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Nonhuman Animal Models of Substance Use Disorders: Translational Value and Utility to Basic Science

Mark A. Smith

Department of Psychology Davidson College

Abstract

Background: The National Institute on Drug Abuse (NIDA) recently released a Request for Information (RFI) soliciting comments on nonhuman animal models of substance use disorders (SUD).

Methods: A literature review was performed to address the four topics outlined in the RFI and one topic inspired by the RFI: (1) animal models that best recapitulate SUD, (2) animal models that best balance the trade-offs between resources and ecological validity, (3) animal models whose translational value are frequently misrepresented or overrepresented by the scientific community, (4) aspects of SUD that are not currently being modeled in animals, and (5) animal models that are optimal for examining the basic mechanisms by which drugs produce their abuse-related effects.

Results: Models that employ response-contingent drug administration, use complex schedules of reinforcement, measure behaviors that mimic the distinguishing features of SUD, and use animals that are phylogenetically similar to humans have the greatest translational value. Models that produce stable and reproducible baselines of behavior, lessen the number of uncontrolled variables, and minimize the influence of extraneous factors are best at examining basic mechanisms contributing to drug reward and reinforcement.

Conclusions: Nonhuman animal models of SUD have undergone significant refinements to increase their utility for basic science and translational value for SUD. The existing literature describes numerous examples of how these models may best be utilized to answer mechanistic questions of drug reward and identify potential therapeutic interventions for SUD. Progress in the field could be accelerated by further collaborations between researchers using animals versus humans.

Keywords

addiction; animal; model; preclinical; substance use disorder; translational

Corresponding Authors: Mark A. Smith, Department of Psychology Davidson College Davidson, NC, 28035, masmith@davidson.edu.
Contributors: M.A. Smith developed the idea and wrote the manuscript.

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1. Background and Purpose

Substance use disorders (SUD) are defined as the recurrent use of alcohol and/or drugs in a manner that causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home (American Psychiatric Association, 2013). Recently, the National Institute on Drug Abuse (NIDA) published a Request for Information (RFI) asking for comments on nonhuman animal models of SUD (Notice Number: NOT-DA-19-036). The RFI affirmed that the use of animal models of SUD remains a critical part of NIDA's mission, but noted that no model fully captures the complexity of human drug use, and that underrecognized limitations of existing models may impede research progress. The stated intent of the RFI was to begin a conversation about the inherent strengths and weaknesses of existing animal models and how animal models may best be utilized to recapitulate human patterns of pathological drug use. To this end, NIDA requested comment on four specific topics:

1. Current animal behavioral procedure(s)/model(s) that BEST recapitulate human substance use/SUD, including the aspect(s) of substance use/SUD targeted by the/these procedure(s)/model(s)
2. Animal procedures/models of SUD that best balance the inherent trade-offs between resources and complexity/ecological validity
3. Animal procedures/models of SUD whose translational value are frequently misrepresented or overrepresented by the scientific community
4. Aspects of substance use/SUD that are NOT currently being modeled in animals and how current procedures/models could be adapted to overcome technical/logistic challenges and address this gap in the field

This review addresses these four topics by briefly describing the use of nonhuman animal models in substance abuse research and characterizing their translational value for SUD. When assessing translational value, both a model's face and predictive validity are considered. Because these models are also used by basic scientists investigating the underlying mechanisms controlling drug intake, the review will also address a fifth topic:

5. Current animal models that are optimal for examining the basic behavioral, pharmacological, and biological mechanisms by which drugs produce their abuse-related effects

Both a model's translational value and its utility to basic science are critical to understand human substance use and to develop effective interventions for the prevention and treatment of SUD. Generally, models that generate stable and reproducible baselines of behavior, minimize the number of uncontrolled variables, and reduce the influence of extraneous factors related to a subject's history are best at uncovering basic mechanisms contributing to drug reward and reinforcement, whereas those models that capture the complexity and dynamic changes that apparent over the course of SUD have greater translational value, even at the expense of losing some degree of experimental control. Regardless of their limitations,

all the models described in this review have significant scientific appeal for almost all substance abuse researchers.

2. Species as Models

One of the primary factors influencing the appeal of an animal model is the species of the subject. Generally, the desirability of an animal model is directly related to the degree to which a species is phylogenetically similar to humans. In regard to substance abuse research, organisms that retain the same critical features as humans tend to make the best models. These features could include common sets of genes and proteins, common neuroanatomical structures, or common behavioral processes related to motivated behavior. Several species have been used successfully to examine the neurobiological and behavioral effects of drugs that relate to drug use and addiction.

2.1. Invertebrates

Planarians, nematodes and insects (e.g., *Girardia tigrine*, *Caenorhabditis elegans*, *Apis mellifera*, *Drosophila*) that have well characterized nervous systems and fully sequenced genomes currently serve as excellent models for studying the functional roles that individual genes and proteins play in neurotransmission, including many of the genes and proteins that are involved in drug reinforcement and neuroplasticity (Amaning-Kwarteng et al., 2017; Dziedowiec et al., 2018; Engleman et al., 2016; Scholz and Mustard, 2013; Sjøvik and Barron, 2013). Their lack of vertebrate nervous systems and restricted behavioral repertoire limit their utility and translatability for behavioral models of neuropsychiatric disorders. Crayfish (*Orconectes rusticus*) are another increasingly popular invertebrate model that has some advantages over other invertebrate models due to their longer life span, more complex nervous system, and expanded behavioral repertoire (Huber et al., 2011; 2018; Imeh-Nathaniel et al., 2019; Shipley et al., 2017). Their translational value as a model of SUD remains to be determined.

2.2. Reptiles and Amphibians

Various reptiles and amphibians have been used in pharmacological and behavioral assays that have relevance to drug abuse; however, only a few studies have modeled aspects of drug reward or addiction (e.g., Presley et al., 2010). Although the brains of these organisms lack the complexity of the primate brain, enough similarity exists in structure and function that these organisms may be useful as models. Moreover, the basic learning and memory mechanisms that are responsible for drug use and drug seeking in humans are evolutionarily conserved in these organisms (Rodríguez et al., 2002). As a consequence, they may represent an underutilized asset for asking basic science questions with some translatability to human neuropsychiatric disorders, including SUD.

2.3. Fish

Zebrafish (*Danio rerio*) represent an increasingly popular animal model of substance use due to the ease at which genes and their resulting phenotypes can be manipulated (Klee et al., 2012; Stewart et al., 2011). Several investigators have developed models of both unconditioned and conditioned drug effects that may be used to address basic science

questions regarding the behavioral effects of addictive drugs (Collier and Echevarria, 2013; Kuroda et al., 2017). Moreover, recent studies have described operant procedures that permit examination of the positive reinforcing effects of drugs in this species (Bossé and Peterson, 2017). Their lack of mammalian brain structures and limited behavioral repertoire limit the translational value of this species; however, the development of more complex behavioral procedures will increase their utility for addressing some of the relevant features of SUD.

2.4. Birds

Avian species have long been used in behavioral research, and much of our knowledge of basic learning processes were derived from the pigeon (e.g., Herrnstein and Loveland, 1964; Rachlin and Hineline, 1967; Skinner, 1948; Terrance, 1963), and to a lesser extent, the Japanese quail (e.g., Kluender et al., 1987; Sanavio and Savardi, 1980). Pigeons have long been used in drug discrimination procedures to examine the discriminative stimulus effects of drugs, including drugs with significant abuse liability (Holtzman, 1985). As described in Section 3.3, these studies have revealed significant information about the basic pharmacological and behavioral mechanisms by which drugs produce their subjective effects, and there is considerable overlap in these data across species (including humans). Avian models of drug self-administration are not well developed or consistently utilized, but at least one model has been described (Winsauer and Thompson, 1991). Until better avian models of drug intake and drug seeking are developed, the translational value of birds as models for SUD will remain mostly unknown.

2.5. Genetically Modified Rodents

Genetically modified mice, and to a lesser extent rats, continue to significantly advance our understanding of the genes and proteins that are responsible for complex behaviors, including pathological behavioral processes that give rise to compulsive drug use and seeking (Befort, 2015; Changeux, 2010; Charbogne et al., 2014; Fowler and Kenny, 2012; Sora et al., 2010; Tammimäki and Männistö, 2011). Moreover, the use of optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) in these organisms has allowed investigators to examine the neurobiological basis of reward with greater specificity than previously permitted with wildtype organisms (Britt and Bonci, 2013; Cao et al., 2011; Cheng and Wang, 2019; Juarez et al., 2019; Runegaard et al., 2019; Stamatakis and Stuber, 2012). Complex behaviors can be trained in these organisms to model many aspects of SUD, but their genetic modifications make them fundamentally and functionally different from unmodified organisms, including humans. Consequently, their value to identify basic mechanisms of drug reward and reinforcement exceeds their appeal as a translational model of SUD.

2.6. Wild-Type Rodents

Wild-type mice and rats represent the most popular organisms used in substance abuse research (see reviews by Ahmed, 2018a; O'Connor et al., 2011; O'Dell and Khroyan, 2009; Sanchis-Segura and Spanagel, 2006; Yan and Nabeshima, 2009). Many of the behavioral, neurobiological, and pharmacological mechanisms that mediate drug use and drug seeking have been described in these species. Moreover, many of the behavioral procedures that model different transitional stages and core symptoms of SUD were originally developed or

later applied to these species (see examples in the sections that follow). Their relatively short life span limits some relevant experimental questions, such as the role of behavioral/pharmacological history in drug intake and the long-term consequence of drug use. Both issues are currently understudied in addiction research, possibly because of inadequacies of rodent models. Furthermore, intravenous catheter life is limited in these species, with patency maintained on the order of a few weeks in mice and a few months in rats (for methods to extend catheter life in rodents, see Thomsen and Caine, 2005; 2007; Gilbert et al, 2015). These inherent limitations to catheter life are relevant for decisions regarding experimental design, placing limits on the use of sophisticated schedules of reinforcement that require extensive training or longer durations of drug exposure. On the other hand, their relatively low cost in terms of procurement and husbandry, mammalian nervous systems, and complex behavioral repertoires often make rodents the preferred choice for both basic and translational research in neuropsychiatric disorders, including SUD. This favorable cost-to-benefit ratio will keep wild-type mice and rats at the forefront of drug abuse research for the immediate future.

2.7. Nonhuman Primates

Nonhuman primates are phylogenetically more related to humans than any other species. Consequently, they are most like humans in terms of neuroanatomy, physiological functions, and behavioral processes, making them uniquely suited to examine the distinguishing features of neuropsychiatric disorders such as SUD (Jimenez and Grant, 2017; Negus and Banks, 2018; Wakeford et al., 2018; Weerts et al., 2007). Importantly, their long lives and complex social systems most closely resemble those of humans, both of which offer further translational advantages for their use as models of SUD (Gould et al., 2014; Howell and Murnane, 2008; Nader and Czoty, 2008; Nader et al., 2012). Many basic behavioral and neurobiological processes common to humans have been discovered and/or confirmed in nonhuman primates, making them an important link between basic science research conducted in rodents and clinical research conducted in humans (Banks et al., 2017). Studies in nonhuman primates are often the critical point in which go/no-go decisions are made regarding clinical translation (Harding, 2017). Research with primates is necessarily limited in terms of costs and regulatory burden. These factors limit the number and types of experimental questions that can be asked, and experimental control can occasionally be limited because of these constraints (e.g., high costs of initial procurement; time and effort required for husbandry, regulatory safeguards limiting some types of distress that are causes/consequences of SUD). Regardless, nonhuman primates are uniquely positioned to best model the complex and dynamic behavioral processes that characterize human substance use and SUD.

3. Behavioral Assays as Models

Several behavioral assays have been developed to model the distinguishing features of SUD, and these assays have provided critical information on the causes and consequences of those features. Other procedures have been adapted from traditional neurobiological and psychological assays to uncover basic behavioral and pharmacological mechanisms that contribute to the use and abuse of addictive drugs. The assays described below reflect some

of the more common behavioral tests that have made significant contributions to our understanding of drug abuse and addiction.

3.1. Unconditioned Behaviors

Behavioral assays that measure locomotion, motor coordination, anxiolysis, antinociception, etc. are useful for determining the basic pharmacological and behavioral mechanisms of some drug effects, including those of addictive drugs (Altarifi et al., 2017; Ewan and Martin, 2013; Negus et al., 2008; Rowlett et al., 2005; Yamamoto et al., 2013; Zadina et al., 2016). They are limited in their ability to inform us on the mechanisms related specifically to drug use and drug seeking, and they do not model the behavioral pathologies that are characteristic of SUD. Consequently, their applicability to basic and applied substance abuse research is limited.

3.2. Intracranial Self-Stimulation

Intracranial self-stimulation (ICSS) is an operant procedure in which behavior is maintained by contingent pulses of electrical brain stimulation. Manipulations (including drug manipulations) that increase low rates of responding are seen as having abuse-related effects, whereas manipulations that decrease high rates of responding are seen as having abuse-limiting effects (Wise, 1996). The procedure can differentially predict the abuse liability of drugs almost as well as drug self-administration procedures (see Section 3.5), and the procedure has successfully been used to identify both the mediators and moderators of drug reward (Moerke and Negus, 2019; Negus and Moerke, 2019). ICSS is also used to probe the function of brain reward circuits during different transitional phases of SUD, providing information on the neurobiological adaptations that drive drug intake (Markou and Koob, 1991; Paterson et al., 2000; Stoker and Markou, 2011). Recent studies using optogenetic and chemogenetic methods have revealed that direct and selective self-stimulation of ventral tegmental area (VTA) dopamine neurons is sufficient to induce some core behavioral symptoms of addiction (Pascoli et al., 2015; Corre et al., 2018), thus expanding our knowledge of the neuropathology of SUD. Additional advantages of this model include its ability to simultaneously evaluate the abuse and abuse-limiting effects of drugs, its flexibility across various routes of administration, its adaptability for both drug-naïve and drug-experienced subjects, and its utility for examining dose- and time-dependent drug effects (Negus and Miller, 2014). ICSS lacks an obvious behavioral correlate to human substance use and thus cannot be viewed as a model of SUD that recapitulates the human condition; however, it continues to demonstrate its utility in determining the basic mechanisms of drug reward and motivated behavior, particularly during periods of intoxication and withdrawal.

3.3. Drug Discrimination

In drug discrimination procedures, a subject is trained to recognize (i.e., discriminate) the unique interoceptive effects produced by a drug (i.e., the discriminative stimulus). Because drugs with similar pharmacodynamic mechanisms of action produce similar interoceptive effects, they share discriminative stimulus effects in this procedure. This procedure has been used successfully to identify the pharmacological mechanisms of novel and existing drugs, as well as predict their abuse liability in humans (Cunningham and Callahan, 1994; Grant, 1999; Sanger 1988; Swedberg, 2016; Walker 2018). Technical features of drug

discrimination procedures limit their translational value as a model of SUD. For instance, drugs are typically administered by the experimenter and responding is maintained by a nondrug reinforcer (e.g., food). Consequently, it is not a substitute for assays that measure drug reward or reinforcement, and it does not recapitulate the behavioral pathology of SUD. Some investigators have combined drug discrimination with drug self-administration procedures, allowing the subject to self-administer the drug that serves as the discriminative stimulus (Hodge et al., 2001; Shelton and Macenski, 1998). Although this manipulation enhances the translational value of drug discrimination procedures, this methodology has not been widely adopted.

3.4. Conditioned Place Preference and Aversion

The conditioned place preference (CPP) and conditioned place aversion (CPA) procedures are widely used procedures that continue to grow in popularity. These procedures establish a Pavlovian association between an interoceptive drug cue and a unique context. A preference for the drug-associated context following conditioning serves as a measure of conditioned reward and drug seeking. Conversely, an aversion for the drug-associated context serves as a measure of abuse-limiting effects and “dysphoria”. The CPP and CPA procedures have advanced in recent years and are now used to examine basic behavioral processes involved in the acquisition, maintenance, extinction, and reinstatement of drug seeking (Aguilar et al., 2009; Liu et al., 2008; Tzschentke, 2007). They are predictive in that drugs that produce a place preference tend to have high abuse liability, and interventions that increase/decrease a drug-induced place preference often produce similar changes in the abuse liability of that drug (Bardo and Bevins, 2000; Napier et al., 2013; Tzschentke, 1998). Although conditioned drug effects are critical for the establishment and maintenance of drug use in humans, and are directly related to cue-induced craving and relapse, these procedures do not involve contingent drug administration, and thus are not measures of reinforcement. Many studies have made implicit or explicit conclusions about a drug’s reinforcing effects from data derived from these procedures, which misrepresents the data and may contribute to an overrepresentation of these procedures in the literature. Regardless, they remain important assays to measure critical features of addiction (i.e., conditioned reward and aversion) and thus have relevance for both basic and translational science.

3.5. Drug Self-Administration

In drug self-administration procedures, an organism emits a response that leads to the contingent administration of a drug (Spragg, 1940). Intravenous drug self-administration procedures have consistently demonstrated good-to-excellent face and predictive validity for over five decades (Aarde and Taffe, 2017; O’Connor et al., 2011; Panlilio and Goldberg, 2007; Schuster and Thompson, 1969). They are frequently used to answer basic science questions that enhance our understanding of drug use and to test manipulations that can be directly translated into prevention and treatment interventions for SUD (Campbell and Carroll, 2000; Corrigall, 1999; Ewan and Martin, 2013; Gardner, 2000; LeSage et al., 1999; Meisch, 2001; Schindler et al., 2002; Stafford et al., 1998; Woolverton, 1992; Young et al., 1981). In fact, past collaborations between animal and human investigators have established the translational and reverse translational value of these procedures (e.g., Freeman et al., 2011; Lile et al., 2019). Of all the models available, these procedures have the greatest utility

for basic science and the greatest translational value for SUD. Moreover, they are the most technologically advanced procedures and have been continuously revised and refined to answer the most complex and varied questions regarding substance use and SUD.

The remainder of this document will describe the utility and appeal of the more common variations of drug self-administration procedures, before concluding with recommendations for how these procedures should best be used to recapitulate human substance use and SUD.

4. Modeling the Distinguishing Features of Substance Use Disorders

Drug self-administration studies use numerous experimental designs and manipulations to address different aspects of drug reinforcement. Each variation has its specific utility to basic science and can be used to recapitulate the distinguishing features of SUD. Some commonly used variations are described in Sections 4.1 to 4.6; however, the list is not exhaustive and additional variations are used with lesser frequency.

4.1. Consumption and Demand Procedures

Measures of drug intake (i.e., consumption) are often the primary outcome variable of drug self-administration experiments. In many of these studies, there is a one-to-one correspondence between response rate and reinforcement rate, and the fewest restraints possible are placed on responding. Consequently, simple fixed ratio schedules of reinforcement (e.g., FR1) are often preferred due to their predictability and low-effort requirements. The ability of these simple schedules to maintain stable and predictable patterns of responding make them reliable baselines of behavior from which to examine the effects of various experimental manipulations; however, their stability and predictability do not reflect the complexity of drug use in humans, which limits their translational value. Furthermore, these simple schedules have been criticized for their limited ability to adequately capture the incentive-motivational effects of drugs (Arnold and Roberts, 1997), and they may better be described as measures of drug satiety (Olmstead et al., 2000; Tsibulsky and Norman, 1999).

One important utility of these simple schedules of reinforcement is that they are frequently used to answer mechanistic questions with applicability to some of the more complex features of SUD. For example, behavioral economic studies of drug demand often rely on simple schedules in which consumption is the primary outcome measure. These types of studies vary the unit price of a drug (e.g., responses/mg/kg) by systematically varying either the dose and/or ratio requirement to determine the sensitivity of drug intake to cost manipulations (Bentzley et al., 2013; Hursh, 1993). Such studies can quantitatively separate measures of demand intensity (i.e., unconstrained consumption) from demand elasticity (i.e., sensitivity to price increases), each of which differentially predicts various features of problematic drug use in humans (Hursh, 1991).

4.2. Incentive-Motivational Procedures

The reinforcing effects of drugs primarily (but not exclusively) involve appetitive motivational processes described by incentive-motivational theories of learning (Bozarth, 1990). According to these theories, drugs serve as incentives that motivate the organism to

respond in ways that lead to their procurement (Robinson and Berridge, 1993). The incentive-motivational effects of drugs are often operationalized on the basis of behavioral output and overall response rate (as opposed to drug intake), and studies examining the incentive-motivational effects of drugs often use schedules of reinforcement in which there is not a consistent one-to-one correspondence between response rate and reinforcement rate.

Progressive ratio schedules require the organism to emit an increasing amount of work (i.e., responses) to obtain each subsequent delivery of the drug. The point at which responding stops, known as the breakpoint, reflects the efficacy of the drug to serve as a reinforcer and is assumed to measure motivated behavior (Brady and Griffiths, 1976). Breakpoints are typically stable within organisms, and thus serve as a reliable baseline to measure the effects of various manipulations (Richardson and Roberts, 1996). Moreover, because the motivation to use drugs differs markedly over the course of SUD, breakpoints serve as a reliable indicator of these motivational changes in translational studies (Stafford et al., 1998). Progressive ratio schedules do not recapitulate the schedule contingencies that naturally operate in substance-abusing humans, which limits its translational value as a model of SUD. Furthermore, responding on progressive ratio schedules are particularly sensitive to the motoric effects of a drug, which complicates comparisons across drugs with different behavioral and pharmacological profiles (e.g., stimulants vs. benzodiazepines).

Second-order schedules employ conditioned stimuli (e.g., an audiovisual stimulus) previously paired with drug administration to maintain high levels of behavior between scheduled but infrequent deliveries of the drug. As such, these schedule conditions more closely match the human condition in which behaviors necessary to procure the drug are often temporally displaced from obtaining the drug, but are maintained by reliable indicators that drugs will again be available (e.g., a text message from a dealer). This characteristic gives them more appeal than simple schedules of reinforcement in translational studies of SUD (Schindler et al., 2002). Moreover, once second-order schedules are trained, they maintain stable patterns of responding from which to examine manipulations that may increase or decrease a drug's incentive-motivational effects, giving them considerable utility for basic research (Everitt and Robbins, 2000).

4.3. Intermittent-Access Procedures

Intermittent-access procedures limit drug availability by limiting either the time or opportunities in which the drug is available, using means other than limiting session length, number of infusions, or post-infusion timeouts. The procedural details of intermittent access differ across laboratories, but all lessen the consistency of drug availability within a test session. For instance, discrete-trial procedures prevent unconstrained free-operant responding by limiting the opportunities to emit the drug-reinforced response (e.g., the response lever is only available for a limited time and retracts after each drug delivery). Other intermittent-access procedures allow periods of unconstrained free-operant responding, but only during discrete periods of drug availability within a session. The commonality among these procedures is that they result in repeated "spikes" in brain concentrations of the drug within a test session, thus differing from unconstrained free-operant procedures that tend to yield stable drug concentrations within a session (Zimmer

2011; 2012). Importantly, these procedures have demonstrated their utility to induce translationally relevant “addicted phenotypes” in laboratory animals, characterized by sensitization to a drug’s reinforcing and motivational effects (Allain et al., 2015; Kawa et al., 2019; Roberts et al., 2007). To date, these procedures have only been extensively tested with stimulants, and their applicability to other drugs of abuse remain largely unknown.

4.4. Conflict and Punishment Procedures

Conflict and punishment procedures involve appetitive (e.g., drug presentation) and aversive (e.g., shock presentation) contingencies operating sequentially or simultaneously to influence responding (Grove and Schuster, 1974; Panlilio et al., 2003). In drug self-administration procedures, organisms may first have to endure an electric shock by walking over an electric grid to press a response lever (e.g., Bamea-Ygaël et al., 2012). Alternatively, lever pressing could be simultaneously reinforced by a drug and punished by electrical shock (e.g., Pelloux et al., 2018) or an aversive pharmacological agent such as histamine (e.g., Negus, 2005). These procedures model a diagnostic feature of SUD in which drug use is maintained even in the presence of adverse consequences, making this model particularly useful for both basic and translational research (Marchant et al., 2019; Peck et al., 2015; Pelloux et al., 2007; 2015). On the other hand, most of these procedures use electric shock or aversive pharmacological agents to punish responding, which does not mimic the adverse consequences of drug use in humans and lessens its translational value for SUD.

4.5. Concurrent Choice Procedures

Concurrent choice procedures require the subject to choose between two response alternatives, generally between a drug and nondrug reinforcer. The choice of the alternative reinforcer varies across studies, but it is generally a stimulus that is biologically relevant and tends to elicit approach behaviors in the natural environment (e.g., food, exercise, social contact). These procedures are ideally suited to address the factors influencing the pathological choice of drugs over nondrug reinforcers, and hence have significant utility as both basic and translational models (Banks, 2017; Banks and Negus, 2017; Moeller and Stoops, 2015). These procedures can also be used to examine how behavioral interventions (e.g., concurrent access to physical activity or a drug-free social partner) can reduce drug intake and other measures of drug-seeking behavior, which furthers their translational value for SUD research (Cosgrove et al., 2002; Venniro et al., 2018). Recent research using these procedures has also advanced our understanding of factors that predict the propensity for developing a substance use disorder and the likelihood of recovery. These factors include high-risk settings that contribute to drug intake, behavioral traits that increase vulnerability, nonpharmacological factors that influence choice, and medications that promote recovery (Ahmed, 2018b; Ahmed et al., 2018; Negus and Banks, 2013). One limitation of some concurrent choice procedures is their reliance on discrete-trial designs that limit unconstrained free-operant responding, making them imperfect reproductions of the human condition. Although several free-operant procedures have been described, including a 24-hour, three-alternative, food-water-drug, concurrent-choice procedure (e.g., Dworkin et al., 1984), they are underutilized in the field.

4.6. Drug-Seeking Procedures

Many procedures measure “drug seeking” as opposed to “drug taking” in order to examine drug-motivated responses in the absence of explicit drug administration. Such measures have translational value because individuals with SUD sometimes engage in behaviors that may not lead to drug administration but have been associated with drugs in the past, such as repeatedly returning to places where drugs have been obtained or contacting individuals who have provided drugs previously. As already discussed, second-order schedules serve as translational models in which responding is maintained for long periods of time by stimuli previously associated with drug administration (see Section 4.2).

Drug-seeking behavior is most often examined using extinction procedures. In these procedures, drug self-administration is used to establish and maintain responding for a period of time, but then is subsequently withdrawn so the persistence of responding can be measured in its absence. Different manipulations that increase or decrease responding during extinction are presumed to reflect corresponding increases and decreases in the motivation to obtain the drug. Extinction procedures have limited face validity because they do not mimic the natural contingencies that control drug availability in human populations. Furthermore, to date, their translational value in predicting interventions that decrease drug seeking in individuals with SUD has been limited (see Chesworth and Corbit, 2017; McNally, 2014). On the other hand, extinction procedures have shown considerable utility in examining the underlying mechanisms contributing to the extinction of drug seeking (Gibson et al., 2018; Malvaez et al., 2009; Millan et al., 2011). This is relevant because measures of drug seeking are often considered an animal analog of craving, which is believed to motivate drug seeking and contribute to relapse in humans (Markou et al., 1993).

5. Modeling Different Transitional Phases of Addiction and Recovery

Drug self-administration procedures are frequently used to model the different transitional phases of drug addiction and recovery. These models have generally shown good face and predictive validity, and they collectively have advanced our understanding of the complexity and dynamic nature of SUD. All the procedures described in Sections 5.1 to 5.6 have repeatedly demonstrated their utility for basic science and translational value as models of SUD.

5.1. Acquisition of Drug Use

Drug self-administration procedures that model the acquisition of drug use measure the transition from initial drug exposure to the development of stable patterns of drug intake according to some predetermined criterion (e.g., minimum number of infusions; separation of active vs. inactive lever presses). These procedures may use autoshaping or free-operant techniques, but all use experimentally-naïve animals with no significant pharmacological history. Acquisition procedures are particularly useful for examining manipulations that increase or decrease the establishment of drug use in drug-naïve individuals, making it ideally suited to examine drug abuse prevention interventions for SUD (Campbell and Carroll, 2000).

5.2. Maintenance of Drug Use

Procedures that model the maintenance of drug use measure stable patterns of drug intake over extended periods of time, often by limiting the amount of drug available or the amount of time in which the drug is available (Gauvin et al., 2019; Koob and Weiss, 1990). These models are arguably the most commonly used in preclinical research, but they do not capture either the complexity or the dynamic changes associated with SUD. An argument may be made that these procedures are overrepresented in the preclinical literature. Regardless, their contribution to basic science is exceptionally high (Gardner, 2000), and they have predictive validity at identifying interventions that reduce drug use in clinical populations (Haney and Spealman, 2008).

5.3. Escalation of Drug Use

Drug self-administration procedures that model the transition from occasional drug use to pathological patterns of use that meet the diagnostic criteria for SUD typically use experimental designs that promote the escalation of drug intake over time. Traditionally, this has been accomplished using long-access procedures, in which daily self-administration sessions are extended to 6 hours or longer in duration (e.g., Ahmed and Koob, 1998; Krasnova et al., 2010). Similar effects have been obtained using intermittent-access procedures, in which a drug is available repeatedly over several days but only intermittently within a single session (e.g., Allain and Samaha, 2019; also see discussion in Section 4.3). Both types of procedures induce relevant behavioral and neurobiological changes that characterize the transition to addiction in humans (Kawa et al., 2019), and long-access procedures have demonstrated their utility at identifying the neurobiological mechanisms that mediate this transition, as well as interventions that can facilitate and attenuate this process (Ahmed and Kenny, 2011; Cadet et al., 2015; Koob and Kreek, 2007; Koob et al., 2004; Lynch, 2018; Paterson, 2011; Smith and Lynch, 2012). The behavioral mechanisms contributing to the escalation of drug intake remain unresolved, but several potential mechanisms have been described previously in a comprehensive review (Zernig et al., 2007).

5.4. Binge and Compulsive Patterns of Drug Use

Compulsive drug use, often described as a defining feature of SUD, is “a pattern of drug consumption that is stimulus bound, stereotyped, difficult to regulate, and identified by a loss of control over intake” (Tiffany and Carter, 1988). The compulsive patterns of drug use that characterize SUD differ across pharmacological classes, but uninterrupted “binges” of drug self-administration are common for many drugs, such as alcohol and cocaine (Foltin et al., 1995; Waszkiewicz et al., 2018). Investigators have occasionally used extended periods of unlimited drug intake (24-72 hours) to model the highly dysregulated patterns of drug intake that emerge during an extended binge (e.g., Mutschler et al., 2001; Robinson et al., 2016). These procedures uniquely capture the basic behavioral and neurobiological processes that occur during the most dangerous periods of compulsive drug use in humans (Fowler et al. 2007; Mutschler and Miczek 1998; Tornatzky and Miczek 2000); however, these procedures are not extensively used in the field and tend to be underutilized in identifying potential therapeutic interventions.

5.5. Drug Withdrawal

Drug-seeking procedures that model withdrawal from drug use examine the behavioral and physiological consequences of the cessation of drug use, either in the presence or absence of physical dependence (Lyvers, 1998). Drug withdrawal results in both short-term and long-term changes in neurobiological systems that contribute to relapse as new behavioral, cognitive, and affective symptoms emerge and evolve. Consequently, animal models with the greatest translational appeal consider the effects of withdrawal on drug-seeking both immediately after drug cessation and throughout longer periods of abstinence. In humans, medical interventions change over the course of abstinence, as the goals of treatment move from detoxification to relapse prevention. Preclinical models have examined the ability of some of these interventions to decrease drug-seeking immediately following drug cessation, but success has been limited (e.g., clonidine during opioid withdrawal; Negus and Rice, 2009; Townsend et al, 2019). Preclinical models have also examined the role of anhedonia and dysphoria that emerge over time and how these negative affective states may contribute to relapse (Koob and Le Moal, 2005; Koob and Mason, 2016; Koob and Volkow, 2016). Such procedures are particularly important for examining the incubation of craving over time, which may contribute to relapse even after extended periods of successful abstinence (Lu et al., 2004; Venniro et al., 2016). Although drug withdrawal procedures capture critical features of SUD that are relevant to both short-term and long-term recovery, they have been more successful at identifying neurobiological adaptations following drug cessation than relapse-prevention interventions.

5.6. Relapse to Drug Use

Procedures that model relapse typically use the reinstatement procedure in which responding is extinguished and then a stimulus is presented to “reinstatement” the extinguished response, but in the absence of contingent drug administration. The reinstatement procedure has good predictive validity, in that stimuli that reinstate responding in animals also trigger relapse in humans (e.g., drug-associated cues, addictive drugs, stress), and interventions that reduce reinstatement in animals often attenuate relapse in clinical populations (Epstein et al., 2006; but see Katz and Higgins, 2003, for an opposing view on the predictive validity of these models). Adaptions of the traditional model have replaced the reinstatement of an extinguished response with the reacquisition of response-contingent drug self-administration. Other adaptations have replaced forced abstinence via extinction with voluntary abstinence via concurrent choice of an alternative nondrug reinforcer (Reiner et al., 2019; Venniro et al., 2016). These adaptations have increased the face validity of the relapse model, but their predictive validity to identify novel treatment interventions is still being determined.

6. Modeling the DSM-5 Criteria for Substance Use Disorders

Drug self-administration procedures are increasingly being used to model many of the diagnostic criteria of SUD as described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). These models are advantageous because they recapitulate some of the cardinal features of SUD in human populations (Domi et al., 2019; Lamontagne and Olmstead, 2018). As such, they have high face validity and are optimally suited for

questions of basic science and the identification of potential therapeutic interventions. The DSM-5 criteria (with the exception of tolerance and withdrawal) are shown below, along with procedures that are particularly well suited to serve as models.

1. *The substance is often taken in larger amounts or over a longer period than was intended.* Models that employ long-access conditions that engender an escalation of intake over time are useful for addressing this diagnostic criterion.
2. *Users have a persistent desire or unsuccessful efforts to cut down or control use of the substance.* Procedures that measure the escalation of use, the reinstatement of responding after a period of abstinence, and the reacquisition of use after a period of abstinence, particularly after voluntary abstinence, may all be used to examine some of the essential features of this criterion.
3. *A great deal of time is spent in activities necessary to obtain the substance, to use the substance, or to recover from its effects.* Extended-access periods of unlimited drug intake can be used to capture some of the temporal features of this criterion. Second-order schedules that require extended durations of work to obtain the drug capture another important feature of this criterion.
4. *Users have cravings, or strong desires to use the substance.* Models that employ extinction and other types of drug-seeking procedures are optimally designed to measure aspects of craving and similar “desires” to use the drug. Progressive ratio and second-order schedules of reinforcement can measure motivational aspects of craving and desire.
5. *Recurrent use of the substance results in a failure to fulfill major role obligations at work, school, or home.* Concurrent choice procedures that require the subject to choose between drug and nondrug rewards capture some of the basic features of this criterion.
6. *Use of the substance is continued despite having persistent or recurrent social or interpersonal problems caused, or exacerbated, by the substance.* The use of a drug despite adverse consequences are best measured by conflict procedures, in which an aversive event must be endured prior to, concurrent with, or immediately after the operant response that results in drug administration.
7. *Use of the substance is recurrent so that important social, occupational, or recreational activities are given up or reduced.* Concurrent choice procedures that require the subject to choose between a drug and nondrug reward are designed specifically to measure this aspect of pathological choice.
8. *Use of the substance is recurrent in situations in which it is physically hazardous.* Punishment procedures that employ biologically relevant aversive stimuli are particularly useful in measuring drug-maintained responding under physically hazardous conditions.
9. *Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.* Conflict and punishment procedures that

employment positive punishment contingencies (e.g., delivery of electric shock) or negative punishment contingencies (e.g., removal of food or social partner) may be used to model drug-maintained behaviors that result in problematic consequences for the subject.

One limitation of modeling the diagnostic criteria of SUD is that many criteria refer to intentions, feelings, or knowledge that are private to the subject and cannot be assessed directly by an external observer. Consequently, these features must be inferred from behavior in the absence of a verbal report by the individual. Accordingly, a major challenge in the development and use of preclinical models of SUD is the back-translation of these features into operational terms of behavior analysis.

7. Other Considerations of the Drug Self-Administration Model

Many factors influence the utility of drug self-administration procedures to answer basic science questions regarding drug reinforcement and its translational value as a model of SUD. Several important factors are listed below, but they should not be considered exhaustive.

7.1. Dose

One significant limitation of many (if not most) self-administration studies is the use of single-dose designs. The use of only a single dose significantly limits the inferences that can be made about basic behavioral, biological, and pharmacological principles applicable to drug effects (Kelleher and Morse, 1968). Moreover, single-dose designs have limited applicability to the human condition, in which the drug concentration can vary markedly for drugs obtained illicitly. For most drugs tested in self-administration procedures, a 10- to 100-fold dose range can be tested easily, with doses that range from those that fail to differentiate from vehicle to doses that suppress rates of operant responding (Hiranita, 2015).

7.2. Route of Administration

Oral routes of administration are frequently used in animal models of alcohol use. These procedures have undergone numerous refinements and typically have good-to-excellent face and predictive validity (Bell et al., 2006; Lê and Shaham, 2002; McBride and Li, 1998; McBride et al., 2005; Samson et al., 2000). This route is used much less frequently for other drugs, despite the popularity of the oral route of administration for most drugs with high abuse and addiction liability. Methodological issues related to the oral route limit its utility as an animal model due to several difficult-to-control factors ranging from the bitter taste of drugs to the long delay between consumption of the drug and the production of psychoactive effects that contribute to its reinforcing effects (Meisch, 2001). Voluntary inhalation of smoke or vapor is limited by existing technologies, although investigators have recently made significant strides at overcoming some of these limitations (Foltin, 2018; de Guglielmo et al., 2017; Javadi-Paydar et al., 2019; Marusich et al., 2016; Vendruscolo et al., 2018). The current reliance on intravenous self-administration is arguably limiting the ability of animal models to address some of the most immediately pressing problems of public health, including the abuse of orally administered prescription opioids and the increasing popularity

of nicotine and cannabinoid products administered via vaping. Much more work and technological advances are needed in these areas.

7.3. Species

Mice, rats, and monkeys remain the most popular species used in drug self-administration studies, and there is generally good-to-excellent concordance across species in regard to which manipulations increase drug intake and which decrease drug intake. Importantly, these same manipulations tend to increase and decrease drug intake in the human laboratory, indicating that all three species can serve as excellent models of the human condition under the right circumstances. Given their low cost and expense, mice and rats are often preferred when asking basic science questions related to drug reinforcement, especially when considering that stable baselines of behavior can rapidly be achieved in experimentally naïve subjects, and that extraneous variables can either be controlled or completely eliminated (Bell et al., 2012; O'Connor et al., 2011; O'Dell and Khroyan, 2009). Owing to their high cost, monkeys are typically used for multiple years across multiple studies, and thus tend to have much more complicated behavioral and pharmacological histories. Their complex histories make them more similar to humans than other species, thus making nonhuman primates the best translational model for neuropsychiatric disorders, including SUD (Amedee et al., 2014; Barr et al., 2003; Camus et al., 2015; Dettmer and Suomi, 2014; Grant and Bennett, 2003; Nader and Czoty, 2005; Wakeford et al., 2018).

7.4. Behavioral and Pharmacological History

Experimentally naïve subjects are often preferred in basic science research, which is a core advantage of animal models. Moreover, aspects of a human's behavioral and pharmacological history that may contribute to the development of SUD can be isolated and examined in animal models while holding other factors constant (Lynch et al., 2010). Rodent models are particularly adept at examining these factors in isolation. On the other hand, the complicated interactions across multiple variables related to a subject's history are arguably best examined in monkeys with extensive experimental backgrounds (Nader et al., 2012). As such, nonhuman primates offer the best models when predicting how a specific intervention will work in a human population, where very few factors related to an individual's behavioral and pharmacological history can be controlled.

7.5. Social and Environmental Context

The social and environmental context can also impact measures of drug intake and drug seeking. Traditionally, this has led researchers to isolate animals in the home cage and during testing, while providing minimal environmental enrichment. It is becoming increasingly apparent that these extreme conditions of social and environmental impoverishment are not necessary unless such conditions are being investigated as an experimental manipulation (Stairs and Bardo, 2009). Indeed, models that enrich the social environment have greater translational value without sacrificing experimental control over behavior (Smith and Strickland, 2017). The use of social and environment enrichment should be expanded in all animal models of SUD.

7.6 Individual Variability

Individual differences in sensitivity to initial drug effects, vulnerability to developing a substance use disorder, and susceptibility to the neuropsychiatric consequences of drug use contribute to difficulties in developing effective prevention and treatment interventions for SUD. Animal models have widely been used to characterize individual variability in drug intake across relevant biological variables such as age (Helms et al., 2014; Shahbazi et al., 2008) and sex (Lynch 2006; 2018), as well as genetic variants that increase or decrease levels of drug intake (Niwa et al., 2008; Stoker and Markou, 2013). Animal models have also been used to identify naturally occurring and artificially induced behavioral phenotypes that predict drug intake and compulsive patterns of use (Bush and Vaccarino, 2007; Flagel et al., 2009; Homberg, 2014; Nishida et al., 2016; Shimamoto et al., 2015). Animal models that include diverse subject populations and treat individual subject characteristics as biological variables have the most translational value for developing prevention and treatment interventions for diverse human populations.

8. Responses to the Four (Plus One) Topics Targeted by the RFI

Although not meant to be exhaustive, the procedures reviewed in this manuscript reflect the majority of nonhuman animal models currently being used in the field of addiction research. In many cases, the citations used to evaluate these models were derived from high-quality literature reviews by established investigators. Consequently, evaluations of the strengths and weaknesses of the various models should not be considered controversial or even particularly novel. Nevertheless, these evaluations can be used to construct specific responses to the four (plus one) topics targeted by the RFI to advance future research in basic and translational science.

1. *Current animal behavioral procedure(s)/model(s) that BEST recapitulate human substance use/SUD, including the aspect(s) of substance use/SUD targeted by the/these procedure(s)/model(s).* Drug self-administration procedures, in which drug administration is contingent on the behavior of the subject, are the behavioral assays that most closely recapitulate human substance use and SUD. The translational value of these procedures is enhanced when mammalian species that are phylogenetically similar to humans, such as nonhuman primates, are used as subjects. Nonhuman primates bring the additional advantage of biological and behavioral similarity to humans, allowing the fine tuning of procedures to most closely match the human condition. Moreover, nonhuman primates have complex social environments and behavioral histories that are difficult to model in other species, which furthers their appeal when making direct translational comparisons to humans. The utility of drug self-administration procedures is further enhanced when complex schedules of reinforcement are used to capture the complex relationships between drug seeking and drug intake. Procedures that model the various transitional stages in the development of and recovery from SUD (e.g., acquisition of use, escalation of use, relapse to use) are best at identifying specific interventions to reduce or prevent drug use in targeted populations. Finally, procedures that measure one or more of the behavioral symptoms of SUD (e.g., use despite adverse

consequences, pathological choice) best capture the essential features of addictive behavior that serve as primary outcome measures in human populations.

2. *Animal procedures/models of SUD that best balance the inherent trade-offs between resources and complexity/ecological validity.* Drug self-administration models using wild-type rodents currently represent the optimal balance between resource demand and ecological validity. Relative to nonhuman primates, rodents can be obtained and maintained at much lower monetary costs. Much greater numbers can be maintained at once, and fewer personnel and less personnel time are required for their upkeep. Regulatory burden is less with rodents than nonhuman primates, allowing for more rapid and efficient data collection. As reviewed in the sections above, investigators have made considerable advances in modeling the distinguishing features of SUD in laboratory rodents, and the ecological validity of these models continues to increase. Indeed, all major transitional stages of SUD and most of the diagnostic features of SUD can be examined rapidly and easily in rodents, making them an optimal choice when resources are limited. Finally, rats are generally preferred to mice because of their larger size and longer lifespans, and because intravenous catheters can be maintained for longer periods of time.
3. *Animal procedures models of SUD whose translational value are frequently misrepresented or overrepresented by the scientific community.* There are several examples of animal models being misrepresented in the scientific literature. For instance, procedures that measure unconditioned behaviors are critical for understanding the neuropharmacological mechanisms by which addictive drugs produce their behavioral effects, but they should not be considered as models of SUD. Similarly, drug discrimination procedures are critical for understanding the unique interoceptive effects produced by drugs, but they do not model any of the distinguishing features or diagnostic criteria of SUD. CPP assays are critical for understanding the conditioned rewarding effects of drugs, but they do not measure a drug's reinforcing effects as sometimes claimed. In contrast, drug self-administration procedures are uniquely capable of measuring the reinforcing effects of drugs and serve as the best translational models of human substance use and SUD. Despite the translational value of drug self-administration procedures, their ability to recapitulate the complexity and dynamic nature of SUD is often underutilized. For instance, the majority of studies have used limited-access procedures that constrain the amount of drug consumed and prevent the escalation of drug use that is characteristic of SUD. Similarly, most studies use simple schedules of reinforcement (e.g., FR1) that do not capture the complexity of the relationship between drug seeking and drug intake. These types of procedures are often misrepresented as measuring addictive behavior, which is more complex than studies using these simple procedures often suggest. The use of single-dose experimental designs permeates the literature, reducing scientific appeal and translational relevance, and limiting the types of conclusions that can be drawn. Similarly, the use of a single sex, age, or other

biological characteristic in self-administration studies limit the populations that are likely to benefit from positive findings. Finally, with the exception of alcohol, intravenous drug self-administration is overrepresented in the literature, given that this route of administration is infrequently or never used by the majority of individuals with SUD.

4. *Aspects of substance use/SUD that are NOT currently being modeled in animals and how current procedures/models could be adapted to overcome technical/logistic challenges and address this gap in the field.* Investigators have markedly increased the translational value of drug self-administration procedures over the past decade, but further refinements are necessary to more closely match the complexity and dynamic nature of SUD, and more adequately model the goals of treatment. As mentioned previously, current models of substance use and SUD are over-reliant on intravenous methods of self-administration that do not model the more commonly used routes of ingestion, inhalation, and insufflation. New technologies are needed to better model these routes of administration, especially those that are becoming increasingly common in human populations (e.g., vapor inhalation). Current models are also still imperfect at capturing the dynamic shift from occasional drug use to pathological patterns of use that meet the diagnostic criteria for SUD. Recent work with intermittent-access models represent a promising possibility, but the predictive validity of these models has not been established. Most models of SUD artificially deprive the subject of social and environmental stimuli that are characteristic of the human condition, thus limiting their ability to inform clinical research with humans. New methods are needed to examine drug intake and drug seeking under social/environmental conditions applicable to humans, particularly in the presence of a social partner who may or may not also be using drugs. New behavioral strategies are also needed to capture the irregular, intermittent, and unpredictable patterns of drug intake that may contribute to the transition from recreational drug use to addiction. This could be accomplished by making use of increasingly complex schedules of reinforcement that more closely mirror the unpredictable availability of drugs in human populations. New procedures are also needed to model more precisely the diagnostic criteria of SUD and the goals of treatment, similar to the way choice procedures have modeled the use of drugs at the expense of other reinforcers, and the way conflict procedures have modeled the use of drugs despite negative consequences. Very few preclinical researchers are modeling drug self-administration in special populations. For instance, models of alcohol self-administration in aged subjects and opioid self-administration in chronic-pain subjects have been described (e.g., Martin et al., 2007; Rintala et al., 1988); however, neither of these models are being extensively used in addiction research, despite their current relevance for public health. Given that models of these special populations are already being used in other areas of biomedical research, they could easily be adapted for behavioral studies of drug reward and reinforcement. Finally, clinical research is markedly ahead of preclinical research in examining some types of novel therapeutics, such as the use of hallucinogens (e.g., psilocybin, ayahuasca, ibogaine) to decrease drug

craving and relapse. The reverse translation of these studies using preclinical models are urgently needed to inform future clinical trials of these novel interventions.

5. *Current animal models that are optimal for examining the basic behavioral, pharmacological, and biological mechanisms by which drugs produce their abuse-related effects.* Many of the same procedures that are sometimes misrepresented and overrepresented in the literature as models of SUD make excellent assays for examining the basic mechanisms by which drugs produce their rewarding and reinforcing effects. For instance, ICSS, drug discrimination, and CPP procedures are ideally suited to address basic behavioral, pharmacological, and neurobiological mechanisms contributing to reinforcement learning, drug-induced discriminative stimuli, and drug-induced conditioned reward/aversion. Moreover, drug self-administration procedures that use simple schedules of reinforcement provide stable and reproducible baselines from which to examine the effects of experimental manipulations on drug intake. Similarly, procedures that limit drug intake via limited-access designs engender stable and predictable patterns of behavior over exceptionally long periods of time than can be reestablished repeatedly over the course of a study. Procedures that artificially constrain extraneous variables related to a subject's social environment and behavioral history can increase the signal-to-noise ratio and increase an assay's sensitivity to detect the effects of experimental manipulations. Furthermore, the intravenous route of administration, despite being infrequently used in human populations, produces effects that are large, rapid, and predictable, all of which are desirable and often critical in mechanistic studies of reinforcement. Finally, species with comparatively limited behavioral repertoires and simple neural networks often are ideally suited to address targeted mechanistic questions with applicability to reward and reinforcement. The expanded use of some of these species (e.g., crayfish, amphibians) represent an opportunity for growth in basic science research.

9. Concluding Comments

Animal models of drug self-administration continue to undergo significant refinements that increase their utility for basic science and translational value for SUD. Indeed, new models are constantly being developed and each brings the field closer to recapitulating the distinguishing features of SUD. Regardless, progress in these domains can be accelerated by both individual investigators and funding organizations. In addition to devoting resources necessary to address the issues noted above, greater collaboration is needed between preclinical, human laboratory, and human clinical researchers. For instance, preclinical researchers must not only model the distinguishing features of SUD but also the impediments to recovery that operate in the natural environment and prevent effective translation (e.g., presence of substance using peers). Moreover, preclinical researchers must know what concurrent neuropsychiatric conditions may adversely impact recovery (e.g., substance-induced impairment in cognitive function), so that models may take these factors into consideration (e.g., by including measures of cognitive performance). These and similar

issues must be resolved if preclinical researchers are to design new models with greater translational value, and this will require greater communication with clinicians to identify the key roadblocks to recovery.

Similarly, preclinical researchers are perfectly situated to inform go/no-go decisions in regard to translation, saving time and monetary resources on clinical trials that are likely to fail. For instance, by including functional impediments that prevent recovery and contribute to relapse, by including measures of adverse side effects that limit the adoption of an intervention, and by treating subject characteristics as biological variables, preclinical researchers can preemptively identify those interventions that are unlikely to work when translated to diverse human populations. Relatedly, preclinical researchers must begin the process of back-translating active negative controls that initially appeared promising in preclinical studies but failed during clinical trials. Back-translation of both positive and negative controls would be useful to evaluate the predictive validity of new models as they are developed. This will require greater collaboration with clinical researchers so that negative findings are equally as likely as positive findings to be considered when designing clinical trials and developing clinical interventions.

NIDA has an outstanding track record of encouraging successful collaborations across investigators working within a given species to combine their expertise to address the complexity of SUD; however, NIDA has had less success at bringing together researchers who study humans versus laboratory animals to address substance use as collaborative teams. The lack of communication between animal and human researchers is unfortunately getting worse, with journals and scientific conferences becoming increasingly specialized and catering to smaller and smaller constituencies. NIDA and other funding organizations are uniquely positioned to reverse this trend by encouraging and supporting animal-human research collaborations to advance basic, translational, and reverse translational science. This call for greater collaboration between researchers who study humans versus laboratory animals is neither controversial nor novel, and several investigators have outlined convincing arguments why such collaborations are urgently needed (e.g., Czoty et al., 2016; Haney and Spealman, 2008; Moeller and Stoops, 2015).

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