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Status and Future Directions of Preclinical Behavioral Pharmacology in Tobacco Regulatory Science

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Abstract

Behavioral pharmacology is a branch of the experimental analysis of behavior that has had great influence in drug addiction research and policy. This paper provides an overview of recent behavioral pharmacology research in the field of tobacco regulatory science, which provides the scientific foundation for the Food and Drug Administration Center for Tobacco Products (FDA CTP) to set tobacco control policies. The rationale and aims of tobacco regulatory science are provided, including the types of preclinical operant behavioral models it deems important for assessing the abuse liability of tobacco products and their constituents. We then review literature relevant to key regulatory actions being considered by the FDA CTP, including regulations over nicotine and menthol content of cigarettes, and conclude with suggesting some directions for future research. The current era of tobacco regulatory science provides great opportunities for behavioral pharmacologists to address the leading cause of preventable death and disease worldwide.

Keywords

Behavioral Pharmacology; Tobacco; Nicotine; Regulatory Science; Policy

Behavioral pharmacology is a branch of the experimental analysis of behavior (EAB) that weds the fundamental concepts, methods, and measures of EAB and traditional pharmacology to explain the behavioral effects of drugs. The specific features of behavioral pharmacology have been thoroughly discussed by others and will not be covered in depth here (Branch, 1991; Poling & Byrne, 2000; Thompson & Pickens, 1971; Thompson & Schuster, 1968). Briefly, behavioral pharmacologists consider the behavioral effects of drugs of interest in their own right, not as a sign or symptom of underlying central nervous system (CNS) function. The methodology involves intensive study of relatively few subjects, usually using within-subject designs, direct and repeated measures of behavior, experimental rather than statistical control of extraneous variability, and preference for visual over inferential statistical analysis to detect drug effects (Poling & Byrne, 2000). From traditional

pharmacology, behavioral pharmacologists recognize that drugs have multiple effects that are dose dependent and emphasize the importance of obtaining dose-response curves to fully understand drug effects. They also carefully consider the pharmacokinetics of a drug (levels in blood and brain, and rate of absorption, distribution, metabolism, and excretion) in the design and interpretation of experiments.

The influence of behavioral pharmacology on our understanding of behavioral effects of drugs is vast. Although behavioral pharmacology began with a primary focus on how drugs interact with operant and respondent behavioral processes (i.e. behavioral mechanisms of drug action), its concepts and methods have been increasingly applied to elucidate genetic, molecular, and neural mechanisms of drug effects (Barrett & Sanger, 1991; Henningfield, Buchhalter, & Fant, 2016; van Haaren, 1993). The influence of behavioral pharmacology is evident in the widespread adoption of the concept that drugs serve as environmental stimuli that control behavior in the same ways as other types of stimuli, particularly with respect to their roles as positive reinforcers and discriminative stimuli in the development and persistence of drug abuse (Thompson & Pickens, 1971; Wise, 1987). In addition, government agencies like the FDA and Drug Enforcement Agency (DEA) rely on behavioral pharmacology research to regulate medications, controlled substances, and tobacco products with respect to their safety, efficacy, and abuse potential, and specifically request use of procedures developed by behavioral pharmacologists (Food and Drug Administration, 2010). In a previous issue of this journal, Henningfield et. al. (2016) provided an excellent illustration of this in a historical account of how behavioral pharmacology contributed to the now generally accepted notion that nicotine is addictive and the subsequent authority given to the Food and Drug Administration (FDA) to regulate tobacco products.

The aim of this review is to build upon the review of Henningfield et. al. (2016) by providing an overview of more contemporary research addressing some of the current regulatory issues facing the FDA Center for Tobacco Products (CTP). The primary focus is on findings from nonhuman research, but studies in humans are also covered to provide relevant context. It is not meant to be a comprehensive review of the tobacco regulatory science literature, which is already provided by several excellent reviews (Carter et al., 2009; Donny et al., 2012; Hatsukami et al., 2007; Hatsukami, Perkins, et al., 2010b; Smith et al., 2017). One purpose of this paper is to introduce research in this area to behavior analysts with an interest in behavioral pharmacology, but who may not keep abreast of the tobacco addiction literature. Another purpose is to suggest that behavior analysts have an opportunity to make a unique contribution to the science base supporting policies that could have an enormous positive impact on public health. We begin with briefly describing the scope of the FDA's authority under the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act, TCA), the duties of the CTP and Tobacco Product Scientific Advisory Committee as mandated by the TCA, and the types of preclinical behavioral models it deems important with respect to assessing the abuse liability of tobacco products. We then review literature relevant to key regulatory actions being considered by the FDA CTP, and conclude with suggesting some directions for future research.

Tobacco Regulatory Science

Scope of the TCA

Passed in 2009, the TCA is the law that provides the FDA authority to regulate tobacco products. The CTP is the division of the FDA charged with enforcing the law (Ashley & Backinger, 2012). The goal of the TCA and current mission of the FDA CTP is to reduce tobacco associated death and disease by reducing the prevalence of tobacco use and the toxicity of tobacco products. The broad provisions of the TCA include regulating the manufacturing, marketing, and distribution of tobacco products. With respect to manufacturing, the FDA CTP can now set standards for the design and content tobacco products, including reduced nicotine content/yields (but not to zero), if deemed appropriate for protection of public health (Donny et al., 2014). The FDA is also required to examine new products to determine if they are “substantially equivalent” to current products, or whether they pose a new or increased threat to public health (Berman et al., 2015). One of the first steps in this process is to identify Harmful and Potentially Harmful Constituents (HPHCs), which are chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to users or nonusers (CTP, 2014). HPHCs must be measured and reported for all tobacco products by industry. HPHC data are essential to FDA CTP tobacco regulatory efforts because they are used for identifying constituents that may require product standards, determining whether a new product is substantially equivalent to a currently marketed product, and informing the public on the risks of tobacco use. Constituents on this list are associated with the major adverse health effects of tobacco use, including known or potential human carcinogens, chemicals with adverse respiratory or cardiovascular effects, developmental or reproductive toxins, chemicals banned in food, and chemicals with abuse liability. Because they moderate tobacco use, addiction-related HPHCs are unique in that they also mediate degree of exposure to other HPHCs (e.g., carcinogens). Currently, only four addiction-related HPHCs are included on the FDA’s full list of 93 HPHCs (nicotine, nornicotine, anabasine, acetaldehyde), of which only two (nicotine and acetaldehyde) are included on an abbreviated list of 20 HPHCs that must currently be reported by industry. The FDA is required to periodically review the HPHC list based on emerging scientific data and revise it accordingly. Given the logistical and ethical challenges to studying potentially harmful chemical in humans, this area is arguably the one in which preclinical behavioral pharmacology can make the most critical contributions.

Role of the Tobacco Products Scientific Advisory Committee (TPSAC)

Duties—The TCA mandates establishment of the TPSAC, which provides advice, information, and recommendations related to regulation of tobacco products to assist the FDA Commissioner and the CTP in their rulemaking and enforcement of the TCA (Food and Drug Administration, 2009). TPSAC submits reports evaluating the safety, toxicity, dependence, and other health issues related to tobacco products. The five disease outcomes of most interest are cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction (Food and Drug Administration, 2012). For example, the TPSAC submitted a report in 2011 that reviewed the scientific literature on the impact of menthol on initiation of tobacco use in adolescents, level of tobacco dependence, difficulty quitting, and disease risk, among other issues (TPSAC, FDA, 2011). TPSAC also evaluates

applications submitted by manufactures that claim to have reduced toxicity or addiction risk (Modified Risk Tobacco Products [MRTPs]) and assists with developing guidance documents that make recommendations to manufacturers on the types of procedures and data that should be used to evaluate their products.

Operant models recommended by TPSAC for abuse liability assessment—One of the TPSAC’s mandates under the TCA is to establish and revise the list of HPHCs mentioned above. Regarding addiction-related HPHCs, there must be evidence of at least two measures of abuse liability. Among other criteria, TPSAC recommends four measures that can be obtained using operant behavioral procedures in nonhuman models; CNS effects, drug discrimination, drug self-administration, and signs of withdrawal (Food and Drug Administration, 2012). These recommendations are in accordance with the Institute of Medicine’s report advocating the use of preclinical models to for tobacco product evaluation (Stratton, Shetty, Wallace, & Bondurant, 2001). Nonhuman models are vital for evaluating tobacco products because they allow a) examination of critical phenomena that cannot be studied experimentally in humans (e.g., initiation of tobacco use in adolescents, a key FDA priority), b) isolation of the role of nicotine and other tobacco constituents from other factors (e.g., taste, social factors, polydrug use, co-morbidities), c) premarket screening of novel tobacco constituents/formulations to avoid human exposure to compounds that may increase abuse liability or toxicity, and d) control over history of drug intake. These models are the primary focus of this review. They are each briefly described next with an example of some relevant findings to tobacco regulatory science.

Drug discrimination: Initially used extensively by Overton (Overton, 1991) and later developed into its popular form by Harris and Balster (Harris & Balster, 1971), the drug discrimination procedure involves establishing a drug as a discriminative stimulus. In nonhumans for example, this involves differentially reinforcing (e.g. with food) one response (e.g. right lever press) in the presence of the drug (e.g. the interoceptive effects following nicotine administration) and reinforcing a different response (e.g. left lever press) in the absence of drug (i.e. vehicle administration). If this results in the subject emitting the drug-associated response more often following drug administration and emitting the vehicle-associated response more often following vehicle administration, then it can be concluded that the interoceptive stimulus arising from drug administration is serving as a discriminative stimulus. To the extent that substituting a different drug for the training drug evokes the same response, it indicates that drug produces similar interoceptive effects (i.e. that their effects “feel” similar). This model has proven useful for determining whether non-nicotine constituents in tobacco produce interoceptive effects similar to nicotine and potentially contribute to the abuse liability of tobacco products. For example, some minor alkaloids in tobacco, such as nornicotine and anabasine, can evoke nicotine-associated responding in nonhumans trained to discriminate nicotine from saline, indicating that minor alkaloids may contribute to the subjective effects of tobacco use (Caine et al., 2014; Smith & Stolerman, 2009). This finding served, in part, as the basis for placing these constituents on the list of HPHCs (Hoffman & Evans, 2013).

Drug self-administration—Initially developed by Weeks (Weeks, 1962), Thompson and Schuster (Thompson & Schuster, 1964), and Yanagita (Yanagita, Deneau, & Seevers, 1963), drug self-administration in nonhumans involves making the delivery of a drug (e.g. via the intravenous route) contingent upon a response (e.g. a lever press on a Fixed-Ratio [FR] 1 schedule). If this contingency results in a selective increase in the rate of that response rather than a nonspecific increase in all activities, and that response extinguishes when drug is withdrawn, it is evidence that the drug is serving as a reinforcer. Many of the drugs that serve as reinforcers in nonhumans (e.g. nicotine, cocaine, heroin) are abused in humans, which is why drug self-administration is considered by the FDA and Drug Enforcement Agency (DEA) to be the gold standard model for assessing the abuse liability of drugs (Ator & Griffiths, 2003). Accordingly, data showing that nornicotine is self-administered in rats provided another basis for the FDA CTP to place this constituent on the list of HPHCs (Hoffman & Evans, 2013).

Reliable drug self-administration under a low FR schedule, while providing evidence that a drug serves as a reinforcer, does not necessarily quantify the reinforcing efficacy or abuse liability of a drug relative to other drugs of abuse. Pharmacokinetic and pharmacodynamic factors (e.g., drug metabolism, unit dose, receptor affinity, etc.) have a substantial impact on the level of drug consumption and potential for non-specific side effects. As a result, relative rate of responding under low FR schedules may not always be indicative of relative abuse liability unless the schedule parameters take these factors into account (e.g. use appropriate timeout durations). Behavioral pharmacologists have employed various other operant paradigms to scale the abuse liability of drugs, including: a) breakpoints under progressive-ratio (PR) schedules, b) elasticity of demand (i.e. resistance of consumption to increases in unit price) in behavioral economic models (see below) and c) drug preference under concurrent availability. Generally, drugs that maintain higher breakpoints, exhibit less elasticity of demand and are more preferred are considered to have greater reinforcing efficacy and thus, greater abuse liability (Ator & Griffiths, 2003; Hursh, 1991; Johanson & Schuster, 1975; Stafford, LeSage, & Glowa, 1998).

Intracranial self-stimulation (ICSS)—Although any drug that alters operant behavior besides discrimination and self-administration might be a sign of CNS effects, ICSS is a model that provides measures particularly relevant to abuse liability. As first reported in seminal work by Kornetsky and colleagues (Kornetsky & Esposito, 1979; Kornetsky, Esposito, McLean, & Jacobson, 1979), acute injection of low to moderate doses of nicotine and other drugs of abuse lowers the minimal (i.e., threshold) stimulation intensity that maintains operant responding for electrical brain stimulation (e.g. typically via electrodes implanted into the lateral hypothalamus). This phenomenon is thought to reflect the ability of drugs to enhance the function of brain reinforcement systems and increase the reinforcing effects of non-pharmacological sensory stimuli (Caggiula et al., 2009; Harrison, Gasparini, & Markou, 2002; Huston-Lyons & Kornetsky, 1992; Wise, 2002). At high doses, acute injection of nicotine and other drugs increase ICSS thresholds, indicating that they produce aversive effects or anhedonia (diminished effectiveness of reinforcing stimuli (C. D. Fowler, Lu, Johnson, Marks, & Kenny, 2011; Kenny, Polis, Koob, & Markou, 2003; Spiller et al., 2009)). This ability of nicotine to enhance or attenuate the function of brain reinforcement

pathways may influence initiation and maintenance of tobacco use (Donny et al., 2003; Laviolette & van der Kooy, 2003; Liu, Palmatier, Caggiula, Donny, & Sved, 2007; Sellings, Baharnouri, McQuade, & Clarke, 2008; Wilmouth & Spear, 2004). Based on the work by Markou and colleagues, ICSS has also become the leading preclinical approach for measuring the sign of anhedonia during withdrawal from chronic exposure to nicotine and other abused drugs (Cryan, Bruijnzeel, Skjei, & Markou, 2003; Epping-Jordan, Watkins, Koob, & Markou, 1998; Markou & Koob, 1991; Watkins, Koob, & Markou, 2000a; Watkins, Stinus, Koob, & Markou, 2000b). ICSS can therefore be used to evaluate compounds according to two of the FDA's criteria for addiction-related HPHCs (i.e., evidence of CNS activity, ability to elicit withdrawal effects (Food and Drug Administration, 2012). Recent work from our lab indicating that nornicotine and anabasine can produce acute reinforcement-enhancing effects (i.e. decrease ICSS thresholds) in the ICSS model supports their inclusion on the list of HPHCs (Harris, Tally, Muelken, et al., 2015a).

Regulatory Issues Being Addressed

Product Standards Currently Being Considered for Tobacco Constituents

Nicotine Regulation—One of the leading concerns of the FDA CTP is the level of nicotine in tobacco products. Although several factors are important contributors to tobacco use (e.g., sensorimotor stimuli, other smoke constituents), the primary role of nicotine's reinforcing effects is well established (Benowitz, 2008; Matta et al., 2007; Stoleran & Jarvis, 1995). Nicotine content is therefore a logical target for setting tobacco product standards. Indeed, reducing the nicotine content in tobacco products to the point where cigarettes are no longer reinforcing was proposed decades ago as a regulatory strategy to reduce population-wide tobacco use (Benowitz & Henningfield, 2013; Henningfield et al., 1998; 2004; Henningfield, London, & Benowitz, 1990; Kessler, 1994). The primary goal would be to reduce the nicotine content in cigarettes to a level that would be below the threshold for producing reinforcing effects (i.e., the nicotine reinforcement threshold (Sofuoglu & LeSage, 2012)) in adolescents experimenting with tobacco in order to prevent development of addiction. As such, tobacco regulation would be a novel approach to smoking prevention in adolescents, which is important given that smoking is almost always initiated during adolescence and the effectiveness of current smoking prevention programs is limited (Thomas, McLellan, & Perera, 2013). Another goal of reducing the nicotine content in cigarettes below the nicotine reinforcement threshold is to facilitate smoking cessation or reduction among established smokers. On July 28 2017, the FDA announced its intention to issue an Advanced Notice of Proposed Rulemaking to seek input on the public health benefits and potential adverse effects of reducing the nicotine content in cigarettes (Food and Drug Administration, 2017). In order to provide the science base for the deliberation and rulemaking, a priority of the FDA CTP and the NIH Tobacco Regulatory Science Program (TRSP) has been to fund research to determine the nicotine reinforcement threshold and the impact of nicotine reduction on tobacco use (<https://www.fda.gov/TobaccoProducts>; <https://prevention.nih.gov/tobacco-regulatory-science-program>).

In order to set a nicotine standard below the reinforcement threshold, the FDA CTP needs data from smoke or nicotine self-administration studies that use a dose range wide enough to

determine a non-reinforcing dose (Sofuoglu & LeSage, 2012). Currently, the dose ranges used in human studies is not sufficient to precisely estimate the nicotine reinforcement threshold. Despite decreasing nicotine intake and level of nicotine dependence, reducing the nicotine content in cigarettes down to less than 0.3 mg/cigarette (a level comparable to so-called “denicotinized” cigarettes) has produced, at most, a 33–50% reduction in cigarettes per day (CPD) over six to 12 weeks (Donny et al., 2015; Donny, Houtsmuller, & Stitzer, 2007; Hatsukami, Kotlyar, et al., 2010a). Given that these cigarettes are capable of maintaining substantial rates of smoking, the nicotine levels in them may still be above the reinforcement threshold for many individuals. Some studies have examined the dose-response curve for intravenous nicotine self-administration in humans, but only reinforcing doses were studied or the dose ranges that encompassed a threshold reinforcing dose has been inconsistent between studies and varied by sex (Goodwin, Hiranita, & Paule, 2015; Jensen, DeVito, Valentine, Gueorguieva, & Sofuoglu, 2016; Sofuoglu, Yoo, Hill, & Mooney, 2008). Therefore the nicotine reinforcement threshold for tobacco products in humans remains unclear.

Nonhuman research that explicitly addresses nicotine regulation issues has only recently begun. Older studies typically did not use a dose range wide enough to allow identifying a threshold. Additionally, many of these studies manipulated dose across groups rather than within-subjects, which more closely models the impact of a nicotine reduction policy on current smokers. More recently, Smith et al. (Smith et al., 2013) reported that, regardless of the form of dose reduction in a 1hr-access model (i.e., gradual versus immediate), doses equal to or below 0.00375 mg/kg were not reinforcing, whereas doses equal to or higher than 0.0075 mg/kg were. Similarly, Grebenstein et al. (Grebenstein, Burroughs, Zhang, & LeSage, 2013) reported a reinforcement threshold dose of 0.0032 and 0.0037 mg/kg in male and female rats, respectively, exposed to gradual dose reduction in an 23hr-access model. Grebenstein et al. (Grebenstein, Burroughs, Roiko, Pentel, & LeSage, 2015a) replicated this finding in a larger cohort of male rats, with a reinforcement threshold of 0.0033 mg/kg. All three studies showed marked variability between subjects, with some rats exhibiting extinction at doses as high as 0.015 mg/kg and others at doses as low as 0.001mg/kg. Although the nicotine dose range that maintains self-administration is similar across species, it is important to note that the purpose of nonhuman research is not to specify a particular nicotine standard for products. Rather, the goal is to identify factors that may moderate the effectiveness of a standard and warrant further study in humans (see (Donny et al., 2012) for further discussion).

A critical concern about nicotine regulation is that smokers would increase their tobacco use to compensate for the reduction in nicotine content, increasing their likelihood of contracting tobacco-related diseases. For example, smokers switching to cigarettes with reduced nicotine yield can show marked compensation (i.e., a change in nicotine intake that is proportionately less than the change in nicotine unit dose (Rose & Behm, 2004; Scherer, 1999) by changing their puff topography (e.g. taking bigger puffs) and increasing puff frequency. However, studies with reduced nicotine content cigarettes report little or no compensation (Benowitz et al., 2012; 2007; Donny et al., 2015; Hatsukami, Donny, Koopmeiners, & Benowitz, 2015). This may be because, in contrast to low yield cigarettes, they actually contain less nicotine and are not highly ventilated, making it harder to compensate (Benowitz & Henningfield,

2013). However, smokers can also be noncompliant in these studies by supplementing low nicotine content cigarettes with conventional cigarettes (Benowitz, Nardone, Hatsukami, & Donny, 2015), suggesting the degree of compensation in these studies may underestimate what would be observed if low nicotine cigarettes were the only ones on the market.

Few preclinical self-administration studies have specifically quantified compensation during nicotine dose reduction in nonhumans. Harris et al. (Harris, Pentel, & LeSage, 2009; Harris, Pentel, Burroughs, Staley, & LeSage, 2011) reported that, as in humans, compensation was partial (i.e., nicotine intake was below baseline) and associated with a considerable degree of individual variability following a 50% reduction in unit dose. Interestingly, while extinction of NSA elicited nicotine withdrawal (i.e. increased ICSS thresholds), the reduction in nicotine intake resulting from dose reduction was not sufficient to elicit withdrawal, suggesting that rats compensated enough to attenuate the evocative effect of nicotine withdrawal on ICSS. This is consistent with studies reporting only moderate or no withdrawal symptoms in humans smoking cigarettes with reduced nicotine yields or content (e.g., Benowitz et al., 2007). Grebenstein et al (Grebenstein et al., 2013; Grebenstein, Burroughs, Hernandez, & LeSage, 2015b) showed similar partial and variable compensation over the course of progressive reductions in nicotine dose, with the greatest compensation after an initial 50% reduction in dose and lesser compensation with each subsequent dose reduction.

Menthol Regulation—Another leading concern of the FDA CTP is the contribution of flavors and other additives to the initiation and maintenance of tobacco use. Menthol is an additive in tobacco products that is used to improve the flavor of tobacco and smoke, as well as reduce the harshness of smoke via its anesthetic effects. In 2013, the FDA published a comprehensive review of the scientific literature on the effects of menthol on tobacco use and disease risk (Food and Drug Administration, 2013). The review concluded that menthol is associated with increased initiation of smoking, greater signs of nicotine dependence, and greater difficulty quitting, and that menthol cigarettes likely pose a greater public health risk than non-menthol cigarettes. Consequently, the FDA issued an Advanced Notice of Proposed Rulemaking (<https://www.regulations.gov/docket?D=FDA-2013-N-0521>) and opened a docket for public input on potential regulatory options for menthol, including product standards and restrictions on sales and distribution. At the time of those deliberations, the available research addressing the effect of menthol on tobacco abuse liability was in humans. More recently, preclinical behavioral pharmacologists have shown that systemic injection of menthol, thus bypassing its peripheral sensory effects (i.e. taste, smell), can increase the reinforcing efficacy of nicotine in rats in a self-administration model (Biswas et al., 2016). Thus menthol may impact the abuse liability of tobacco products through its direct CNS effects (e.g. altered acetylcholinergic and monoaminergic neuronal structure and/or function in brain, AlSharari et al., 2015; Ashoor et al., 2013; Henderson et al., 2016) in addition to its peripheral sensory effects. Other evidence suggests it may alter the magnitude of nicotine reinforcement by changing nicotine pharmacokinetics (e.g. nicotine concentrations in brain, Abobo, Ma, & Liang, 2012; AlSharari et al., 2015). Given these findings, it will be important to fully characterize menthol's effects on the nicotine dose-response curve for self-administration to determine whether and to what extent it

lowers the nicotine reinforcement threshold. It is possible that the threshold differs between menthol and non-menthol products.

Identifying Other HPHCs for Potential Product Standards

Surveillance of isolated constituents—While the primary role of nicotine in tobacco dependence is well accepted, non-nicotine constituents may also contribute to tobacco dependence either directly or via an interaction with nicotine. For example, the minor alkaloid nornicotine produces several neurobiological and behavioral effects in rats that are similar to nicotine, including activation of the mesolimbic dopamine system and reinforcing effects, albeit with lower potency compared to nicotine (Bardo, Green, Crooks, & Dwoskin, 1999; Crooks & Dwoskin, 1997; Dwoskin, Buxton, Jewell, & Crooks, 1993; Dwoskin, Crooks, Teng, Green, & Bardo, 1999; Green, Phillips, Crooks, Dwoskin, & Bardo, 2000; Hoffman & Evans, 2013). While not as well studied, other minor alkaloids including anabasine, anatabine, and myosmine can also produce qualitatively similar effects as nicotine on certain behavioral and/or neurobiological measures (Caine et al., 2014; Clemens, Caillé, Stinus, & Cador, 2009; Goldberg, Risner, Stolermand, Reavill, & Garcha, 1989; Hall et al., 2014; Hoffman & Evans, 2013; Pratt, Stolermand, Garcha, Giardini, & Feyerabend, 1983; Stolermand, Garcha, & Mirza, 1995; Stolermand, Garcha, Pratt, & Kumar, 1984). In addition, the tobacco constituent acetaldehyde activates the mesolimbic dopamine system (Foddai, Dosia, Spiga, & Diana, 2004), is self-administered (Amit & Smith, 1985; Myers, Ng, & Singer, 1982; Takayama & Uyeno, 1985), and increases the reinforcing effect of nicotine in adolescent rats (Belluzzi, Wang, & Leslie, 2005). Monoamine oxidase (MAO) inhibitors, such as the beta-carbolines harmaline and norharmaline, are present in tobacco and tobacco smoke (Castagnoli et al., 2002; Khalil, Steyn, & Castagnoli, 2000; P. H. Yu & Boulton, 1987), and inhibit MAO activity in smokers (Fowler, Volkow, Wang, Pappas, Logan, MacGregor, et al., 1996a; Fowler, Volkow, Wang, Pappas, Logan, Shea, et al., 1996b; Hogg, 2016). Preclinical data also indicate that MAO inhibitors increase nicotine-induced dopamine release in the mesolimbic dopamine system (Villégier, Lotfipour, McQuown, Belluzzi, & Leslie, 2007) and enhance a variety of nicotine's behavioral effects, including reinforcement, discriminative stimulus effects, and withdrawal effects (Arnold, Loughlin, Belluzzi, & Leslie, 2014; Guillem et al., 2005; 2006; Guillem, Vouillac, Koob, Cador, & Stinus, 2008; Malin et al., 2013; Smith et al., 2016a; Villégier et al., 2007; Wooters & Bardo, 2007). While most of these studies have used commercially available MAO antagonists that are not present in tobacco or tobacco smoke (e.g., tranylcypromine), some have reported similar effects of the tobacco constituent norharmaline (Arnold et al., 2014; Guillem et al., 2006).

Product surveillance—All of the above studies in the previous section examined the effects of each constituent or class of constituents (i.e., alkaloids) in isolation from the thousands of other chemicals in tobacco products. While this approach is important for confirming that a given compound or class of compounds can be behaviorally active, it is not analogous to tobacco exposure in humans. The validity of the relationships between nicotine and isolated tobacco constituents must ultimately be examined in the context of exposure to other tobacco constituents to determine whether additional compounds interact to moderate

or oppose those relationships. Furthermore, the doses administered in many studies using isolated constituents are considerably higher than those delivered during actual tobacco use.

To address these issues, several studies have examined the addiction-related effects of extracts prepared from smokeless tobacco (ST), tobacco smoke, or electronic cigarette (EC) refill liquids. Because these formulations are derived from tobacco products, they contain nicotine and a clinically-relevant range of tobacco constituents (e.g., minor alkaloids). As such, these formulations more accurately simulate tobacco exposure in humans and could provide unique information on interactions among constituents. Our lab has found similar abuse liability for nicotine alone and nicotine dose-equivalent concentrations of two ST extracts and an EC refill liquid in terms of reinforcing effects in self-administration (SA) models and reinforcement-enhancing and aversive/anhedonic effects in an ICSS model, except that EC liquid produced less aversive/anhedonic effects at a high nicotine dose (LeSage, Burroughs, Muelken, & Harris, 2016a; LeSage, Staley, Muelken, Smethells, Stepanov, et al., 2016b). These findings suggest that any contribution of non-nicotine constituents to the abuse liability of ST and ECs is primarily through peripheral sensory (e.g. taste, smoothness) and/or pharmacokinetic mechanisms (e.g. nicotine absorption) rather than through their direct CNS effects. In contrast, others have shown that cigarette smoke extracts can produce greater addiction-related neurobiological and behavioral effects than nicotine alone under certain conditions (e.g., (Brennan, Laugesen, & Truman, 2014; Brennan, Putt, & Roper, 2013a; Costello et al., 2014; Danielson, Putt, Truman, & Kivell, 2014; Lee et al., 2016; Touiki, Rat, Molimard, Chait, & de Beaupaire, 2007), which may reflect higher levels of addiction-relevant constituents in smoke extracts or the presence of constituents not found in non-combustible tobacco products.

Some Suggestions for Future Preclinical Research

Individual differences: the need for “targeted tobacco regulatory science”

Estimation of the population variability in response to tobacco product standards needs to be a key focus of future research. A standard that reduces the addictiveness of a tobacco product in the general population might still support initiation and maintenance of use in more vulnerable subpopulations. Therefore, in order to achieve the greatest net population reduction in smoking and improvement in public health, a guiding principle for future tobacco regulatory science should be to target the needs of vulnerable subpopulations (Zeller, 2013). Under this rubric, “targeted tobacco regulatory science” on nicotine and other standards for tobacco products should utilize vulnerable subpopulations to determine their potential impact on relative risk for addiction. Future preclinical studies can address this issue by studying the impact of factors related to key vulnerabilities to initiation of tobacco use or difficulty quitting. The factors discussed below have been shown to influence smoking or nicotine self-administration in humans, yet very little tobacco regulatory research per se has been done on them.

History of nicotine intake—Baseline nicotine intake may be a useful predictor of whether smokers will be more resistant to tobacco control policies and need other interventions to help them quit or reduce their smoking. Quit rates are typically lower in

heavy smokers (Abrams, Herzog, Emmons, & Linnan, 2000; Borland, Yong, O'Connor, Hyland, & Thompson, 2010), suggesting they may have a lower reinforcement threshold for nicotine and be more likely to continue smoking reduced nicotine cigarettes. In addition, some studies report that smokers who normally smoke intensely or have higher baseline nicotine intake exhibit less compensation when switching to lower nicotine yield cigarettes (Benowitz, Jacob, Kozlowski, & Yu, 1986), suggesting they may have a lower risk of this potential side effect of nicotine reduction policy. The few nonhuman studies that have examined these issues in rat self-administration models have found that, although baseline nicotine intake was not predictive of the nicotine reinforcement threshold, higher baseline nicotine intake predicted less compensation following dose reduction (Greibenstein et al., 2015a; Harris et al., 2009). Further nonhuman research is important to examine the generality of these relationships and whether baseline nicotine intake might be predictive of responses to other forms of tobacco control policies (see Harris, Burroughs, Pentel, & LeSage, 2008).

Age—Adolescence is generally considered a period of greater vulnerability to substance abuse disorders, including tobacco addiction (Adriani & Laviola, 2004). It is well established that the majority of smokers begin smoking and can quickly become nicotine dependent during adolescence (Difranza et al., 2002; O'loughlin et al., 2003). Several nonhuman studies have also shown that adolescent rats and mice are more sensitive than adults to the reinforcing effects of nicotine (Adriani, Macri, Pacifici, & Laviola, 2002; Chen, Matta, & Sharp, 2007; Kota, Martin, & Damaj, 2008; Levin et al., 2007; Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003; Natividad, Torres, Friedman, & O'Dell, 2013), although others have not (Gellner, Belluzzi, & Leslie, 2016; Shram, Funk, Li, & Lê, 2008). To date, little is known about how age might moderate the impact of tobacco product standards. One study has shown that adolescent rats exhibit lower rates of self-administration at low unit doses compared to adults, suggesting that a nicotine standard that reduces the abuse liability of tobacco products in adult smokers may also do so in adolescents (Schassburger et al., 2016). Another study reported that adolescents may be more sensitive to the reinforcing effects of certain non-nicotine constituents (e.g. acetaldehyde), highlighting that product standards for those constituents should be set accordingly to protect this vulnerable population (Belluzzi et al., 2005). In contrast, another study showed that the reinforcing efficacy of an extract of a smokeless tobacco product was similar to nicotine alone in both adolescent and adult rats, suggesting that the CNS effects of non-nicotine constituents may not impact the abuse liability of smokeless tobacco products in either age group (LeSage, Burroughs, Muelken, & Harris, 2016a). Given that initiation of smoking in adolescents cannot be studied experimentally in humans, research in adolescent nonhumans will be critical to address regulatory questions relevant to this subpopulation (e.g. abuse liability of isolated constituents or novel formulations).

Sex—Sex differences in smoking/nicotine self-administration have been reported in humans (Goodwin et al., 2015; Perkins, 2009). Women tend to be less sensitive to the discriminative stimulus, subjective, and reinforcing effects of nicotine (Perkins, 2009; Perkins, Donny, & Caggiula, 1999). However, they exhibit greater responsiveness to smoking-paired cues (Perkins, 1996), and less success in quitting smoking (Perkins, 2001). Moreover, some

studies show that female adolescents, in particular, develop early milestones of addiction (e.g., cravings, tolerance, monthly smoking) faster than males, although incidence rates of later milestones (e.g., daily smoking, ICD-10 dependence) may be similar to males (DiFranza et al., 2002; DiFranza et al., 2007; Gervais, O'Loughlin, Meshefedjian, Bancej, & Tremblay, 2006). Several preclinical studies in rats have also shown faster acquisition of NSA at lower doses, higher baseline intake, higher breaking points under PR schedules, and greater resistance to extinction in females than males (Chen et al., 2007; Donny et al., 2000; Feltenstein, Ghee, & See, 2012; Grebenstein et al., 2013; Levin et al., 2003; Lynch, 2009; Sanchez, Moore, Brunzell, & Lynch, 2013, but see Swalve, Smethells, & Carroll, 2015).

Gaining a better understanding of sex differences in the abuse liability of tobacco products, nicotine, and non-nicotine constituents is important for predicting how men and women might react differently to tobacco control policies and may be at differential risk for their side effects. For example, preclinical studies have shown that, despite no difference in the nicotine reinforcement threshold or elasticity of demand, male rats exhibited significantly greater compensatory increases in NSA during dose reduction compared to females (Grebenstein et al., 2013). This is consistent with the lower sensitivity of women to changes in cigarette nicotine content and suggests that males may be a greater risk of compensation if a nicotine reduction policy was implemented. Whether females may be more or less sensitive to abuse-related effects of non-nicotine tobacco constituents is largely unknown, but one study showed that higher rates of self-administration of a nicotine/acetaldehyde mixture were sustained from early adolescence into adulthood in females compared to males (Park, Belluzzi, Han, Cao, & Leslie, 2007). More generally, inclusion of both sexes in future studies is important to better capture the heterogeneity of participants in human studies, as well as the general population of smokers.

Nicotine pharmacokinetics—Nicotine metabolism may moderate smokers' responses to tobacco control policies. Individuals with faster metabolism (i.e. nicotine elimination) typically smoke more cigarettes per day and are less successful at quitting (Benowitz, 2008; Benowitz, Pomerleau, Pomerleau, & Jacob, 2003; Chenoweth, O'Loughlin, Sylvestre, & Tyndale, 2013; Schnoll et al., 2014; Schnoll, Wileyto, Leone, Tyndale, & Benowitz, 2013). A faster decrease in plasma nicotine levels after a cigarette could increase the rate of smoking by shortening the duration of nicotine deprivation needed (i.e. time to reach low plasma nicotine levels) to evoke smoking the next cigarette. This could reduce the reinforcing effects of low nicotine content cigarettes (i.e., increase the reinforcement threshold) and induce greater compensatory increases in smoking. To our knowledge, only one human study has examined the relationship between nicotine metabolism and compensation while smoking reduced nicotine content cigarettes, and no correlation was found (Bandiera et al., 2015). In the few preclinical studies that have examined this, nicotine clearance was not associated with compensatory NSA in rats after a 50% reduction in dose (Harris et al., 2009). However, faster nicotine clearance was associated a lower reinforcement threshold, greater compensation, but also less elastic demand in adult rats exposed to larger reductions in nicotine dose (Grebenstein et al., 2015a). These findings suggest that smokers with fast nicotine clearance are at greater risk of compensatory smoking and overall persistence of smoking when the cigarette nicotine content is reduced.

To date, no preclinical studies have been reported that examined the relationship between nicotine clearance and the reinforcement threshold for acquisition of NSA in adolescents. Interestingly, some human studies suggest that slower nicotine clearance is associated with faster development of tobacco dependence in adolescents, suggesting slow nicotine clearance may be associated with a lower reinforcement threshold for acquisition of NSA (Karp, O'loughlin, Hanley, Tyndale, & Paradis, 2006; Rubinstein et al., 2013). This presumably would be due to prolonged presence of higher brain nicotine concentrations at low nicotine doses, resulting in a higher magnitude (or longer duration) of reinforcement. It maybe that fast nicotine metabolizers are a vulnerable subpopulation in one context (maintenance in adults) but not in another (initiation in adolescents), but further research is needed to confirm this.

Psychiatric comorbidities—A chief limitation of preclinical studies on reduced nicotine content cigarettes in humans is that they have largely been conducted in healthy adult volunteers, excluding individuals with psychiatric or medical comorbidities that may increase vulnerability to tobacco addiction. (but see Tidey et al., 2016b; Tidey, Rohsenow, Kaplan, Swift, & AhnAllen, 2013). Because many smokers have some form of comorbidity (Lasser et al., 2000), any nicotine standard based on data in healthy volunteers may not apply to a large number of smokers. Currently, no preclinical studies have examined tobacco regulatory issues (e.g. nicotine reinforcement threshold) in nonhuman models of smoking comorbidities (e.g. schizophrenia, depression, obesity). However, some studies suggest that alcohol can enhance nicotine self-administration in adult rats, suggesting that alcoholics may be more likely to smoke low nicotine content cigarettes (Hauser et al., 2012; Lê, Funk, Lo, & Coen, 2014; Lê et al., 2010). Similar findings have been reported with an animal model of diabetes (O'Dell et al., 2013). Further work smoking comorbidities will be particularly important in nonhuman adolescents.

Expand research on non-nicotine tobacco constituents

Analyses of constituents in tobacco or tobacco smoke extracts used in behavioral studies have been limited to 2–3 compounds (Brennan et al., 2013a; Harris, Tally, Schmidt, et al., 2015b; Lee et al., 2016) or not conducted at all (Brennan, Putt, & Truman, 2013b; Costello et al., 2014; Gellner et al., 2016), preventing identification of the non-nicotine constituents contributing to any enhanced addiction-related effects of the extracts. This lack of chemical verification of extracts may also contribute to inconsistencies in detection of differences between effects of extracts and nicotine alone across studies (Costello et al., 2014; Gellner et al., 2016; Harris, Stepanov, Pentel, & LeSage, 2012; Harris, Tally, Schmidt, et al., 2015b). Characterization of a comprehensive range of non-nicotine constituents in extracts is necessary to gain insight into their potential contribution to differences in abuse liability between formulations, and help power future studies on the role of specific constituents or mixtures. Moreover, chemical confirmation of constituent levels in extracts could also lead to greater consistency in dosing and, in turn, their behavioral effects within and across studies.

Numerous non-nicotine constituents remain to be comprehensively evaluated for their potential role in tobacco addiction. Even though some have received considerable attention,

such as the minor alkaloids and menthol discussed above, it is still unclear to what extent they contribute to tobacco use, as well as the behavioral and pharmacological mechanisms through which they do so. Non-nicotine constituents could influence tobacco use through several stimulus functions. On the one hand, they could have unlearned stimulus functions as a primary reinforcer or unconditioned establishing operation for nicotine or other reinforcing constituents (e.g., nornicotine). On the other hand, they could have learned stimulus functions as conditioned reinforcers or discriminative stimuli. From a pharmacological standpoint, constituents could act on receptors in either the peripheral or central nervous system, or both.

Flavorants represent a class of constituents that may contribute to tobacco use via peripheral pharmacological mechanisms. However, few studies have incorporated oral delivery of flavorants in nicotine self-administration studies (Wickham et al., 2018). Examining the stimulus functions of flavorants is particularly important given the FDA CTP's interest in nicotine reduction. For instance, if a non-nicotine constituent is a particularly salient flavorant in a product, it may have considerable primary or conditioned reinforcing effects that engender and maintain use of that product despite a reduction in its nicotine content. It would be important to examine how the presence and absence of this flavor modulates the effects of reducing nicotine exposure (i.e. how it changes the nicotine reinforcement threshold), as concurrent standards for salient flavorants may be necessary to ensure the maximal net effectiveness of a nicotine reduction policy. Behavioral pharmacologists are well suited to study the stimulus functions of tobacco constituents and to examine how to modify those functions to facilitate effective policy.

Increase use of behavioral economic methods

The use of behavioral economic methods to assess the abuse liability of drugs and the effectiveness of interventions and public policies was originally proposed by Hursh (Hursh, 1984; 1991) over 25 years ago. However, while clinical researchers often use this approach to study tobacco abuse liability (Bickel, Marsch, & Carroll, 2000; DeGrandpre, Bickel, Higgins, & Hughes, 1994; M. W. Johnson & Bickel, 2003; Shahan, Bickel, Madden, & Badger, 1999; Tidey, Cassidy, Miller, & Smith, 2016a), preclinical research has only recently begun to utilize this paradigm to address tobacco regulatory issues (Grebenstein et al., 2015a; 2013; Smith, Rupperecht, Sved, & Donny, 2016b). Extending behavioral economics to tobacco addiction research in nonhumans is important because it provides a common conceptual and methodological framework to facilitate translation between preclinical studies, clinical trials, epidemiological studies, and public policy concerned with tobacco regulation. In the behavioral economic model, several factors can be collectively assessed, including demand intensity (i.e., the amount of consumption with free access [e.g., an FR 1]), breakpoint (i.e., the unit price where zero consumption occurs) and demand elasticity (i.e., the rate at which drug consumption decreases with increases in its unit price). Of these measures, demand elasticity is used as an overall metric for the abuse liability of a drug since it captures how sensitive drug consumption is to an increase in unit price (operationally defined as the cost/benefit ratio of response requirement divided by unit dose of drug). Recent preclinical research has shown that demand elasticity for nicotine may be a useful predictor of the nicotine reinforcement threshold during nicotine dose reduction in

rats, suggesting this measure may be useful for anticipating a smokers response to nicotine regulation (Greibenstein et al., 2015a). Studies comparing demand elasticity for nicotine alone versus extracts of commercial tobacco products (e.g. smokeless tobacco and ECs, LeSage, Burroughs, Muelken, & Harris, 2016a; LeSage, Staley, Muelken, Smethells, Stepanov, et al., 2016b) have not found differences, suggesting that non-nicotine constituents do not impact the CNS-mediated reinforcing effects of these products. However, a limitation of these studies is that demand elasticity of these nicotine formulations were examined in isolation and not under a concurrent choice situation, which more closely models human use.

Smokers have myriad choices within a vast marketplace of combustible and noncombustible products. Indeed, human studies have found that the abuse liability of tobacco products is not static and depend on the availability of substitutes (Johnson & Bickel, 2003; Johnson, Bickel, & Kirshenbaum, 2004). In contrast, only a few preclinical SA studies in the tobacco addiction field have examined choice between nicotine and an alternative drug or form of nicotine delivery, (Manzardo, Del Rio, Stein, & Belluzzi, 2001; Sorge & Clarke, 2009) and none have used a behavioral economic approach to examine the effect of a choice alternative on the demand elasticity of various nicotine formulations (i.e., extracts). This is surprising in light of the greater sensitivity of choice procedures over single-reinforcer procedures in animal research on other drugs of abuse (Wang, Brown, Grabowski, & Meisch, 2001; Ward, Morgan, & Roberts, 2004) and human research on the demand elasticity of tobacco products. (Johnson et al., 2004; Shahan et al., 1999). As such, the use of choice procedures in which rats have concurrent access to nicotine alone and either tobacco-product extracts or isolated constituents could provide a particularly sensitive approach for detecting effects of non-nicotine constituents on the abuse liability of tobacco. This approach could facilitate identification of novel addiction-related constituents by focusing on constituents that are particularly prevalent in tobacco products with greater abuse liability. It would also be a better model of human use and may help anticipate effects of setting standards on one product/constituent on consumption of other products.

Assess the interaction between policy and pharmacotherapy

Several medications are available to smokers for cessation that could also be used to assist them through the process of reducing nicotine levels in cigarettes (Henningfield, Fant, Buchhalter, & Stitzer, 2005). The goals of pharmacotherapy in this context are to attenuate potential withdrawal symptoms, minimize the degree of compensatory smoking, and increase the nicotine reinforcement threshold below which smoking cessation occurs, so that smokers quit earlier in the process. However, the ability of medications to increase the nicotine reinforcement threshold in smokers is unknown, as no studies have examined the effects of medications on smoking over the course of progressively reducing cigarette nicotine content to the point of extinguishing smoking. Effective medications for smoking cessation are a logical first choice for facilitating cessation or reduction under nicotine regulation interventions or policy. However, potentially critical differences between nicotine regulation strategies and cessation interventions are that regulation strategies a) allow continued ad lib smoking and b) would be imposed on many smokers who are unwilling or unable to quit. Because some medications have the unwanted effect of increasing ad lib

smoking or show little or no efficacy in reducing smoking in people not motivated to quit (Lerman et al., 2007), it is important to examine whether smoking cessation medications facilitate or impede smoking cessation or reduction in a nicotine regulation context (e.g. during nicotine dose reduction). Preclinical studies can help address this issue, particularly with respect to emerging novel pharmacotherapies.

Apply concepts and methods of behavioral toxicology

Behavioral toxicology is another branch of EAB that uses many of the same concepts and methodology as behavioral pharmacology. In contrast to behavioral pharmacology, its primary focus is on the deleterious behavioral effects of central nervous system toxins (e.g. venoms, pesticides, heavy metals, organic solvents, and other environmental contaminants). Major impetus for development of the field was provided by the Toxic Substances Control Act of 1976, under which new and existing commercial chemicals are regulated and assessed for adverse effects on the environment and health (Evans & Weiss, 1976). As such, behavioral toxicologists have dealt with many of the same types of regulatory issues as those being considered for tobacco. For instance, a key concern in behavioral toxicology is providing threshold estimates for setting chemical exposure standards, much like the current concerns faced by tobacco regulatory scientists in setting product standards for nicotine and other tobacco constituents. This task is fraught with conceptual, methodological, and analytical challenges (e.g. dependence of variance in threshold estimates on choice of model criteria), and tobacco regulatory scientists may benefit from following the lead of behavioral toxicologists in addressing them (Bogdan, MacPhail, & Glowa, 2001; Dews, 1986; Evans & Weiss, 1976; Glowa & Macphail, 1995; Weiss, 1985).

The research covered in this review has been focused on factors influencing the abuse liability of tobacco products, but other behavioral endpoints are also of interest. Some research suggests that smoking is a significant risk factor for cognitive decline and dementia (Baumgart et al., 2015; Toda & Okamura, 2016; Xu, Yang, & Shang, 2016). Although the mechanism for this is not well understood, the cardiovascular effects of both nicotine and non-nicotine constituents (e.g. carbonyl compounds) are thought to play a role (Toda & Okamura, 2016). In addition, some constituents have been shown to be developmental neurotoxins, such as the current generation of pesticides known as neonicotinoids (Abreu-Villaça & Levin, 2017; Rodgman & Perfetti, 2009). As the name implies, preclinical behavioral toxicology provides methods specifically intended for detecting the behavioral toxicity of chemicals. Behavioral toxicologists have adopted several operant procedures from the EAB and independently developed others that have proven sensitive to the effects of chronic low-level exposure to CNS toxins (e.g. changes in patterns of schedule-controlled behavior, repeated acquisition, (Krasnegor, Gray, & Thompson, 1986). These models may be useful for identifying HPHCs that might have adverse developmental effects in smokers.

Concluding Remarks

The concepts and methods of behavioral pharmacology have had an extensive influence on the development and current status of tobacco regulatory science. By offering state-of-the-art approaches to evaluating the addictiveness of tobacco products and modeling the effects of

proposed policies, it is also well positioned to further advance the field. Toward this end, behavioral pharmacologists should keep abreast of the FDA's needs. (Food and Drug Administration, 2017). The CTP regularly issues notices of proposed rulemaking and guidance documents that identify their research priorities and outline the type of information the agency expects to adequately address them. The notices on Premarket Tobacco Applications (PMTAs), Modified Risk Tobacco Products (MRTPs) applications, and reports to demonstrate Substantial Equivalence (SE) are some examples. They will also be finalizing guidance on how it intends to review PMTAs for electronic nicotine delivery systems (e.g. e-cigarettes). In addition, the agency assists industry in complying with federal tobacco regulations through online information, meetings, and webinars (see <https://www.fda.gov/TobaccoProducts>). There is great opportunity for behavioral pharmacologists, and behavior analysts in general, to thrive in this important field of research. The FDA has recently posted Funding Opportunity Announcements (FOAs) for several types of grants (e.g. center grants, various individual research projects) totaling approximately \$50 million dollars (<https://www.fda.gov/TobaccoProducts/PublicHealthScienceResearch/Research>). To facilitate success in seizing this opportunity, behavioral pharmacologists need to be aware of the distinction between basic science and regulatory science. The former places greater emphasis on innovative approaches to elucidating the mechanisms of drug action, while the latter relies on use of well-validated approaches to gather data to support or refute a specific regulatory action, without necessarily understanding the mechanisms involved (Donny et al., 2012). Success in addressing the FDA's needs (and obtaining funding) will require behavioral pharmacologists to take a different perspective from their more common focus on the behavioral mechanisms of drug action, as discussed earlier. Fortunately, the sister field of behavioral toxicology provides a wealth of information on how to accomplish this. Behavioral analysts are strongly encouraged to participate in tobacco regulatory research. Given that tobacco addiction is the leading cause of preventable death and disease worldwide, they would be hard pressed to find a more important cause to improve public health.

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