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Review

Translational research in addiction: Toward a framework for the development of novel therapeutics

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ABSTRACT

The development of novel substance use disorder (SUD) therapeutics is insufficient to meet the medical needs of a growing SUD patient population. The identification of translatable SUD models and tests is a crucial step in establishing a framework for SUD therapeutic development programs. The present review begins by identifying the clinical features of SUDs and highlights the narrow regulatory end-point required for approval of a novel SUD therapeutic. A conceptual overview of dependence is provided, followed by identification of potential intervention targets in the addiction cycle. The main components of the addiction cycle provide the framework for a discussion of preclinical models and their clinical analogs, all of which are focused on isolated behavioral end-points thought to be relevant to the persistence of compulsive drug use. Thus, the greatest obstacle to successful development is the gap between the multiplicity of preclinical and early clinical end-points and the regulatory end-point of sustained abstinence. This review proposes two pathways to bridging this gap: further development and validation of the preclinical extended access self-administration model; inclusion of secondary end-points comprising all of the measures highlighted in the present discussion in Phase 3 trials. Further, completion of the postdictive validation of analogous preclinical and clinical assays is of high priority. Ultimately, demonstration of the relevance and validity of a variety of end-points to the ultimate goal of abstinence will allow researchers to identify truly relevant therapeutic mechanisms and intervention targets, and establish a framework for SUD therapeutic development that allows optimal decision-making and resource allocation.

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1. Introduction

Substance use disorders (SUDs) present a major unmet medical need, with the human costs of dependence on the licit drugs of abuse nicotine and ethanol reaching 440,000 and 80,000 deaths annually in the US, respectively [1,2]. In the United States alone, illicit drug abuse and addiction costs society $180.9 billion per year [3] and SUDs are associated with increased risk of death from multiple causes [4]. The large numbers of individuals dependent on one, or multiple, drugs of abuse contrasts with the paucity of clinically effective therapeutics. The multi-faceted nature of the maladaptive behaviors exhibited by SUD individuals presents both opportunities and challenges for the development of effective medications. For example, the recidivist nature of SUDs presents an additional target for novel therapeutics, in so far as it may be mediated by separable neural substrates compared to acute intoxication or acute withdrawal after abrupt termination of chronic substance use. At the present time, however, the complexity of SUD has increased the risk inherent in the development of novel therapeutics.

One reason for the relative lack of SUD therapeutics is the clinical development process: specifically, the tremendous costs and high levels of risk involved at each stage in the development process. For example, the development cost for a compound that successfully moves from Phase 1 to approval is estimated to be $1.2 billion, with higher costs for central nervous system therapeutics [5]. Furthermore, the costs are amplified as the size of clinical trials increases during successive phases of development. Therefore, the elimination of compounds that exhibit low probabilities of success is highly important, because this allows the re-allocation of resources to other programs. In addition to development costs, early identification and selection of candidates with high chances of success maximizes the time on the market prior to patent expiration. Conducting efficacy trials with a clinical endpoint accepted by regulatory authorities – abstinence from drug use for SUD therapeutics – can be long and costly, and in the worst case, inconclusive. Therefore, objective measures in early clinical studies that are predictive of clinical efficacy with respect to abstinence from drug use can significantly reduce the risk of failure. In addition, early clinical studies provide important information such as pharmacokinetics, safety profile and efficacious dose range. The relevance of these efficacy model end-points to the final regulatory end-point of abstinence is highly important, and may be evaluated via Phase 3 trials designed to capture the efficacy model end-points as secondary end-points or via the execution of postdictive translational studies with approved SUD medications. For example, clinical trials of varenicline and bupropion included measures of nicotine withdrawal and cigarette reward in addition to the primary abstinence measure [6,7].

At present, there is a lack of preclinical and clinical models that have demonstrable predictive validity. The relative paucity of effective therapeutics that is the results of rational design has limited assessment of the predictive validity of the dizzying array of preclinical models of compulsive drug use. In addition, early research required delineating the complexity of SUD into tractable components. This resulted in a multiplicity of preclinical and clinical models/assays that focus on a variety of specific, often single, end-points. Nonetheless, regulatory approval of a novel SUD therapeutic requires demonstration of sustained abstinence over a specified period of time. Therefore, a gap exists between the many models and assays focused on specific components of SUD, that represent potential therapeutic intervention targets, and the ultimate goal of abstinence in Phase 3 trials. This gap presents a major hurdle to effective drug development. It is suggested here that postdictive validation of preclinical and early clinical models/assays, utilizing all of the currently available SUD medications, can provide initial evidence for the relevance of the end-points used. Further evidence can be obtained from two sources: (1) continued development of the extended access self-administration (SA) procedure, a preclinical model that allows distillation of the complexity of SUD into a single end-point of drug intake, but also allows demonstration of specific mechanisms of action/intervention targets in the same subjects; (2) Phase 3 trials of potential novel medications that include these intervention targets as secondary end-points in addition to the primary end-point of abstinence.

The present review is intended for researchers interested in translational models (preclinical and clinical) to aid development of novel therapeutic drugs for the treatment of SUD. The review aims to outline a path toward the establishment of a framework for the development of novel SUD therapeutics that rests on a solid theoretical understanding of SUD and a deep knowledge of the relevant neurobiological substrates, and is comprised of validated and highly translatable preclinical and clinical models. The review begins by identifying the clinical features of SUDs and the clinical endpoints required to demonstrate efficacy of pharmaceutical treatments for regulatory approval. We then establish likely intervention targets in SUDs, based on current conceptualization of the dependence process, and highlight preclinical models that may provide high translational value. In addition, we identify weaknesses and/or recent advances in the array of preclinical models available and suggest potential opportunities in adapting existing models or developing novel models. In identifying clinical analogs of these preclinical procedures, we also discuss currently available SUD therapeutics in terms of postdictive validity (recently referred to as the Rosetta Stone approach [8]). Finally, we highlight the extended access SA model as a preclinical model of Phase 3 trials. In summary, the present discussion provides an overview of currently available and potential translational models and proposes the development of a framework for the successful development of novel SUD therapeutics in a risk-averse environment.

2. The clinical characteristics of SUDs

The Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association [9] generally defines substance dependence as 'a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following occurring at any time in the same 12-month period: (1) tolerance (a need for markedly increased amounts of the substance to achieve intoxication or desired effects/markedly diminished effect with continued use of the same amount of the substance); (2) withdrawal (the characteristic withdrawal syndrome for the substance, the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms); (3) the substance is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities necessary to obtain or use the substance or recover from its effect; (6) important social occupational or recreational activities are given up or reduced because of substance use (7) substance use 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.

The International Classification of Diseases (ICD-10) of the World Health Organisation [10] uses criteria virtually identical to the above, with the only real difference related to the time-course of the symptoms (ICD-10: three or more of these manifestations present together for at least 1 month, or repeatedly over 12 months; DSM-IV: three or more manifestations present at any time in a 12-month period). Beyond the first two manifestations, the

description clearly indicates that the behavioral changes associated with SUDs are maladaptive, as defined by the negative consequences of those behavioral changes.

This behavior-based definition underlies the distinction of SUDs from other medical disease states. Thus, drug-taking and drug-seeking provide measurable end-points in both animals and humans for the assessment of potential therapeutic effects. From the perspective of regulatory approval, the establishment and maintenance of abstinence is the crucial end-point. Nonetheless, the behavioral consequences of drug withdrawal and prolonged drug exposure have provided additional avenues of research in the preclinical field. In clinical studies, measures of withdrawal such as negative affect or anhedonia, and measures of the rewarding effects of substances of abuse, or the effects of exposure to drug-associated stimuli, can provide primary end-points in early clinical studies, but abstinence is the only endpoint for regulatory approval of novel SUD therapeutics. Such additional measures can improve confidence by providing valuable data for decision-making in the development of novel compounds, including whether to invest heavily in a Phase 3 trial, and can provide evidence of efficacy at what may be the primary target. The relevant of these secondary end-points to the goal of abstinence should be confirmed via comprehensive Phase 3 trials and postdictive validation of clinical laboratory-based models/assays. Finally, further development and validation of the extended access SA model should enhance the translatability of preclinical SUD models/assays.

3. Conceptual framework for addiction models

'Addiction' has been used to label a variety of behaviors related to the use of drugs. For our purposes, 'addiction' may simply be defined as the compulsive use of a substance, which is the critical element of a SUD from which various manifestations and maladaptive behaviors arise, as described in DSM-IV [9]. Thus, the development of addiction has been conceptualized as a progressive loss of control over drug-taking and drug-seeking behaviors, in which initial, controlled drug use becomes habitual and finally compulsive through repeated drug use [11,12]. Koob and Le Moal [13] suggest that each episode of drug use is characterized by three stages – binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Repeated cycling through these stages results in the transition from voluntary to habitual and compulsive use of the drug, due to time-dependent alterations in each stage of the cycle such that chronic use results in diminished binge/intoxication for a given dose ('tolerance'), increased withdrawal/negative affect during abstinence or between drug use episodes, and increased preoccupation/anticipation with resumption of drug use [14].

Other researchers have focused on different components of the addiction process. The emergence of habitual and compulsive drug use is thought to represent drug-induced enhancement of habit formation and drug-induced impairment of the ability to regain control over habitual responding [15]. The emergence of habitual and compulsive drug-seeking behavior explains continued drug-seeking and -taking even when the acute rewarding effects of the drug are diminished, for example due to tolerance, or are associated with negative consequences [12]. Counter-adaptive mechanisms, for example linked to alterations in receptor number/function, result in increased withdrawal/negative affect [16,17]. Allostatic change in hedonic set point refers to a downward shift in the brain reward system, mediated by altered brain reward and stress mechanisms [18,19], and is essentially an extension of the counteradaptation theory. Finally, increased incentive salience of drug-associated cues has been linked to increased preoccupation/anticipation [20]. In addition, the salience of cues and context, and the effect of re-exposure to drug, has all been investigated in rodent models of relapse [21]. Consistent with the loss of control over drug use is an increased recognition that impaired prefrontal cortical function may be important in SUD persistence [14], and as such, researchers have begun to focus on the cognitive sequelae of drug use and the role of pre-existing cognitive deficits as risk factors for drug use [22]. Preclinical work exploring each of these components of addiction – binge/intoxication, withdrawal/negative affect, loss of control over drug use (preoccupation/anticipation) – has yielded multiple animal models that are hypothesized to provide measures of the relevant behavior with varying degrees of validity, practicability, and the availability of clinical analogs (see Fig. 1 for a synthesis of these models). Finally, it should be noted that the degree to which each stage of the addiction cycle promotes the development and maintenance of addiction is thought to vary by drug class [14], and this is likely to be very important in the development of clinically efficacious SUD therapeutics, not least with regard to the selection of relevant translational models.

4. Potential SUD intervention targets

The conceptual framework described above allows the discussion of possible pharmacologic interventions at one or more points within the addiction cycle or at the mechanisms that mediate the longitudinal progression of the addiction process. However, the complexity of the addiction cycle, including interactions between the different stages of the cycle, suggests that it could be difficult to predict treatment success or failure (i.e., with the clinical endpoint required for regulatory approval) based on clinical results that address only a single stage of the cycle. In addition, a no-go decision based on negative findings from a single clinical translational model would require a high level of confidence in the model. From a decision-making standpoint in the development process, this points to a need for additional translational models that address multiple addiction cycle stages in order to make decisions with confidence. Finally, as noted above, different classes of substances of abuse are likely to require demonstration of efficacy in different combinations of translational models to enhance confidence in achieving the final clinical end-point (abstinence) required for regulatory approval.

In targeting the binge/intoxication stage of the addiction cycle, the most obvious strategy is to prevent the drug from reaching its target at intoxicating concentrations. Thus mechanisms that block drug absorption, prevent distribution of the drug to the brain, or block the drug at a target receptor, are all viable candidates for this strategy. Drug vaccines, opioid antagonists (in this case, when used specifically for opiate addiction), and the antagonist-like properties of a partial agonist such as varenicline (Chantix®/Champix®) are all relevant examples. Other mechanisms target the binge/intoxication stage downstream of the actual drug target by affecting the mechanisms that mediate the rewarding effects of drug-taking, as in the case of naltrexone (Depade®, ReVia®) when used for alcohol addiction, or by producing aversive effects after drug ingestion, as in the case of disulfiram (Antabuse®) for alcoholism.

Mechanisms targeting the withdrawal/negative affect stage address the negative reinforcing effects of drug-taking that occur when drug is taken to relieve the symptoms of acute, or chronic, withdrawal after cessation of chronic use. This mechanism is believed to play a major role in the efficacy of drug replacement therapies that work, generally as agonists or partial agonists, directly at the drug target. Notable examples include methadone for opiate addiction and nicotine replacement therapy for nicotine dependence. Partial agonists such as varenicline, however, may also act via a 'replacement' therapeutic mechanism. Specifically,

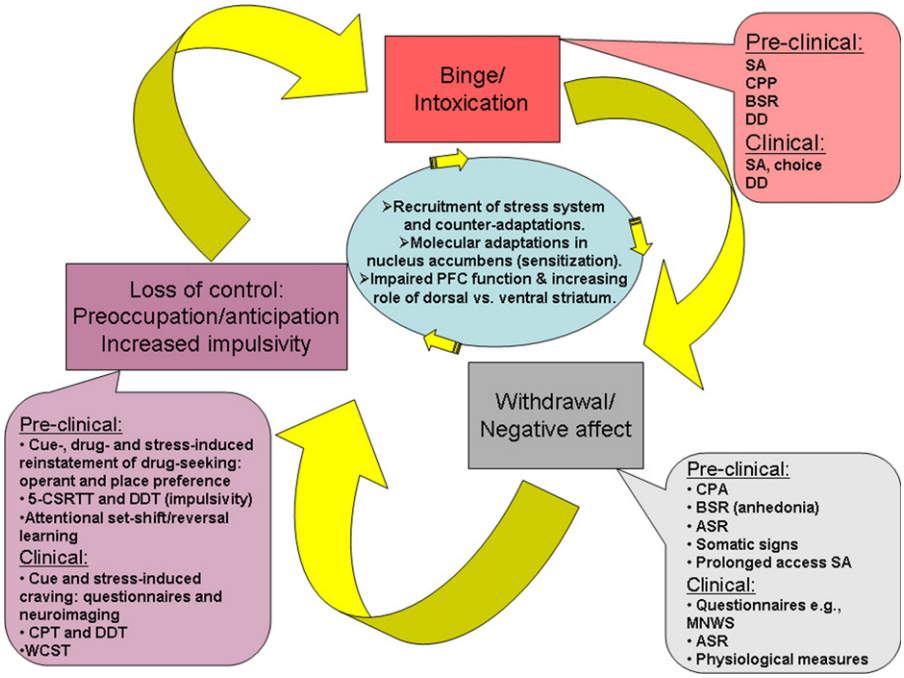

Fig. 1. The addiction cycle: preclinical and clinical models/assays and underlying mechanisms. The figure is an adaptation of the addiction cycle as proposed by Koob and colleagues, with the preoccupation/anticipation stage replaced by 'loss of control', thereby incorporating the cognitive sequelae of drug dependence, the pathological formation and persistence of habitual responding, and perhaps the effects of behavioral sensitization on motivational processes. The three stages of the cycle (squares) are linked by the spiraling arrows, with preclinical and clinical assays of the relevant behaviors indicated in the speech-balloons. Finally, the central oval contains the substrates underlying (1) negative affect/withdrawal, (2) loss of control/increased motivation to obtain drug, (3) cognitive sequelae including pathological habitual responding. *Abbreviations*: SA: self-administration; CPP: conditioned place preference; BSR: brain stimulation reward; DD: drug discrimination; CPA: conditioned place aversion; ASR: acoustic startle reflex; MNWS: Minnesota Nicotine Withdrawal Scale; 5-CSRTT: 5-choice serial reaction time task; DDT: delayed discounting task; CPT: continuous performance task; WCST: Wisconsin Card Sort Task; PFC: prefrontal cortex.

the rewarding and reward-enhancing properties of abused drugs are at least partly replaced by partial agonist therapies such as varenicline for nicotine dependence or buprenorphine (Schering-Plough's Subutex®) for opiate dependence. As indicated above, partial agonist therapies also provide blockade of the acute binge/intoxicating effects of the drug of abuse by occupying the target receptor. Thus, 'replacement' therapies provide (1) attenuation of withdrawal, (2) blockade of binge/intoxication, (3) replacement of reward/reward-enhancing effects of drugs of abuse. Other potential treatments could target the mechanisms that mediate signs of physical withdrawal or the negative affective states associated with drug cessation after chronic use. For example, benzodiazepines are used to treat the physical manifestations of severe alcohol withdrawal, and the atypical antidepressant bupropion likely ameliorates the dysphoric and anhedonic effects of nicotine withdrawal.

An additional intervention target is the treatment of the increased preoccupation/anticipation with drug-seeking and drug-taking observed in SUD individuals. Research has identified multiple processes that may underlie this phenomenon, but the most relevant from a translational and drug development perspective, currently, is the control of behavior by environmental and physiological stimuli associated with relapse to habitual or compulsive behavioral patterns, which includes relapse to drug-taking and/or drug-seeking behavior. This is a difficult area due to the multiplicity of triggers for relapse, for example, environmental stimuli such as contextual cues or advertising of the abused substance; but also pharmacological stimuli such as the ingestion of a commonly co-administered drug for polydrug users; and finally neuropsychiatric stimuli such as increased anxiety or stressful life events. The persistence of maladaptive behavioral patterns constitutes an additional hurdle to efficacious treatment, and may be linked to long-lasting cognitive deficits. The persistence of these behavioral changes is likely mediated by neurobiological changes, such as altered synaptic transmission in brain reward circuitry or impaired function of subregions of the prefrontal cortex. Such biological targets raise the possibility of developing disease-modifying therapeutics, where alteration of the neurobiological substrates would result in normalization or modification of maladaptive behavioral patterns.

The concept of controlled or reduced use of drugs of abuse is typically achieved through social or healthcare policies. Thus, opiate-dependent individuals who receive methadone are typically asked to provide 'clean' urine samples in order to continue receiving a methadone prescription. For about 100 years, British heroin addicts were prescribed heroin, although that practice greatly declined after 1965 [23]. Switzerland and the Netherlands introduced similar systems, including supervised drug injection facilities [24], and other social policies have aimed at harm reduction via the provision of syringes to intravenous drug users. Pharmacological therapeutics are unlikely to focus on this potential intervention target, although the provision of methadone or the use of oral/dermal delivery of nicotine in opiate/nicotine dependence, respectively, may be considered a form of harm reduction (discussed here as replacement therapies). A new endpoint for alcohol dependence studies (percentage of subjects with no heavy drinking days [25]) may be acceptable to the FDA, and is an example of controlled or reduced use of a substance of abuse. For preclinical models, an easy first-step would be toward evaluating the effects of potential therapeutics in procedures hypothesized to model the development of 'dependence', for example, escalation of psychostimulant SA or increased alcohol SA after dependence induction. Such therapeutics would ideally reduce the excessive intake in 'dependent' individuals, without attaining total cessation or affecting intake in non-dependent subjects.

5. From preclinical models to clinical studies

As implied in the above discussion, although addiction is a highly complex disorder, decades of research have provided a basic understanding and recognition of the discrete components of the disorder, their inter-relationship and temporal dynamics. The development of clinically efficacious therapeutics will most likely be achieved by targeting specific components of the disorder outlined above. During the development process, selection of the relevant translational model(s) must be based upon (1) the SUD of interest (drug class), (2) the availability of a model validated for a therapeutic compound with a similar mechanism of action or based on the target SUD, (3) the possibility of multiple intervention targets for a single drug candidate, and (4) our understanding of the biology underlying the model. In this section, the most relevant preclinical models of SUD are highlighted and briefly described within this conceptual framework. In determining the utility of these models, it is important to consider their validity to the disease processes, the availability of related clinical assays, and therefore their translatability to clinical endpoints. Further, practical considerations such as ease of use and expense are important. Finally, necessary improvement or gaps are suggested or identified. In general, the discussion focuses on Types 4 and 5 biomarkers specific to SUD, that is, physiological and pathophysiological measures of the disease process [26]. Earlier biomarkers are highlighted where relevant – for example, neuroimaging (Type 3) and receptor occupancy (Type 2) are increasingly important in terms of providing cross-species data.

Due to the narrow end-point required for regulatory approval (abstinence), the present discussion proposes that extended access SA procedures, shown to recruit multiple sources of motivation for continued drug use, provide potentially the most valuable preclinical model available as an analog of Phase 3 trials (see Fig. 2). It is proposed that preclinical assays that focus on specific components of the addiction cycle are highly useful preliminary steps for demonstrating efficacy at selected intervention targets. After obtaining positive data in these preliminary assays, candidate therapeutics should be evaluated in extended access SA procedures to provide proof of concept: that is, successful targeting of a specific component of the disease process results in a significant decrease in drug intake. Similarly, early clinical studies should first provide confirmatory data that a candidate therapeutic exhibits efficacy at the same intervention target as previously shown in preclinical studies. Having done so, and having thereby gained valuable data such as optimal dose, safety and tolerability, the compound can be confidently advanced to Phase 3 trials for final proof of efficacy. Of course, the relevance of the early clinical measures must first be demonstrated by validation with currently available SUD therapeutics.

5.1. Binge/intoxication stage

Within the preclinical literature, the binge/intoxication stage is typically framed as the rewarding ('reinforcing' and 'reinforcement-enhancing') and subjective ('interoceptive') properties of drugs of abuse. Included in this section is the recruitment of aversive effects of drug ingestion.

5.1.1. Blockade of rewarding effects

5.1.1.1. Preclinical assays and models. Drug-induced blockade of the rewarding properties of drugs of abuse is often thought of as a key characteristic for a potential SUD therapeutic. Consistent with the putative importance of acute rewarding ('intoxicating') properties of drugs of abuse, there is a wealth of animal models and assays to evaluate rewarding properties. It is important to note that reward may be sub-divided into the reinforcing properties of a compound alone, and the facilitatory or enhancing effect of the compound on other reinforcing stimuli. Furthermore, the repeated pairing of drug delivery with specific environmental stimuli confers conditioned reinforcing properties on those stimuli – these are mainly discussed under the models of relapse, due to their hypothesized importance as inducers of craving and relapse to drug-seeking/-taking.

Two major animal models are hypothesized to provide a measure of the reinforcing properties of drugs of abuse: SA and

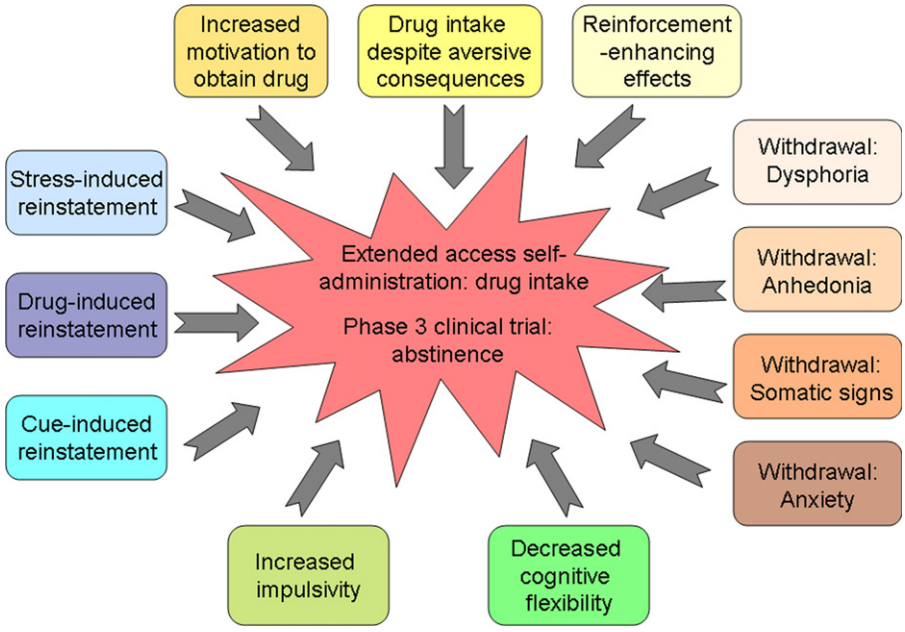

Fig. 2. Compulsive drug use intervention targets. The figure shows the currently demonstrated and potential intervention targets/mechanisms recruited by the extended access self-administration model and hypothesized to play a role in compulsive drug use in Phase 3 trials. It is proposed that identification or validation of all of these targets/mechanisms in early preclinical and clinical assays will provide preliminary data that allows confident decision-making on whether a compound should be moved ahead to extended access self-administration studies (preclinical stage) or Phase 3 trials (clinical development).

conditioned place preference. The most common, and most widely accepted, model is SA. Frequently SA studies utilize intravenous delivery of the drug (e.g. [27–29]), although alternative routes are also used – particularly for ethanol which is typically available in solution for oral ingestion [30]. Usually the drug of abuse is delivered after the completion of an instrumental response by the test subject – most often a lever-press, although nose-pokes are also frequently utilized, particularly for mouse studies (e.g. [31]). Within the operant SA methodology, task variants include the degree of access – in other words, the frequency and duration of the test sessions – and the specific type of reinforcement schedule used (e.g., fixed-ratio or progressive-ratio). Of most relevance to providing valid models for SUD is the increasing use of prolonged, often 23 h daily, SA sessions (e.g. [32–35]), and these are further discussed in Section 6. A final factor in SA study design is the typical use of acute administration of receptor antagonists and other potential therapeutic compounds. Clearly, clinical efficacy in an SUD requires chronic administration of the test compound, and it is important to demonstrate efficacy of chronic administration in preclinical studies (e.g., see [36] for review of preclinical studies with bupropion (Zyban ®)).

In addition to SA, conditioned place preference (CPP) is commonly used to provide a measure of the reinforcing properties of a drug of abuse and the conditioned reinforcing properties of the drug-paired environment. In the CPP assay, the experimental subject undergoes a number of conditioning trials where the drug or vehicle is administered by the experimenter prior to the subject being confined to a specific drug- or vehicle-paired environment. On the test day, the subject is allowed to freely move between the drug- or the vehicle-paired environment: the relative amount of time spent in the previously drug-paired environment provides a measure of the conditioned reinforcing properties of the drug-paired environment that are dependent on reinforcing properties of the drug itself (e.g. [37–40]). Typically, groups of subjects can be treated with a drug of abuse plus various doses of a novel therapeutic medication during the conditioning trials. Blockade of the reinforcing property of the drug of abuse will block the induction of the conditioned place preference (e.g. [40,41]). Thus, while the CPP assay can provide measures of primary and secondary reinforcing properties, the assay relies on experimenter-administered drug rather than control of drug intake by the experimental subject, as in SA. An advantage of the CPP assay, however, is that bivalent effects of a drug treatment can be assessed. Specifically, pre-treatment with a novel therapeutic compound that rendered the drug aversive would result in a decrease in time spent in the (drug + treatment)-paired environment relative to vehicle and relative to (drug + no treatment), rather than equaling the time spent due to blockade of rewarding effects.

As indicated above, drugs of abuse enhance the reinforcing properties of non-drug, or alternative, reinforcers. Again, there are a number of procedures available to quantify the reinforcement-enhancing properties of drugs of abuse. Unlike the CPP assay, which typically assesses the effects of experiment-administered drugs on hedonically neutral (i.e., non-preferred) environments, the reinforcement-enhancing assays generally measure the effects of experimenter-administered drugs on reinforcing stimuli. Thus, drugs of abuse have been shown to enhance operant responding for sucrose pellets (e.g. [42]) or visual reinforcers [43]. Most commonly, however, intracranial self-stimulation (brain stimulation reward, BSR) has been used. This procedure requires subjects to emit an operant response (e.g., a quarter turn of a wheel manipulandum) to obtain short bursts of electrical stimulation delivered to sub-regions of the brain reward circuit. The acute administration of drugs of abuse enhances the reinforcing properties of the electrical stimulation (e.g. [44–46]). Similarly to CPP, the ICSS procedure provides a bivalent read-out, with enhancement of BSR after acute administration of drugs of abuse and, conversely, attenuation of BSR after cessation of chronic administration of drugs of abuse (see Section 5.2). Although most commonly performed using non-contingent administration of the drug of abuse, the BSR procedure has also been used in catheterized rats allowed to self-administer a drug (e.g. [47,48]). In addition to enhancement of other primary reinforcers, acute administration of drugs of abuse also enhances the motivational properties of conditioned reinforcers [49–51]. Thus, there is an array of approaches for assessing the reward-enhancing properties of drugs of abuse, which likely play a role in the development and maintenance of SUD.

5.1.1.2. Clinical end-points and assays. Some of the procedures highlighted above are readily applicable to the clinical setting. Laboratory-based measurement of the reinforcing properties of drugs of abuse is already performed via human SA of nicotine, methamphetamine, cocaine, morphine, heroin and ethanol (e.g. [52]). Differences exist, however, with the preclinical methodology. For example, many human SA studies utilize a choice procedure where human subjects are allowed to choose between delivery of drug or saline/placebo (e.g. [53,54]). Nonetheless, examples do exist of operant responding for intravenous delivery of drug, in a manner that is very similar to the typical SA study in animals (e.g. [55,56]). Alternatively, combinations of reinforcement schedule and choice procedures are also used (e.g. [57]). The effects of potential SUD therapeutics could be readily measured utilizing these procedures to provide proof-of-concept data (e.g. [57]). As indicated by the use of choice procedures in the human SA literature, human subjects can perform operant tasks where the reinforcer is non-drug – either physiological (e.g., a sweet food) or abstract (e.g., money). The effects of potential SUD therapeutics on enhancement of such behaviors by drugs of abuse could be assessed. Clearly, however, BSR cannot be measured in humans via electrode implantation, although transcranial magnetic stimulation (e.g. [58]) could provide a viable non-invasive clinical approach. The state (i.e., withdrawal/intoxication) of the subjects in laboratory-based SA studies has to be carefully controlled as potential confounding factors. As indicated above, Phase 3 trials provide evidence of clinical efficacy in SUD out-patient populations, where multiple sources of motivation maintain compulsive drug use. Thus, artificial/novel setting and multiple motivational states may limit the predictive value of laboratory-based limited-access SA of drugs with respect to efficacy in an out-patient setting.

5.1.1.3. Validity. From a drug discovery perspective, the crucial feature of a preclinical model is predictive validity. In the absence of clinically efficacious treatments, one must consider additional forms of validity to provide an adequate level of confidence in the model. Self-administration in animals has long been considered to have a reasonable amount of face validity, enhanced by the use of prolonged/unlimited access rather than limited access (e.g., one to several hours daily test sessions) models. Of the clinically available SUD therapeutics, different drug classes provide varying evidence of postdictive validity. For example, acute administration of the nicotinic acetylcholine receptor partial agonist varenicline is effective in decreasing nicotine SA [59,60] and attenuated nicotine-induced enhancement of BSR [61]. Importantly, varenicline was also found to attenuate the acute rewarding effects of cigarettes [6,62] and intravenous nicotine [63] in humans. For the atypical antidepressant bupropion, however, the data are mixed (for review [36]). Both compounds are associated with at least a doubling of quit rates in smokers [64,65]. Naltrexone decreased ethanol SA and is effective in the treatment of alcohol dependence, apparently due to blockade of rewarding effects. Interestingly,

varenicline has been reported to decrease heavy drinking in alcoholic smokers [66] and decreased ethanol SA in rats [67]. Finally, there is some limited evidence from studies with the anticonvulsant medication topiramate (Topamax®) for the validity of preclinical assays of ethanol intake. Specifically, topiramate has been shown to significantly and selectively decrease ethanol intake in rats [68–70], although the effect appeared to diminish during chronic treatment and was variable under free-access conditions [69,70]. Overall, however, the preclinical data indicated that topiramate decreased ethanol SA, and this is consistent with the data from full-scale clinical trials indicating that topiramate decreased alcohol consumption in alcoholics, including the achievement of total abstinence or a reduction in heavy drinking days [25,71,72]. Cocaine SA is sensitive to passive vaccination with cocaine antibodies [73], and preliminary clinical studies indicated decreased likelihood of cocaine use in vaccinated subjects [74], and decreased subjective effects of smoked cocaine [75]. For dependence on heroin and other opiates, the blockade of rewarding effects (for example, via naloxone or naltrexone) is complicated by low patient compliance, perhaps due to the precipitation of withdrawal ([76]; Table 1). Given the multi-faceted nature of SUDs, and the likely variation across abused substances in the relative importance of the various intervention targets, efficacy in models of the reinforcing properties of drugs of abuse may not accurately predict ultimate clinical efficacy. Furthermore, a limited access SA study in humans could have less relevance to a clinical out-patient situation where drugs are available either continuously or in an unpredictable manner. Nonetheless, early clinical studies utilizing human SA, for example, should provide concordant data with the animal studies, and would provide support for studies of greater complexity and cost.

Neuroimaging and microdialysis studies provide at least some evidence, as Type 3 biomarkers, for the commonality of neural substrates in both animal and human SA. Specifically, positron emission tomography (PET) studies demonstrated increased striatal dopamine during the acute intoxicating effects of drugs of abuse [77,78], and functional magnetic resonance imaging (fMRI) revealed diminished ventral striatal activity during human cocaine SA [79]. In rats, microdialysis studies consistently reveal the elevation of dopamine overflow during SA of d-amphetamine, cocaine and ethanol [80–82]. Voltammetry (e.g. [83]) and amperometry (e.g. [84]) have provided similar biomarkers in preclinical studies. Overall, elevated striatal dopamine overflow has been repeatedly demonstrated in human and animals during SA of drugs of abuse. It should be noted, however, that the functional significance of tonic dopamine release in the striatum is still a matter of debate; furthermore, additional brain reward circuitry sub-regions and neurotransmitters are likely to be crucial to these behaviors across multiple species. Brain stimulation reward studies demonstrate the involvement of striatal dopamine [85–87], and sucrose SA has also been associated with elevated dopamine efflux in the ventral striatum [88]. Thus, dopamine in the ventral striatum provides a Type 3 biomarker of reinforced behavior. Such a translational biomarker could be used as a secondary end-point in preclinical and clinical studies assessing the effects of potential SUD therapeutics on reinforcing and reinforcement-enhancing effects of drugs of abuse.

5.1.1.4. Practicality. The preclinical assays outlined above vary in the apparatus required and the degree of technical difficulty. For example, CPP is relatively easy and inexpensive to perform, but operant SA and intracranial self-stimulation require surgical intervention and sophisticated apparatus. Further, due to the chronic nature of the studies (e.g., requirement for training), these studies are relatively expensive. Human versions of these procedures are also expensive, and for ethical reasons require the use of volunteer drug users. The use of such populations requires additional safeguards against the confounding effects of current exposure to illicit drugs or withdrawal states. Nonetheless, before embarking on costly full-scale clinical trials, human SA studies could provide a valuable proof-of-concept, albeit requiring interpretation in the context of additional studies depending on the SUD of interest.

5.1.1.5. Methodological improvements and opportunities. The use of striatal dopamine overflow or receptor occupancy could provide a valuable secondary end-point for preclinical studies assessing the effects of SUD therapeutics on the rewarding effects of drugs of abuse. An additional opportunity for improving the preclinical SA model is related to the selection of the test subjects. Traditionally, a cohort of rats is trained to self-administer, for example, cocaine. Only catheter failure or sickness results in exclusion of the subjects from the study. However, recent work demonstrated that only a subset of rats allowed extended access to cocaine SA will persist in drug-taking when cocaine delivery is paired with foot-shock [89], or when an alternative, non-essential physiological reinforcer is available [90]. Clearly, this subset of rats may represent a far more relevant test population with greater predictive validity for tests of SUD therapeutics. This issue is discussed further in the section of extended access SA procedures.

5.1.2. Interoceptive ('subjective') drug effects: blockade and substitution

5.1.2.1. Preclinical assays and models. Substitution for the interoceptive properties of drugs of abuse is traditionally measured by drug discrimination procedures. In a drug discrimination procedure,

Table 1
Validation of preclinical models and clinical analogs: The table shows potential intervention targets, currently available preclinical models/assays, their corresponding clinical analogs and whether the approach has been validated (i.e., approved SUD medications give a positive signal) across both preclinical and clinical assays.

Intervention target	Preclinical model/assay	Clinical assay	Translational validation
Intoxication	Self-administration	Self-administration	Yes
Intoxication	Conditioned place preference	None	–
Intoxication	Brain stimulation reward	Transcranial magnetic stimulation?	–
Intoxication	Non-drug reinforcer-enhancement	Non-drug reinforcer-enhancement	No
Intoxication	Drug discrimination	Drug discrimination	Yes
Withdrawal	Conditioned place aversion	Questionnaires	Yes
Withdrawal	Brain stimulation reward	Questionnaires	Yes
Withdrawal	Acoustic startle reflex	Acoustic startle reflex	No
Withdrawal	Somatic signs of withdrawal	Clinical signs	Yes
Loss of control	Cue-induced reinstatement	Cue-induced craving	No
Loss of control	Drug-induced reinstatement	Drug-induced craving	Yes
Loss of control	Stress-induced reinstatement	Stress-induced craving	No
Loss of control	5-Choice serial reaction time task	Cont. performance test	No
Loss of control	Delay discounting task	Delay discounting task	No
Loss of control	Attentional set-shift	Wisc. Card Sort Test	No
Loss of control	Reversal learning	Wisc. Card Sort Test	No

experimental subjects are trained to make an operant response that varies in the presence or absence of the training drug or vehicle. For example, a rat may be trained to respond on the right-hand lever in an operant box after it receives an injection of a drug such as cocaine, but on the left-hand lever after receiving an injection of saline. The correct response is rewarded by a non-drug reinforcer (typically a food pellet). After successful acquisition of the task, a novel compound can be administered, in which case responding on either lever is not reinforced (or both levers are reinforced). The proportion of responses made on the previously drug-associated lever provides a measure of the similarity of the interoceptive properties of the training and test compounds [91,92]. Although most often used to assess the abuse liability of a novel chemical entity that is psychoactive and may be chemically or pharmacologically similar to known drugs of abuse (e.g. [93]), this procedure can also be used to assess the effects of novel SUD therapeutics in blocking the interoceptive effects of the drug of abuse [94].

The development of partial agonists as SUD therapeutics with relatively reasonable clinical efficacy (buprenorphine, varenicline) has led to the idea that some degree of substitution for the interoceptive properties of a drug of abuse may be a desirable feature of an SUD therapeutic (e.g., varenicline: [59]). Of course, this assumes that the compound can still be shown to exhibit decreased abuse liability [59,95]. Beyond substituting for the interoceptive properties of nicotine, varenicline also enhances BSR [61] and increased dopamine overflow in the ventral striatum [59]. Preclinical evaluation of a potential SUD therapeutic that is based on the 'substitution' approach should include assessment of the effects of that compound in (1) drug discrimination, (2) SA, (3) BSR or reinforcing properties of a non-drug reinforcer, (4) withdrawal assays (currently lacking for varenicline). It should be noted, however, that a partial agonist medication must exhibit decreased intrinsic reinforcing and reinforcement-enhancing properties compared to the drug of abuse, and should attenuate the reinforcing properties of the drug of abuse.

5.1.2.2. Clinical end-points and assays. Drug discrimination is performed in human laboratory studies with experimental subjects who are experienced illicit drug users, typically in the context of assessing the abuse liability of novel psychoactive therapeutics (e.g. [96]). Discriminative stimulus properties of all major drugs of abuse have been demonstrated in human laboratory studies (cocaine [97], amphetamine and methamphetamine [98], ethanol [99], μ-opiate agonist [100], nicotine [101]). These procedures are very similar methodologically to the animal studies described above, except that money is often used as the reinforcer, and subjects are asked to allocate some number of points as 'drug' versus 'non-drug', with correct allocation resulting in the exchange of points for money (e.g. [98]). During training days, the drug identity is revealed at the end of the session and the money exchanged. By contrast, on novel compound test days, the identity of the test substance is not revealed, and the amount of money received is equivalent to the greatest number of points allocated to either category (drug or non-drug). The human DD procedure can also be to assess the interoceptive properties of a potential SUD therapeutic and interactions between the interoceptive properties of the novel therapeutic and the drug of abuse (e.g. [102]). As for the SA studies, steps must be taken to avoid confounding data due to intoxicated or withdrawal states during laboratory testing. An added benefit of the human task is the ability to directly assay subjective effects (e.g., 'liking' or 'high') via well-structured and validated questionnaires. Such tasks are fully capable of providing valuable data for therapeutics aimed to blocking or substituting for drugs of abuse in SUD.

5.1.2.3. Validity. Although the drug discrimination assay does not exhibit the simple face validity that is apparent for SA, the assay can be considered valid in so far as the preclinical and clinical subjects undergo repeated administration of the training drug sufficient to provide familiarity with the drug's interoceptive properties. One caveat is that drugs of abuse are self-administered by humans, but the DD assay uses non-contingent drug delivery: drugs can differ in their physiological effects as a function of contingency [103,104]. Nonetheless, drugs that share pharmacological mechanisms of action share interoceptive effects in the DD assay, and positive read-outs in the DD assay require central nervous system activity. Finally, there is high concordance between animal and human DD studies. It is worth noting that SUD therapeutics currently aimed at substituting for the relevant drug of abuse can all be reliably discriminated in humans (buprenorphine [105], nasal nicotine [101]), non-human primates (methadone [106]) or rats (varenicline [95,107,108], Table 1). Thus, the DD assay represents a preclinical assay with face and predictive validity for an important property of drugs of abuse, and one which is likely to be useful in the evaluation of SUD therapeutics that aim to either disrupt or mimic the subjective effects of a drug of abuse.

5.1.2.4. Practicality. The preclinical DD assay requires a relatively long period of training, although this is offset to some extent by the long useful life of the trained subjects. The clinical version appears to require a much shorter period of training (for example, less than 10 sessions) before testing can begin. Of course, human studies bring additional costs, issues with subject recruitment and retention, controlling for concurrent drug use or withdrawal, etc. Nonetheless, the human studies could provide valuable proof-of-concept data at the Phase 2a level, and potentially provide an important stage in the clinical development of a novel SUD therapeutic.

5.1.2.5. Methodological improvements and opportunities. The preclinical DD literature is rich, and the methodology is well-developed and well-validated. In comparison to the clinical literature, however, it is clear that the issue of 'dependence' is generally avoided in preclinical studies. Clinical studies frequently distinguish between the use of 'dependent' or 'non-dependent' drug users as experimental subjects for DD studies. The DS properties of drugs of abuse could be studied in preclinical subjects that are exposed to levels of drug sufficient to induce withdrawal during cessation, for example, by non-contingent administration of drug during much of the day. This could potentially allow one to manipulate the withdrawal state at the time of DD testing. Use of dependent and non-dependent subjects might allow distinction between 'intoxication'-type effects versus a mixed 'withdrawal-alleviation'/'intoxication' cue. Such a procedure might enhance face validity, but it is unclear whether predictive validity would be enhanced.

5.1.3. Recruitment of aversive effects induced by drug ingestion

To 'flip' the effects of acute administration of a drug of abuse from 'pleasurable' to aversive is an atypical approach in developing SUD therapeutics. Disulfiram has been FDA-approved since 1951, yet no other examples of SUD therapeutics that render a drug of abuse aversive are available. Indeed, the discovery of disulfiram was a serendipitous one, and although efficacious, disulfiram suffers from low compliance. Such a limitation is likely to preclude future development of SUD therapeutics based on the same principle.

If a novel SUD therapeutic development program was aimed at targeting the induction of aversive effects after drug ingestion, there are at least two preclinical assays readily available for the detection of such effects. Specifically, BSR and CPP/conditioned

place aversion (CPA) are capable of detecting the bivalent effects of acute administration of a drug. Of the two procedures, CPP/CPA most likely provides a measure of dysphoria, unlike BSR that is hypothesized to provide a measure of brain reward function (anhedonia or reward-facilitation). A series of studies previously identified pharmacological and neuroanatomical manipulations that rendered nicotine aversive rather than rewarding, or vice versa, utilizing a CPP/CPA procedure [109–111]. A third possibility is the use of the conditioned taste aversion paradigm, in which animals are administered a drug of abuse that is paired with a palatable solution (e.g., saccharin). Subsequently, in a drug-free state, intake of the palatable solution is suppressed. These studies are generally interpreted as demonstrating the aversive properties of drugs of abuse (for review [112]), although Grigson and co-workers [113,114] has suggested a 'contrast' effect whereby the palatable solution is predictive of the more rewarding drug of abuse, and its intake it thereby suppressed. Thus, difficulties or controversies in data interpretation make the CTA procedure an unlikely choice, at present, to assay the aversive properties of a drug of abuse. Clinical studies aimed at assessing such effects should simply be by clinical assessment, for example if the effects include physical symptoms, as seen for disulfiram. Questionnaire or self-report would capture non-physical aversive properties after drug administration in a clinical laboratory setting.

Both BSR and CPP procedures are discussed above in terms of practicality. The face validity of such procedures appears fairly good, although as noted previously, the drugs are administered non-contingently rather than self-administered. As reported recently, it is possible to combine SA with BSR [48,115]: the administration of a therapeutic that induced aversive effects after drug intake would be expected to result in a decrease in drug intake over days, with attenuated BSR or the induction of a CPA response following SA sessions. Such a combined approach would yield a procedure with enhanced face, and hopefully predictive, validity. Disulfiram could provide rapid, but limited, predictive validation of such a procedure.

5.2. Withdrawal/negative affect stage

5.2.1. Treatment of withdrawal

The word 'withdrawal' has been used to describe many behaviors and experimental manipulations. For the purposes of this review, 'withdrawal' is defined as any alteration in a behavioral measure, or a behavioral phenomenon, that is associated with the cessation of chronic or sub-chronic administration of a drug of abuse. This is a wide definition that explicitly excludes 'withdrawal' as used in the locomotor sensitization literature to indicate a break in the repeated, intermittent (low-dose) administration of test compounds. Thus, there are many facets of withdrawal, which include 'affective' signs: generally centrally mediated states such as dysphoria, anhedonia, increased anxiety, reduced pain tolerance, and 'physical' signs: generally peripherally mediated signs such as the flu-like state experienced by opiate-dependent individuals in acute withdrawal, the tremor and convulsions in abstinent alcoholics, and the 'somatic' signs of withdrawal in opiate- and nicotine-exposed rodents.

5.2.1.1. Preclinical assays and models. The conditioned place preference procedure described previously can be used to assess aversive properties of a stimulus, whether it is the aversive properties of an acutely administered drug (see above), or a drug withdrawal state (CPA). In this version of the procedure, repeated pairing of the aversive state with a specific compartment results in decreased time spent in that compartment compared to the non-aversive state-paired compartment when subjects are allowed to freely move between compartments. For the purposes of CPA, withdrawal is generally precipitated by administration of a receptor antagonist, for example naloxone administered to chronically morphine-treated subjects [116,117], because this allows tight temporal control over the induction of the withdrawal state and its pairing with a specific context in the test apparatus. This antagonist-precipitated withdrawal has also been used successfully to demonstrate CPA for chronically nicotine-exposed rodents [118,119]. The role of central nervous system mechanisms in mediating the aversive state was demonstrated for nicotine withdrawal by the induction of CPA after administration of the brain-penetrant nAChR antagonist mecamylamine, but not the peripheral nAChR antagonist hexamethonium [120]. The lack of a specific receptor target for ethanol, amphetamine, methamphetamine or cocaine precludes the use of the CPA approach to assessing aversive states induced by withdrawal. Nonetheless, an aversive state has been identified in rodents after acute administration of ethanol [121,122], suggested to be analogous to a 'hangover'.

As indicated above, CPA studies generally employ chronic drug administration to induce sensitivity to the administration of a receptor antagonist for withdrawal precipitation. Most frequently, researchers utilize morphine pellets or nicotine-filled subcutaneous osmotic minipumps, although repeated acute injections of drug have also been used. Rather than antagonist administration, cessation of chronic administration of nicotine [123,124] or morphine [125] resulted in attenuation of BSR. The attenuation of BSR is interpreted as a measure of anhedonia [132]. BSR provides a reliable measure of withdrawal-associated anhedonia from all major drugs of abuse, and in comparison to CPA, provides the added advantage that 'spontaneous' (cessation of drug administration) withdrawal can be measured in addition to antagonist-precipitated withdrawal effects. Thus, cessation of drug administration has been used to identify anhedonic properties of withdrawal from amphetamine [126,127], cocaine [128] and ethanol [129]. Similarly to the ethanol CPA studies indentified above, BSR is attenuated after acute ethanol exposure [130]. A relatively brief (9 h) exposure to cocaine was also associated with attenuation of BSR [131].

Other measures of drug withdrawal-associated anhedonia/amotivation include diminished operant responding for a variety of reinforcing stimuli. A substantial literature exists assessing the 'behavioral disruption' effects of drug withdrawal (e.g., morphine [133], phencyclidine [134], cocaine [135], nicotine [136,143]). In the context of subsequent work in the field, these studies most likely provide measures of anhedonic/amotivational effects of withdrawal, as they are based on operant responding for reinforcing stimuli such as food pellets. As indicated in the previous section of the rewarding effects of drugs of abuse, SA behavior can be assessed under a variety of schedules of reinforcement, with progressive-ratio schedules hypothesized to provide a measure of motivation to obtain the reinforcer [137]. Thus, a variety of schedules have been used to assess the effects of drug withdrawal on responding maintained by non-drug reinforcers, including progressive-ratio schedules. Withdrawal from amphetamine was associated with significantly decreased break-points for sucrose solution [138] or food pellets [139]. Similar effects were observed for morphine [140], nicotine [141] and methamphetamine [142] withdrawal. These data indicate the utility of operant responding for a range of reinforcers as a measure of the anhedonic/amotivational facets of drug withdrawal. In an interesting variation, rather than use CPA to assess the aversive component of drug withdrawal, diminished CPP induced by exposure to novel objects was utilized to measure anhedonia associated with nicotine withdrawal [144].

Unlike the previous sections that outlined preclinical assays designed to explore reinforced behaviors directly related to dependence, the recognition of anxiety as a component of

withdrawal from multiple drug classes in humans [9] led, naturally, to the utilization of the large number of assays that capture anxiety-like behaviors in rodents for the measurement of increased anxiety-like behavior during withdrawal from drugs of abuse. While this approach has the benefit of allowing researchers to use extensively characterized and validated tests of anxiety-like behavior, it has also led to an uneven body of work. For example, it is not possible to point toward a single assay that has provided evidence of increased anxiety-like behavior during withdrawal from all major drugs of abuse. Limitations of space preclude the discussion of all of the assays of anxiety-like behavior that have been utilized in drug withdrawal studies. Furthermore, although several assays have been most commonly used in drug dependence research or in preclinical drug discovery programs [elevated plus maze and closely related assays; conflict procedures (Vogel test, Geller–Seifter conflict test, conditioned emotional response); social interaction test], most of these assays have no clinical analog. In contrast, the acoustic startle response (ASR) that occurs after the unexpected presentation of an auditory stimulus, is a validated measure of anxiety that can be assessed in rodents, non-human primates and humans [145]. Enhanced ASR is observed during withdrawal from morphine (e.g. [146]), ethanol [147] and nicotine [148]. The startle response can be enhanced by the addition of stressors such as a brightly lit test environment (light-enhanced startle response; [149]) or presentation of a previously shock-paired cue (fear-potentiated startle; [150]). Increased anxiety-like behavior during nicotine withdrawal has been demonstrated using light-enhanced startle response in rats [151], and morphine withdrawal was associated with enhanced fear-potentiated startle [152].

Finally, physical signs are associated with drug withdrawal. Morphine withdrawal signs were reported in rats in 1971, following the cessation of chronic morphine administration or the administration of opiate receptor antagonists such as naloxone to chronically morphine-exposed subjects [153]. Signs included behaviors such as 'wet-dog shakes', increased defecation and weight loss. Elevation of somatic signs of nicotine withdrawal was one of the first preclinical models of nicotine withdrawal [154]. The nicotine withdrawal signs were adapted from previously recognized somatic signs of opiate withdrawal, and included some minor changes such as an absence of defecation and weight loss. The physical signs of ethanol withdrawal, including increased susceptibility to audiogenic seizures, can be observed in rats [155]. These observational measures of withdrawal-related behaviors provide a straightforward assay for determining the effects of novel SUD therapeutics on drug withdrawal.

5.2.1.2. Clinical end-points and assays. Clinical analogs of reinforced operant behavior are available and can be used to assess anhedonia/amotivational states (e.g. [156]). More commonly, anhedonia is measured via questionnaires such as the Snaith–Hamilton Pleasure Scale or the Fawcett–Clark Pleasure Capacity Scale [157,158]. Withdrawal-associated increased anxiety has been demonstrated via enhanced ASR in humans during withdrawal from ethanol [159], nicotine and morphine [160]. In addition, researchers may utilize ratings scales such as the Beck Anxiety Inventory (e.g. [161]). Many of the aspects of negative affect related to withdrawal can be reliably assessed via questionnaires such as the Minnesota Nicotine or Wisconsin Smoking Withdrawal Scales [162], or the Cocaine Craving Questionnaire-Now/-Brief (e.g. [161]). Quantification of the physiological measures of opiate withdrawal in humans was demonstrated in 1978 [163]. Nonetheless, dissociation between physiological measures and subjective ratings of opiate withdrawal [164] underlines the importance of assessing centrally mediated states such as dysphoria and negative affect in addition to physical measures. All of these methods may be used to assess the efficacy of SUD therapeutics in ameliorating withdrawal.

5.2.1.3. Validity. The face validity of all of the models of withdrawal discussed here is reasonably good, despite the frequent use of experimenter- rather than self-administered drug. Frequently, the withdrawal-associated behavior has been shown to be ameliorated by resumption of drug delivery (e.g. [154]), indicating construct validity. Predictive validity of the procedures is more difficult to assess due to the paucity of clinically effective treatments. Nonetheless, the atypical antidepressant bupropion has been shown to decrease anhedonic [165,166], dysphoric [167] and somatic signs of nicotine withdrawal [165–168] in rats, and is effective in attenuating multiple indices of withdrawal in clinical trials ([6,62]; Table 1). The nAChR partial agonist varenicline decreased ratings of nicotine withdrawal in clinical trials (for review, see [169]). Unfortunately, there are currently no published preclinical data on the effects of varenicline on nicotine withdrawal, except an attenuation of a withdrawal-associated learning deficit in mice [170]. Additional studies should be prioritized to further confirm the validity of the preclinical assays. Finally, nicotine replacement therapy diminishes subjective ratings of withdrawal in clinical studies (e.g. [171]), and attenuated somatic signs of withdrawal in rats [154]. Similarly, buprenorphine attenuated the anhedonic and somatic components of spontaneous and precipitated fentanyl withdrawal in rats [172] and is clinically effective in opiate withdrawal [173]. Methadone is effective in attenuating withdrawal in preclinical and clinical studies [174]. Benzodiazepines can be used clinically to treat acute withdrawal in alcohol-dependent individuals (e.g. [175]) and display similar effects in rodents [176]. Benzodiazepines also attenuate preclinical measures of ethanol withdrawal-related anxiety [177,178]. Although clinical guidelines recommend the use of buspirone rather than benzodiazepines in treating anxiety in alcoholics [179], buspirone is also effective in animal models (e.g. [180]). Benzodiazepines decreased physical signs of withdrawal in rats [181] but they are not used for treatment of opioid dependence due to abuse liability. Finally, preclinical studies raise the possibility of significant withdrawal attenuation by novel therapeutics such as aripiprazole for amphetamine withdrawal-associated amotivation [139] and corticotrophin-releasing factor 1 antagonist for withdrawal-associated anxiety after alcohol [182] or nicotine [183] exposure. In summary, there is some evidence for predictive validity of various preclinical withdrawal measures.

In preclinical studies, nicotine withdrawal has been assessed via altered dopamine overflow (Type 3 biomarker) in subregions of the brain reward circuit (e.g. [184]). Building on these studies, Paterson and co-workers [166] assessed the effects of bupropion on depolarization-induced dopamine overflow during nicotine withdrawal as a corollary of anhedonia assessed via brain stimulation reward. Clinical studies could provide evidence of impaired dopamine signaling or altered cerebral blood flow in these same brain areas as a translational biomarker for withdrawal. This would create an opportunity to explore the effects of approved SUD therapeutics such as varenicline or buprenorphine, reported to ameliorate clinical signs of withdrawal, on brain reward function during withdrawal thereby providing a novel translational biomarker.

5.2.1.4. Practicality. The practicality of several of the assays utilized to measure facets of withdrawal has been described elsewhere in this review (BSR, operant responding for reinforcing stimuli, CPP/CPA). Other assays discussed in this section range from relatively simple observational measures of withdrawal to more sophisticated methodologies such as ASR. It should be noted that observational assays appear deceptively simple, but in

practice, rigorous control of the test environment, verification of inter-observer reliability, the use of observers blind to treatment conditions, and preferably electronic recording of behavioral test data are required to obtain a meaningful and reliable read-out. For all of the assays discussed in this section, with the exception of BSR and operant responding techniques, the procedures are relatively quick and allow a reasonable rate of throughput, although observation of somatic signs of withdrawal can be time- and labor-intensive.

5.2.1.5. Methodological improvements and opportunities. One missing element in the face validity of the preclinical withdrawal assays discussed above is the use of non-contingent delivery of the drug of abuse. Thus, significant recent improvements lie in the use of contingent (i.e., self-administered) drug to induce withdrawal. These developments are discussed in Section 6.

5.3. Loss of control over drug use

Within the preclinical literature, a variety of approaches have been adopted to explore the processes underlying the increased preoccupation/anticipation with obtaining and using the abused substance. Specifically, recent work has been done on the pathological formation and persistence of habit-based responding (for review [15]), and a great amount of effort has focused on how environmental stimuli associated with drug delivery become increasingly important in directing and controlling behavior. In addition, a huge literature exists around the phenomenon of behavioral sensitization [20], thought to be relevant to the motivation to obtain drug. Not all of these avenues of research currently provide translational models of SUDs that are likely to be useful in the development of SUD therapeutics, although they may do so in the future. More recently, some assays of cognitive function have been utilized in the context of SUD research in an attempt to model the cognitive deficits that may predispose individuals to compulsive drug use or perpetuate compulsive drug use. The current discussion is limited to those models most relevant to relapse to drug-seeking and -taking, and models of cognitive deficits thought to be relevant to SUDs.

5.3.1. Relapse prevention

5.3.1.1. Preclinical assays and models. Preclinical models of relapse, defined as a return to drug use after a period of abstinence, are comprised of cue-, drug- and stress-induced reinstatement of drug-seeking. These approaches are generally extensions of SA procedures, although CPP procedures have also been adapted (see [21] for discussion of validity of reinstatement models).

In a typical operant-based approach, experimental subjects are trained to self-administer a drug of abuse, the delivery of which is paired with the presentation of an environmental stimulus or stimuli ('cue'). After acquisition of stable SA, the subjects undergo either extinction (i.e., SA of vehicle rather than drug) in the absence of the cue or enforced abstinence (i.e., access to SA is terminated and subjects are confined to their home cages). Subsequently, exposure to the cue (presented during the test session), the previously self-administered drug (administered by the experimenter), or a stressor such as mild foot-shock, induces high levels of responding on the previously drug-associated operant, in the continued absence of the drug itself (e.g. [185,186]). In the case of subjects that have simply been deprived of access to the SA apparatus, re-establishment of access results in high levels of drug-seeking behavior, again in the absence of the drug itself ('spontaneous recovery' [185]). Finally, cues that predict the availability of drug may also be used (e.g. [187]).

In a typical CPP-based approach, the CPP behavior is induced and then extinguished by repeatedly pairing both compartments of the apparatus with vehicle administration; subsequent acute administration of the drug by the experimenter results in the re-expression of the CPP during a free-choice test (e.g. [188–190]).

As indicated above, stimuli previously paired with delivery of the drug, and thus associated with acute intoxication, can induce reinstatement of extinguished drug-seeking. Interestingly, cues associated with drug withdrawal also acquire behavioral significance. Specifically, presentation of environmental cues repeatedly paired with antagonist-precipitated opiate withdrawal in humans, non-human primates or rats precipitated the emergence of physical or behavioral manifestations of withdrawal [191–193]. Recently, Kenny and Markou [194] reported that presentation of a cue previously paired with antagonist-precipitated nicotine withdrawal resulted in significant elevations in ICSS thresholds, similar to withdrawal and indicative of anhedonia. The motivational significance of cue-induced withdrawal remains to be demonstrated, however.

5.3.1.2. Clinical end-points and assays. Clinical assays based on assessing the motivational impact of previously drug-paired cues have been performed using subjective reports of craving following exposure to pictures or videos of drug-taking and/or drug-taking paraphernalia. In addition, exposure to psychological stress (e.g. [195]) or the abused substance (e.g. [196]) induce craving in humans in a laboratory setting. Frequently, physiological correlates such as altered blood pressure and heart rate are measured in addition to questionnaires (see [197] for a review of clinical and laboratory assessment of craving). Interestingly, neuroimaging has provided a biomarker for such craving [198] and more recent neuroimaging studies suggest cue- and stress-induced craving share many important neurobiological substrates [199]. The identification of a role for dorsal striatal dopamine in cue-induced cocaine craving in humans [200] fits very well with preclinical data implicating the dorsal striatum in cue-mediated control over dependence-related behavior [201]. Thus, neuroimaging provides a translational biomarker that could be used in preclinical and proof-of-concept studies for putative anti-relapse medications.

5.3.1.3. Validity. The preclinical reinstatement procedures exhibit some face validity: that is, subjects are drug-experienced, as are SUD individuals, and exposure to drug-paired stimuli, stress or drug itself results in a drug-seeking behavioral response (e.g. [202–206,186]), similarly to the induction of 'craving' (e.g. [207,208]) or relapse (e.g. [209,195]) in SUD individuals. Nonetheless, abstinent SUD patients do not undergo any type of 'extinction' training where attempts to obtain drug are met with failure.

Predictive validity is limited for most drug classes, although there is some evidence for the efficacy of acamprosate (Campral®/Aotal®) and naltrexone in preventing relapse in humans [210,211] and attenuating reinstatement in preclinical subjects [212,213]. In addition, naltrexone [214] appears to work by blocking the effects of a 'lapse' (i.e., drinking ethanol after achieving a period of abstinence), and blocked ethanol-induced reinstatement in a preclinical study [215]. Varenicline attenuated nicotine-induced reinstatement of nicotine CPP [215] and nicotine-seeking [60], but neither varenicline nor bupropion had any effects on cue-induced reinstatement of nicotine-seeking in preclinical studies [60]. Consistent with the preclinical studies, varenicline appears to lack efficacy in attenuating cue-induced cravings in humans [216]. Finally, bupropion also appears to be ineffective in attenuating cue-induced craving in humans that continue to smoke [217] versus humans that exhibit significant reductions in smoking behavior [218,219]. Thus, both varenicline and bupropion provide examples of consistent negative data in preclinical and clinical

relapse studies. For cocaine dependence, neuroimaging studies of the effects of $GABA_B$ receptor agonists in human cocaine addicts indicated lowered activation of relevant brain areas after exposure to drug-associated cues, providing convergent data with the effects of $GABA_B$ receptor activation on reinstatement of cocaine-seeking in preclinical studies [220,221]. For heroin, naltrexone decreased relapse in abstinent, detoxified SUD patients [222,223], and decreased heroin-induced reinstatement of drug-seeking in rats ([224]; Table 1). Ultimately, cue-induced reinstatement is likely to be amenable to similar mechanisms of action across different SUDs, for example, via blockade of metabotropic glutamate receptor 5 [225,226] or non-selective opiate receptor blockade by naltrexone [227–230]. In contrast, drug-induced relapse that appears related to blockade of the primary effects of the abused substance, for example by varenicline binding to nicotinic acetylcholine receptors. In summary, there appears to be some reasonable amounts of evidence for predictive validity of preclinical reinstatement models and a high degree of translatability in the data obtained in those studies. It should be noted, however, that clinical studies frequently use 'craving' as a measure of withdrawal, but this should be distinguished from cue-induced craving that is relevant to relapse.

5.3.1.4. Practicality. Preclinical operant-based assays or CPP-based approaches as translational models of relapse exhibit the same challenges as for drug SA and CPP studies used to explore acute rewarding effects of drugs of abuse due to their methodological similarities.

5.3.1.5. Methodological improvements and opportunities. With the development of neuroimaging technology in awake and behaving rats (e.g. [231]) there is a valuable opportunity to demonstrate similarity in brain area activation in response to drug-associated stimuli in animals and humans. Thus, in conjunction with currently available methodologies, the effects of potential therapeutic compounds on activation of relevant brain areas can be correlated with suppression of drug-seeking responses in preclinical and clinical subjects. As indicated above, experimental demonstration of the motivational impact of cue-induced drug withdrawal would also be a significant advance in terms of a translational animal model for withdrawal-induced craving in SUD patients.

5.3.2. Cognitive function deficits

SUD individuals exhibit high degrees of impulsivity, in addition to other cognitive deficits such as impaired cognitive flexibility (decision-making), impaired attention and deficits in memory function. At least some of these deficits are thought to be important in the maintenance of compulsive drug use, the cardinal characteristic of a SUD, and could therefore be important targets for effective SUD therapeutics. However, the identification of these deficits in SUD patients does not allow their identification as the sequelae of drug use, predisposing factors for the development of compulsive drug use, or both. This question is relatively unimportant in the development of efficacious SUD therapeutics: the important issue is whether treatment or amelioration of those deficits in SUD populations can improve abstinence and recovery. Another issue of importance to SUD therapeutic development is whether these deficits can be effectively treated with therapeutics designed to treat such deficits in non-SUD populations. If so, those medications can be used as adjunct therapies in the treatment of SUD. Nonetheless, regulatory approval for such medications for a specific SUD-related indication would require supporting data from preclinical and clinical studies. Therefore, translatable models of cognitive function that have been used to demonstrate cognitive deficits arising from exposure to substances of abuse in animal and human subjects are briefly discussed here.

5.3.2.1. Preclinical assays and models. Impulsivity has received the most amount of attention as both a predisposing and perpetuating factor in SUD development in humans. Preclinical studies have allowed the identification of distinct components of impulsivity that complement human studies. For example, Belin and co-workers [232] demonstrated that although rats exhibiting high response to novelty (a translational measure of high sensation-seeking) were predisposed to acquire SA of cocaine at a relatively low level of intake ('non-addicted'), rats that exhibited high levels of impulsive action (assessed via the 5-choice serial reaction time task, '5-CSRTT', a preclinical analog of the continuous performance task in humans) were predisposed to develop compulsive cocaine SA. Interestingly, rats that exhibit high levels of impulsive choice in a delay discounting task ('DDT'), closely analogous to clinical tests, exhibited increased propensity to self-administer cocaine [233] or methylphenidate [234]. Both the 5-CSRTT [235,236] and the DDT (for review, see [237]) have been used to demonstrate increased impulsivity in rats previously allowed to self-administer methamphetamine, amphetamine, cocaine and nicotine.

Another, lesser, focus of research into cognitive function deficits in the context of drug abuse is cognitive flexibility, as this is thought to be relevant to the poor decision-making and, perhaps, the narrowing and increasing rigidity of the behavioral repertoire exhibited by SUD patients. Preclinically, reversal learning and attentional set-shifting (ASST) tasks assess cognitive flexibility, which refers to rule-shifting or the ability to inhibit previously rewarded behaviors or behavioral responses. In a typical reversal learning task, rats are trained to make a lever response signaled by an environmental stimulus such as a cue light located above the active lever, with active lever responses delivering a reward, often a food pellet. After acquisition of the task, a change in the 'rule' is imposed, for example the previously inactive lever that is not paired with a cue light becomes active and the active lever becomes inactive. The speed and degree to which the preclinical subject adapts to the new rule provide a measure of reversal learning (e.g. [238]). A more complex task that allows more subtle rule changes is provided by attentional set-shifting. In this task, two sets of stimuli belong to different sensory modalities are utilized: typically a digging medium such as wood shavings or stone chips, and a variety of odors such as clove, nutmeg or paprika [239]. Similar to reversal learning, the reward-predictive stimulus can be changed. However, in an extension of the task requirements, the reward-predictive stimulus can be changed within the same sensory modality (intra-dimensional) or across different modalities (extra-dimensional). Exposure to substances of abuse has been shown to impair performance in reversal learning [238,240] and ASST [241] studies.

5.3.2.2. Clinical. As mentioned above, the cognitive function assays outlined here have close analogs in clinical research. Specifically, the 5-CSRTT is analogous to the continuous performance task where clinical subjects are required to monitor a screen displaying a series of stimuli at a given interval. The subject is asked to make a response whenever a certain stimulus appears. Task variants include identical pair, where subjects have to make a response when they detect the sequential presentation of the same stimulus (e.g. [242]). SUD individuals exhibit deficits in the CPT with increased amounts of premature responses, indicative of increased impulsivity, and exhibit impaired accuracy due to attentional deficits [242,243]. The DDT can be performed in humans, utilizing either real of imaginary rewards [244,245]. The procedural details are very similar across preclinical and clinical versions, with human subjects asked to select between immediate delivery of a small, often monetary, reward or the delivery of larger reward at future intervals stretching from days to a year (e.g. [246]). Again, clinical research has identified high impulsivity in SUD individuals

[245,247,248]. Finally, the Wisconsin Card-Sorting Task (WCST) provides a clinical assay of cognitive flexibility that has been used many times to demonstrate deficits in SUD individuals. In the WCST, subjects are required to match a stack of cards to a variety of stimulus cards that have been presented. The cards differ in terms of color, design, etc. The participant is not told how to match the cards, but is told whether each match made is right or wrong. During the course of the test, the matching rules are changed and the time taken for the participant to learn the new rules, and the mistakes made during this learning process are analyzed [249]. Similarly to the other assays highlighted here, SUD individuals display deficits in WCST performance measures [250,251].

5.3.2.3. Validity. Many similarities have been found between the effects of exposure to substances of abuse and various facets of cognitive deficits, using the assays outlined here, in preclinical and clinical subjects (etiological validity). In terms of face validity, the nature of the exposure of preclinical subjects has varied from experimenter- to self-administered; clearly SA is preferred, and has generally provided similar data as experimenter-administered drugs. The construct validity of these cognitive function assays in humans is good, and the use of close analogs in preclinical studies should ensure similarly high construct validity. Predictive validity is perhaps weakest for cognitive deficits associated with exposure to substances of abuse. Converging evidence from studies in multiple species provides Type 3 biomarkers for functional deficits in discrete brain areas, most strikingly the orbitofrontal cortex associated with compromised executive functioning (for review, see [252]). The identification of these biomarkers could provide a powerful approach for translational studies in the development of novel SUD therapeutics, assuming they are first applied to studies evaluating the effects of approved pro-cognitive medications in SUD populations at both the clinical and preclinical levels. There is limited data available regarding the efficacy of available impulsivity treatments in attenuating symptoms of impulsivity or psychostimulant use in SUD populations. For example, a recent open-label trial found that atomoxetine decreased attention deficit-hyperactivity disorder (ADHD) in cocaine-dependent individuals that met the criteria for ADHD, but had no effect on cocaine use [253]. Interestingly, a fMRI study showed that methylphenidate treatment significantly improved performance in a task assessing impulsivity in cocaine-dependent patients, an effect that was inversely associated with ventromedial prefrontal cortex activation [254]. Although this study did not examine cocaine use, it does provide evidence for treatment-induced improved inhibitory control in cocaine SUD individuals, and a useful biomarker for future studies. A recent preclinical study showed that atomoxetine diminished reinstatement of cocaine-seeking in highly impulsive rats ([255]; Table 1). The continued evaluation of currently approved impulsivity medications in preclinical and clinical SUD assays could greatly enhance the validity of the approach, and the relevance of targeting cognitive deficits in SUD therapeutic development. Currently, however, this area of research is relatively novel and future studies are required [256].

5.3.2.4. Practicality. The preclinical assays outlined here generally require considerable amounts of training. In addition, although 5-CSRTT, DDT and reversal learning allow reasonable throughput after training is completed, the ASST is an extremely time-consuming task. The clinical assays are already well-established and generally require very little in terms of training.

5.3.2.5. Methodological improvements and opportunities. The most important work in this respect is to show whether approved medications for disorders characterized by high levels of impulsivity can be efficacious in helping SUD patients achieve prolonged abstinence. Demonstration of efficacy in preclinical SUD models is also required because current preclinical research has focused largely on identifying specific deficits in subjects exposed to substances of abuse, and seeking to determine whether these cognitive deficits are predisposing or perpetuating factors with respect to compulsive drug use. These pharmacological validation studies are required to provide confidence in the relevance of cognitive deficits to SUD treatment outcomes, and therefore whether such translational models should be included in SUD therapeutic development programs. As indicated above, neuroimaging measures could provide good evidence for the translational value of such studies.

5.4. Summary

Among the high number of preclinical assays and models of various behaviors associated with dependence are a number of assays for which clinical analogs are available. Currently available SUD therapeutics has provided at least partial evidence of the translational value of these approaches, which provide measures of a range of behavioral end-points. Given the narrow regulatory end-point that all novel SUD therapeutics must meet, the value of the assays discussed above lies in their ability to provide data that significantly increases confidence in ultimate success. Nonetheless, the gap between laboratory-based efficacy studies in animals and humans can only be bridged by two approaches: (1) the use of extended access SA models that capture multiple aspects of dependence in a proportion of exposed subjects, and thereby allows the demonstration of the relevance and impact of specific therapeutic targets on drug intake, and (2) the use of comprehensive secondary end-points in Phase 3 trials that encompass the end-points used in the preclinical and clinical assays highlighted above. Data obtained from postdictive validation studies utilizing these two approaches could help provide a necessary experimental framework for confident and successful SUD therapeutic development programs in a risk-averse environment (see Fig. 3).

6. Drug intake in dependent subjects: preclinical and clinical studies

In the preclinical area, recent advances in SA procedures have included the expanded use of unlimited/extended access SA procedures. Primarily used to increase the face validity of the preclinical procedures, such an approach resulted in the recruitment of additional sources of motivation to self-administer drug that should enhance predictive validity. Specifically, the use of extended access conditions appears to result in the emergence of withdrawal states between daily test sessions, thereby providing the crucial substrate for negative reinforcement (withdrawal alleviation) as a motivating factor in continued drug consumption. Building on earlier work [257], these studies provided evidence of anhedonia during daily abstinence in subjects allowed to self-administer heroin [258] or cocaine [259] thus far, with more limited evidence of success in nicotine studies [48,115,183]. Alternative measures of withdrawal have been demonstrated following extended access to nicotine [260,261] and heroin [262] SA. For alcohol SA, combinations of non-contingent high ethanol exposure combined with varying patterns of deprivation and SA have been used to recruit negative reinforcement processes in SA behavior (e.g. [263,182]). Extended access to methamphetamine [35] and amphetamine [264] is associated with escalated drug intake that may be evidence of recruitment of the withdrawal state based on the earlier cocaine studies.

Extended access studies have yielded evidence for other addiction-related behaviors in addition to withdrawal measures. The use of extended access models has provided evidence for

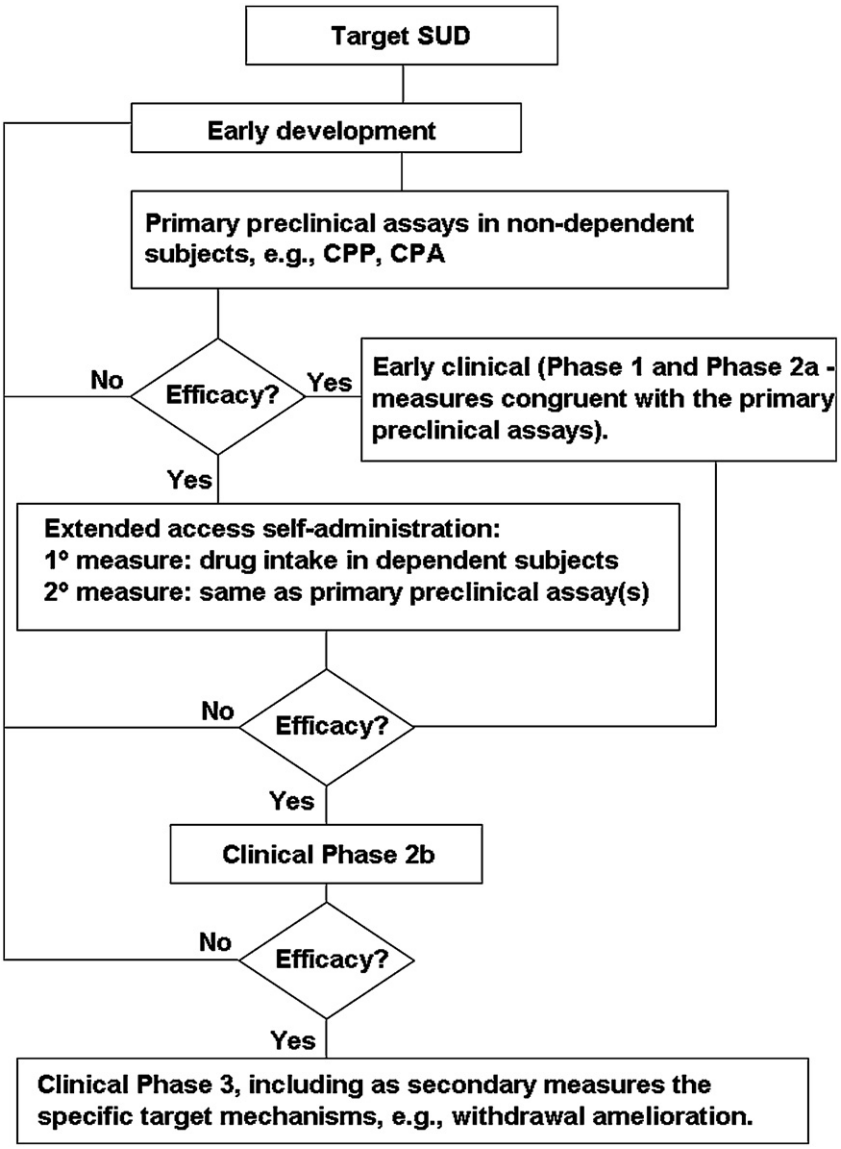

Fig. 3. A framework for the development of novel SUD therapeutics. The figure shows a basic framework for SUD therapeutic development that incorporates extended access self-administration procedures performed in 'dependent' subjects, as a preclinical analog of the Phase 3 clinical trial. The framework begins with identification of the SUD of interest, as this affects the assays selected in the preclinical and clinical stages of development. 'Early development' activities include the universal essentials of development such as medicinal chemistry (structure–activity relationship), pharmacokinetics, pharmacodynamics and basic toxicology. It should be noted that although early clinical studies are indicated as occurring in parallel with the extended access self-administration studies, the timing of these studies may be altered depending on the degree of confidence in the candidate compound and the relevant costs of late preclinical versus early clinical activities. Finally, the framework should represent an evolving process such that the assays employed at different stages are critically reviewed on an ongoing basis as candidate compounds either succeed or fail at specific stages, thus enhancing the predictive power of early stage testing.

increased motivation to self-administer drug, a measure that is relevant to the preoccupation/anticipation component of the addiction cycle (heroin [34], cocaine [265,266], methamphetamine [267]). The use of non-contingent drug delivery to induce withdrawal in rats trained to self-administer morphine induced enhanced drug-seeking after subjects learned the withdrawal-alleviating properties of the drug [268]. Extended access to methamphetamine [269,270] was associated with increased drug-induced reinstatement relative to short access control subjects, although mixed data have been reported for cocaine [271,272]. Cue-induced reinstatement of cocaine-seeking was enhanced in high-impulsive subjects, and further increased by a history of extended SA [255]. Furthermore, extended access studies revealed disruptive effects of methamphetamine on episodic memory, measured via novel object recognition [232], and impulsivity assessed via the DDT [264]. Interestingly, high impulsivity predicted cocaine [232,273] but not heroin [274] escalation. These recent studies identifying cognitive deficits in extended access subjects raise the possibility that additional intervention targets could result in diminished drug intake in this model.

Interestingly, rats deprived of 23 h daily nicotine SA access exhibited significantly increased nicotine intake when returned to SA and increased anxiety-like behavior assessed by defensive burying, in which exposure to a shock-probe induces burying of the probe with bedding material [183]. Both effects were sensitive to blockade of the corticotrophin-releasing factor receptor subtype 1 (CRF-1), thus demonstrating the power of recent advances in animal models of nicotine dependence to uncover novel neurobiological substrates [183]. CRF-1 blockade also selectively decreased heroin [279] or cocaine [280] intake in extended access subjects. Other potential targets may also be identified using the

extended access model (e.g. [281,282]). It remains to be seen, however, whether these more sophisticated models exhibit predictive validity. For nicotine SA, extended access subjects did not exhibit increased sensitivity to varenicline [283].

Finally, recent studies identified a subset of preclinical subjects exposed to extended access conditions that exhibited several important manifestations of dependence, as outlined in DSM-IV and ICD-10. Specifically, a proportion of the experimental subjects exhibited greater motivation to obtain drug, persistence of drug-taking despite aversive consequences or presentation of a conditioned aversive stimulus, increased susceptibility to drug- and cue-induced reinstatement [89,275–278]. These studies raise the possibility of conducting postdictive validation studies in a population of subjects with extended SA access that exhibit several cardinal features of addiction.

There are two important aspects to these extended SA studies: (1) the use of extended access SA procedures resulted in the recruitment of additional sources of motivation to obtain drug, (2) only a subpopulation of subjects exhibited dependence-like behaviors, as defined by clinical criteria in DSM-IV/ICD-10. This approach might be expected to render the SA behavior sensitive to SUD therapeutics that attenuate withdrawal or exhibit efficacy against other intervention targets. From a translational perspective, it would be highly valuable to evaluate the effects of approved therapeutics on drug intake, and additional measures of dependence-related behaviors, in the extended access model. Such data could provide evidence that the preclinical measures of dependence assessed in other assays are relevant to compulsive drug use by distilling effects at multiple intervention targets into a single measure of drug intake in 'dependent' individuals. Thus, despite the technical and labor demands, data obtained from extended access SA studies could be highly valuable as a preclinical analog of Phase 3 trials. In a discovery framework, it is proposed that these studies would be performed only after demonstration of efficacy at the intervention targets in the less complex assays identified in the earlier sections of the present discussion.

There is an increasing realization, at least for alcoholism, that clinical populations represent a heterogeneous group in terms of primary sources of motivation to consume alcohol [284,285]. It remains to be seen whether heterogeneous sub-populations can be identified in preclinical studies. Another difference between Phase 3 trials and preclinical studies is the use of a single regulatory end-point of abstinence in clinical trials versus the quantification of graded responses in preclinical studies. The use of a dichotomous outcome such as abstinence results in data expressed as proportions of responders vs. non-responders, and accepted by the regulatory agencies (U.S. Food and Drug Association (FDA) and European Medicines Agency (EMA)). Even a possible new endpoint for alcohol dependence studies (the percentage of subjects with no heavy drinking days [25]) remains a binary read-out. Preclinical studies using the extended access SA procedures could express data in such a manner by using predefined criteria which differentiate responsive and non-responsive subjects. It would be interesting to see whether such an approach enhanced the predictive power of the assay.

7. Conclusions and future directions

It is clear from the present discussion that there is now a reasonably good theoretical understanding of the key elements of substance use disorders, as defined in DSM-IV, and that many of the key components of the maladaptive behaviors and phenomena that comprise the addiction cycle have been modeled in experimental animals. Nonetheless, although clinical analogs exist for many of these preclinical models, thereby facilitating translational research, regulatory approval for novel therapeutics ultimately hinges on a relatively narrow requirement: the attainment and maintenance of abstinence. Therefore, many preclinical and early clinical (i.e., laboratory-based) assays can only provide data that indirectly increases confidence in ultimate success at the level of Phase 3 clinical trials. Encouragingly, research continues to uncover biomarkers that are consistent across species and should further enhance confidence in preclinical and early clinical data – particularly if these biomarkers form additional end-points in laboratory-based studies. Although not covered here, our knowledge of the neurobiology of addiction continues to expand (for review, see [286]).

At the current time, despite the relative lack of clinically efficacious SUD therapeutics and the generally serendipitous rather than rational discovery of novel SUD therapeutics, currently available medications have provided and do provide opportunities for validation of the available translational models. The extended access SA paradigm requires further development and validation as a preclinical analog of a Phase 3 trial. The identification and use of preclinical subjects that exhibit the hallmarks of dependence is likely to be highly important in demonstrating clinically relevant effects of potential and approved SUD therapeutics. An additional important area for validation is the role of cognitive deficits in the maintenance of compulsive drug use, and the demonstration that targeting those deficits can improve treatment outcomes in SUD populations as either adjunct or single treatments. An important caveat in the use of existing medications for proof of validity is the relatively poor efficacy of approved medications: for example, even with the use of current first-line medications varenicline or bupropion, long-term smoking abstinence rates are rarely greater than 25% (e.g. [6,287]). Thus, 'optimization' of models to achieve detection of highly significant effects of approved therapeutics could result in assays with high false positive rates.

There is a mismatch between promising preclinical data and corresponding clinical proof-of-concept studies for SUD therapeutics based on novel mechanisms. Increasing numbers of early clinical studies to evaluate these possible novel therapeutic compounds or targets would greatly enhance our understanding of the translational value of existing models and assays, and could allow further optimization of existing models and development of novel models – even if many of the clinical data proved to be negative. Such studies are best performed in the academic research space, particularly for compounds that are not strong development candidates or if there is a high likelihood of negative, yet valuable, outcomes.

The high societal and human burden of SUDs and the scarcity of truly efficacious treatments demand the development of novel SUD therapeutics. It is hoped that future work can provide validation of existing models and the development and optimization of novel or existing models and their clinical analogs. As suggested here, the combined approach of the preclinical extended access SA procedure and Phase 3 trials that include comprehensive secondary end-points, plus the continued identification of cross-species biomarkers, could ultimately provide a streamlined and optimized experimental framework for the successful development of novel SUD therapeutics.

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