute to a growing body of work demonstrating that males and females respond differently to nicotine. It is important to note that the DeVito study findings are based on an IV administration procedure that assessed nicotine’s effects in the absence of stimuli that are associated with tobacco product use but not directly related to nicotine dose. The lack of other smoking-related cues may be a particular strength of the IV nicotine paradigm in investigating sex-sensitive dose responses, given the possibility of sex differences in reactivity to smoking-related cues versus nicotine-sensitivity.⁶⁹ In addition, the precise dosing achieved with the IV procedures was important for detecting sex and menstrual phase differences in nicotine’s dose-dependent effects. These significant sex and menstrual cycle phase differences warrant consideration during the development of tobacco control policies that involve nicotine reduction. It is of high public health relevance that any regulation of cigarettes aimed at improving health outcomes has carefully considered the potential for differential impacts on males and females and has considered ways to optimize for each.

IMPLICATIONS FOR TOBACCO REGULATION

Developing more effective approaches to reduce the negative health effects of tobacco products continues to be a top public health priority. The Family Smoking Prevention and Tobacco Control Act gave the FDA authority to pursue several new approaches, including a nicotine reduction strategy, that hold promise for reducing the harm associated with tobacco products. Effective strategies focused on nicotine reduction or on other ingredients that may modify nicotine’s effects need to be empirically supported by carefully controlled studies on nicotine’s dose-dependent effects on reinforcement in humans. IV administration is among the few pure nicotine delivery systems that can achieve the precise, reproducible dosing that is necessary for evaluating dose-dependent effects of nicotine in humans. The effects of nicotine by IV delivery, in contrast to other nicotine delivery systems (eg, EC and tobacco cigarettes), can be observed in the absence of sensory stimuli (eg, taste, olfactory or visual stimuli) that are often paired with tobacco product use, but not directly related to nicotine dose. IV nicotine, unlike several other nicotine delivery devices (eg, nasal spray, gum),

induces subjective effects and behavioral reinforcement (ie, self-administration) similar to cigarettes; this distinction is of crucial value when considering methods to test reinforcement thresholds for regulatory purposes. While IV nicotine does not fully mimic nicotine delivered by tobacco products, IV nicotine will be important for establishing benchmark values for nicotine's reinforcing effects. These benchmark values will be important for evaluating the addictive threshold of nicotine in tobacco products. A strength of the IV approach is in determining the nicotine dose response function and how factors like sex or genetic variation alter the impact of nicotine dose on outcomes related to reinforcement. Extending these findings with studies on smoking behaviors and tobacco product usage will fully inform regulatory science.

It will be important to characterize how individual differences affect the response to different nicotine levels, so that the regulatory policies that are under development have the greatest public health benefit. Individual differences may be particularly important when setting a target threshold for nicotine reduction. In this regard, sex, co-occurring mental health disorders, genetic vulnerability to tobacco smoking and sensitivity to the aversive effects of nicotine are among the important individual differences to consider. The precise dosing achieved with IV administration can help characterize important individual differences in nicotine's dose-dependent effects that could help shape regulatory policies.

In summary, there are several promising new regulatory strategies under consideration that may help reduce the negative health effects of tobacco product use. IV nicotine administration procedures are effective tools for examining the dose-dependent effects of nicotine in humans and these procedures will inform tobacco regulatory science to facilitate the development effective regulatory policy.

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Figure 1.

Sex differences in the reinforcing effects of low doses of intravenous nicotine. IV nicotine self-administration was negatively correlated with nicotine dose among males (N=12) but not females (N=14). The mean ($\pm$ SEM) value at each dose is shown. Reprinted with permission from Jensen et al.⁶⁵

Figure 2.

Individual differences in sensitivity to the aversive effects of nicotine. Subjects with the rs16969968 A-allele (grouped as A-carrier, $N = 59$) had a blunted response to the aversive effects IV nicotine compared to smokers with the rs16969968 G-allele ($N = 133$). The right panel summarizes the aversive effects induced by each dose of nicotine relative to saline for each genotype group, GG ($N = 133$), AG ($N = 53$) and AA ($N = 6$). *** $p < .05$. Modified and reprinted with permission from Jensen et al.⁷¹

Figure 3.

Sex- and menstrual phase differences in the acute response to intravenous nicotine. (A) Males (N=115) reported greater dose-related increases in feel “stimulated” compared to females (N=45). (B) Females in the follicular phase (N=29) reported greater dose-related increases in feel “high” compared to females in the luteal phase (N=16). (C) Females reported greater dose-related reductions in anxiety and (D) more dose-related increases in heart rate compared to males. * $p < .05$, main effect of sex or phase; † $p < .05$ sex-by-dose or phase-by-dose interaction. Modified and reprinted with permission from DeVito et al.⁸⁰