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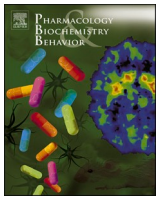

Opinion paper

Confronting the challenge of failed translation in medications development for substance use disorders

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In late 2019, the emergence of COVID-19 triggered a vigorous research response that culminated a year later in approval of several highly effective vaccines (Forchette et al., 2021). By comparison, recent efforts to develop new medications for the parallel epidemic of substance abuse have been less productive. The 21st century has witnessed a sharp increase in drug addiction and overdose deaths (National Institute on Drug Abuse, 2020; Ahmad et al., 2021), and as with the COVID-19 epidemic, this spike in prevalence has triggered a robust research response. For example, the National Institute on Drug Abuse (NIDA) budget more than doubled from $686 million $1.462 billion between 2000 and 2020 (National Institutes of Health, 2020), and the annual number of research publications listed on PubMed with the key words "drug, abuse, self-administration" more than tripled from 156 in 2000 to a peak of 518 in 2018. However, Table 1 shows that this response has not yielded a new Food and Drug Administration-approved medication for drug-abuse treatment in more than 15 years. What explains this lack of progress? Here we argue that stalled medication development reflects in part an avoidable reliance on Single-Operant Drug self-administration procedures (SODs) as a preclinical tool both for testing candidate medications and for basic neuroscience research to identify molecular targets for medications development. SODs are vulnerable to misinterpretation of treatment effects, blind to critical components of addiction, and historically superfluous for development of most approved addiction medications. To address this stalled progress, we propose wider preclinical use of drug-choice procedures both to improve the fidelity of preclinical-to-clinical translation and to chart new paths for mechanistic research (Banks and Negus, 2017a; Negus and Banks, 2018). The challenge of failed translation is neither unique to drug-abuse research nor unexpected in the normal course of scientific research as hypotheses are generated and tested; however, as in other fields, the advancement of addiction-treatment research demands that these failures be openly acknowledged and considered before they can be surmounted.

1. The problem with SODs

Drug self-administration encompasses a family of operant behavioral procedures in which a subject earns test-drug doses by completing a response requirement on an operant manipulandum. As one example, a laboratory rat might earn intravenous cocaine doses by pressing a response lever. SODs are a subtype of self-administration procedure in which there is a single operant manipulandum, and the primary dependent measure is either the rate of responding (e.g. responses per minute) or rate of reinforcement (e.g. drug injections per session). SODs have well-established utility as preclinical tools for predicting human abuse potential of test drugs (Johanson and Balster, 1978; Ator and Griffiths, 2003; Carter and Griffiths, 2009; O'Connor et al., 2011), and SODs have been formally incorporated into Food and Drug Administration guidance to industry for evaluating abuse potential of new pharmacotherapeutics (Food and Drug Administration, 2016). This utility of SODs for predicting abuse potential has also suggested a plausible corollary application for their use in evaluating candidate substance-abuse treatments (Mello and Negus, 1996; Haney and Spealman, 2008; Czoty et al., 2016). The logic goes like this: if increased self-

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Table 1
Food and Drug Administration (FDA)-approved medications for treating substance use disorders in the United States. Dates of FDA approval are shown in parentheses. Despite the widespread use of SODs in current medication-development efforts, preclinical SOD studies in laboratory animals played a significant role in development of only two medications: naltrexone for alcohol use (Altshuler et al., 1980), and varenicline for tobacco/nicotine use (Rollema et al., 2007). Preclinical studies also played a significant role in early development of acamprosate for alcohol use disorder, but these studies used a two-bottle choice procedure rather than a SOD (Boismare et al., 1984). Early evidence for all other medications came from human-laboratory studies or clinical observations, although later SOD studies often provided supportive evidence (Harrigan and Downs, 1978; Mello et al., 1983; LeSage et al., 2002). Of particular importance, results in SODs with methadone for opioid use disorder and bupropion for smoking cessation have often been inconsistent with the clinical effectiveness of these compounds. Methadone (Jones and Prada, 1977; Mello et al., 1983) and bupropion (Rauhut et al., 2003; Shoaib et al., 2003; Rauhut et al., 2005; de Moura et al., 2020) generally decrease rates of drug self-administration only at doses that also produce decrease in responding for other reinforcers along with other evidence for behavioral impairment. This indicates that SODs are vulnerable not only to false-positive effects (i.e. drugs that appear effective preclinically but are not effective clinically), but also false-negative effects (i.e. drugs that appear ineffective preclinically but are effective clinically).

Abused drug		
Opioids	Alcohol	Tobacco/nicotine
Methadone (1972)	Disulfiram (1949)	Nicotine (1984)
Naltrexone (1984)	Naltrexone (1994)	Bupropion (1997)
Buprenorphine (2002)	Acamprosate (2004)	Varenicline (2006)

administration predicts increased likelihood of clinical abuse, then treatment-induced decreases in self-administration of an abused drug might predict treatment efficacy to decrease clinical abuse of that drug. However, this simplistic formulation has a well-known weakness. Yes, treatment-induced decreases in self-administration may result from a therapeutically desirable decrease in sensitivity to the reinforcing effects of the abused drug; however, decreased drug self-administration can also reflect undesirable motor or cognitive effects of the candidate treatment that manifest as unacceptable side effects in clinical use. Strategies to compensate for this weakness have steadily evolved. For example, current experimental designs often compare treatment potency and effectiveness to decrease responding for drug vs. non-drug reinforcers (Mello and Negus, 1996) or escalated vs. non-escalated drug self-administration in subjects exposed to long- vs. short-access sessions (Edwards and Koob, 2013). These strategies have proven inadequate. Medications-development research using SODs remains vulnerable to false-positive results that do not translate to clinical effectiveness.

As an example, Table 2 lists some of the candidate medications that have failed in human testing for cocaine use disorder treatment despite preclinical SOD results interpreted as promising. Perhaps the most conspicuous recent example of failed translation has been the serotonin $5HT_{2C}$ receptor agonist lorcaserin. This target was promoted based on evidence that $5HT_{2C}$ agonists might oppose the activation of mesolimbic dopamine signaling that mediates the reinforcing effects of cocaine and most other abused drugs (Bubar and Cunningham, 2008; Howell and Cunningham, 2015). Preclinical SOD studies were interpreted to support this hypothesis insofar as lorcaserin and other $5HT_{2C}$ agonists were more potent to decrease cocaine as well as opioid self-administration than food-maintained responding by rats and nonhuman primates (Collins et al., 2018; Higgins et al., 2020). Lorcaserin advanced to both human-laboratory studies and a large clinical trial, but its effects in humans did not support the SOD-based hypothesis. In human-laboratory studies, lorcaserin increased rather than decreased choice of either cocaine or oxycodone vs. money (Pirtle et al., 2019; Brandt et al., 2020; Johns et al., 2021). In the clinical trial for cocaine use disorder sponsored by NIDA, lorcaserin was not different from placebo for endpoints reported

Table 2
Effects of candidate medications for cocaine use disorder in preclinical Single-Operant Drug self-administration procedures (SODs), preclinical drug-choice procedures, and human-laboratory studies/clinical trials. Preclinical results include both rats and nonhuman primates as research subjects where data were available, and are intended to be illustrative rather than comprehensive. Preclinical references were prioritized for studies that evaluated subchronic (≥3 consecutive days) treatment effects, although some studies evaluating acute medication effects were also included. Symbols indicate treatment-induced decreases (↓), increases (↑), or no change (—) in cocaine-taking behavior up to doses that produced other behavioral effects, such as depression in rates of operant behavior or clinical side effects. * asterisk indicates treatments that may produce rightward shifts in inverted-U shaped SOD dose-effect curves, decreasing self-administration of low doses but increasing self-administration of high doses.

Candidate medication and mechanism	Preclinical SOD result	Preclinical choice result	Human lab/ clinical trial result	Selected references
Monoamine releasers (e.g., d-amphetamine)	↓	↓	—/↓	(Grabowski et al., 2001; Negus, 2003; Chiodo et al., 2008; Czoty et al., 2011; Thomsen et al., 2013)
DA D_1 antagonists (e.g., SCH23390, ecopipam)	↓/↑*	—	↑	(Woolverton and Virus, 1989; Nann-Vernotica et al., 2001; Barrett et al., 2004; Czoty and Nader, 2021)
DA D_2 antagonists (e.g., olanzapine, risperidone, buspirone)	↓/↑*	—/↑	—/↑	(Gold and Balster, 1992; Grabowski et al., 2000; Howell et al., 2006; Bergman et al., 2013; Mello et al., 2013; Winhusen et al., 2014; John et al., 2015; Hutsell et al., 2016b)
DA D_2 partial agonists (e.g., aripiprazole)	↓	—	—/↑	(Bergman, 2008; Sorensen et al., 2008; Thomsen et al., 2008; Haney et al., 2011; Czoty and Nader, 2013; Lofwall et al., 2014)
5-HT_{2C} agonists (e.g., lorcaserin)	↓	—/↑	—/↑	(Collins et al., 2016; Banks and Negus, 2017b; Pirtle et al., 2019; Anastasio et al., 2020; Johns et al., 2021)
Kappa opioid receptor agonists (e.g., U50,488, enadoline) and antagonists (nor-BNI, LY2456302)	↓	—/↑	—/↑	(Kuzmin et al., 1997; Negus et al., 1997; Mello and Negus, 1998; Walsh et al., 2001; Negus, 2004; Wee et al., 2009; Hutsell et al., 2016a; Reed et al., 2018)

on clintrials.gov (NCT03007394), though full results have yet to be published.

2. Medications development with choice procedures

Drug choice procedures represent a different subtype of drug self-administration procedure with improved predictive validity relative to SODs for testing candidate medications for substance abuse (Negus and Banks, 2011; Czoty et al., 2016; Banks and Negus, 2017a; Venniro et al., 2020). In choice procedures, subjects have concurrent access to at least two operant manipulanda, such that responding on one manipulandum produces drug delivery, while responding on the other produces some non-drug alternative reinforcer, such as food or social interaction. Drug choice procedures were the only source of preclinical data interpreted to refute the utility of lorcaserin to treat cocaine and opioid abuse (Banks and Negus, 2017b; Panlilio et al., 2017; Townsend et al., 2020), and Table 2 shows that preclinical choice procedures have also yielded other results consistent with findings from human studies with both clinically effective and ineffective medications for cocaine use disorder.

Choice procedures have three attributes that likely contribute to their predictive validity (Negus and Banks, 2011; Banks and Negus, 2017a). First, choice procedures generate two dependent variables: (1) percent choice of the drug vs. non-drug alternative, and (2) total rates of responding and reinforcement summed across both reinforcers. These two variables permit dissociation of candidate-medication effects on relative reinforcing effects of the self-administered drug (reflected by changes in % Drug Choice) as opposed to general motor/cognitive impairment (reflected by decreases in overall rates of responding or reinforcement). An optimal medication profile in choice procedures is a decrease in drug choice without a decrease in total rate of responding or reinforcement. This signifies that the treatment has not only decreased drug reinforcement but also promoted behavioral reallocation to responding for the non-drug alternative. Conversely, undesirable treatments fail to decrease drug choice up to doses that decrease overall rates of responding or reinforcement. The availability of these two dependent variables reduces the probability of false-positive effects by treatments that impair motor/cognitive function.

A second feature of preclinical choice procedures in laboratory animals is that they are homologous to choice procedures commonly used to assess candidate medications in human-laboratory studies (Comer et al., 2008; Lile et al., 2020). For example, the human-laboratory studies that tested lorcaserin as a candidate treatment for cocaine and opioid abuse used choice procedures in which subjects had concurrent access to the drug of abuse as one option and to money as an alternative non-drug option (Pirtle et al., 2019; Brandt et al., 2020; Johns et al., 2021). As in any domain of translational research, this alignment of experimental endpoints may improve preclinical-to-clinical translational predictive validity (Yu, 2011; Venniro et al., 2020).

Lastly, choice procedures in both animal- and human-laboratory studies provide a simplistic model of the behavioral allocation between drug and non-drug reinforcers that occurs in natural environments (Vocci and Ling, 2005; American Psychiatric Association, 2013; Banks and Negus, 2017a; Ahmed, 2018). Indeed, a hallmark criterion of substance-use disorders is the expression of drug-taking behaviors at the expense of more adaptive behaviors maintained by nondrug reinforcers. Moreover, major drug-abuse treatment goals include not only a decrease in drug-taking behaviors, but also a reallocation of behavior to more adaptive alternatives. Choice procedures provide opportunities to assess the degree to which candidate treatments can promote this desirable behavioral reallocation.

3. Neuroscience with choice procedures

Drug choice procedures have the potential not only to improve translational validity in medications development, but also to open new opportunities for research on addiction mechanisms (Augier et al., 2018; Townsend et al., 2021). Of course, choice procedures can be used as an alternative to SODs for conventional studies that focus on mechanisms of drug reinforcement, and the same features of choice procedures that protect them from misleading results in medications development will also protect them from misleading results in studies with neurobiological manipulations. That being said, a major lesson from preclinical drug-choice studies is that drug consumption can be influenced not only by the reinforcing effectiveness of the drug, but also by reinforcing effectiveness of competing non-drug alternatives. As one example, Fig. 1A shows that fentanyl potency to maintain drug choice in rats is inversely related to the concentration of an alternative liquid-food reinforcer. Thus, drug choice increased when magnitude of the alternative reinforcer decreased. In this case, the magnitude of the alternative was manipulated directly, but sensitivity to non-drug alternative reinforcers can also be shaped by biological factors inherent to the subject. The implication is that any biological factor that reduces sensitivity to alternative reinforcers can be expected to reduce behavior maintained by those alternatives and increase risk that behavior will be allocated to drug choice.

Reduced biological sensitivity to alternative reinforcers may occur for a variety of innate or acquired reasons, but we suggest that one of the most important for drug addiction is a phenomenon we here call Heterologous Reinforcer Desensitization. Specifically, we propose that chronic consumption of an abused drug can produce neurobiological changes that reduce sensitivity to non-drug alternative reinforcers. This phenomenon is schematically illustrated in Fig. 1B, and well-known examples include withdrawal-induced decreases in reinforcing effectiveness of food, electrical brain stimulation, or social interaction in drug-dependent subjects (Spragg, 1940; Emmett-Oglesby et al., 1990; Negus and Miller, 2014). Moreover, as illustrated in Fig. 1C, if progressive drug use reduces reinforcing efficacy of non-drug alternatives more than the reinforcing efficacy of the drug itself, then the alternative becomes progressively less able to compete with drug, and behavioral allocation can be expected to drift relentlessly toward drug choice (Herrnstein and Prelec, 1992; Rachlin, 1997).

The heuristic framework of Heterologous Reinforcer Desensitization can be conceptualized as one particularly relevant manifestation of drug-induced "negative affect" proposed to be a driver of drug addiction (Hogarth, 2020; Koob, 2021); however, Heterologous Reinforcer Desensitization suggests a subtly different research approach that focuses on drug vs. non-drug choice rather than on rates of drug self-administration in SODs. Indeed, the first drug self-administration study ever conducted in animals demonstrated a withdrawal-induced increase in opioid-vs.-food choice in morphine-dependent chimpanzees (Spragg, 1940), and this phenomenon has been replicated in opioid-dependent baboons (Griffiths et al., 1975), rhesus monkeys (Negus, 2006; Negus and Rice, 2009), and rats (Townsend et al., 2021) (Fig. 1D). Overall, choice procedures can provide a framework to investigate both mechanisms of impaired sensitivity to non-drug reinforcers and strategies to normalize that sensitivity, increase non-drug reinforcer effectiveness to compete with drug reinforcers, and decrease overall drug choice.

4. Conclusions

In summary, medications development for substance abuse has stalled. We attribute this stagnation to an overreliance on Single-Operant Drug self-administration procedures (SODs) to investigate the mechanisms of drug abuse and test candidate medications for drug-abuse treatment. SODs are vulnerable to false-positive effects and neglect the potentially critical role played in addiction by impaired sensitivity to non-drug alternative reinforcers that might ordinarily compete with and constrain drug use. Enhanced use of choice procedures can improve preclinical-to-clinical translation of candidate-medication effects and provide an experimental framework for investigating the expression, mechanisms, and treatment of Heterologous

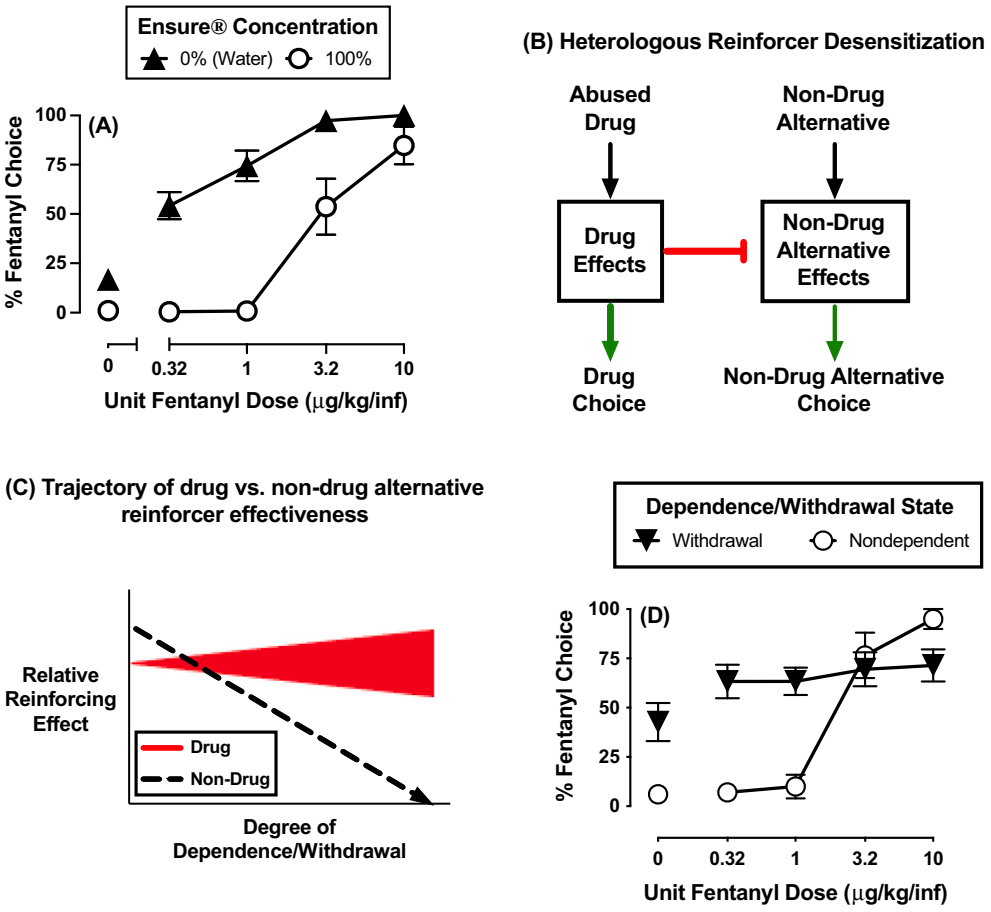

Fig. 1. Heterologous Reinforcer Desensitization may contribute to the development of addiction and serve as a target for drug-abuse treatment. In Heterologous Reinforcer Desensitization, drug consumption reduces reinforcing effectiveness of non-drug alternative reinforcers, thereby reducing effectiveness of those reinforcers to compete with drug for control of behavior and increasing the risk of drug choice. (A) Alternative reinforcer magnitude influences fentanyl potency to maintain drug choice in rats. Rats chose between fentanyl or a liquid alternative (water or 100% Ensure) during daily 2-h sessions divided into 5 20-min components. The fentanyl dose increased across components from 0 to 10 µg/kg/infusion, and the liquid reinforcer was either water or 100% Ensure across all components. N = 6. (B) Schematic of Heterologous Reinforcer Desensitization. Self-administered drug can produce effects leading both to reinforcement of drug-taking behavior and impairment of sensitivity to nondrug alternative reinforcers that maintain other behaviors. Mechanisms of drug-induced Heterologous Reinforcer Desensitization are proposed as a topic for future research in the context of choice procedures. (C) Hypothesized trajectory of changes in reinforcer effectiveness during a period of progressive drug use and Heterologous Reinforcer Desensitization. Sensitivity to drug reinforcement may increase or decrease as dependence progresses, but the more important effect is a progressive loss in sensitivity to nondrug alternative reinforcers. Risk of drug choice increases as relative value of non-drug alternatives decreases. (D) An example of the impact of Heterologous Reinforcer Desensitization in opioid-dependent rats. Withdrawal produces a decrease in food choice and associated increase in opioid choice. Rats were trained to choose between fentanyl and 18% Ensure, then rendered opioid dependent by introducing daily sessions of extended fentanyl access and withdrawal. After two weeks, there was an increase in fentanyl choice and a decrease in 18% Ensure choice (Townsend et al., 2021).

Reinforcer Desensitization as a contributor to addiction.

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