HHS Public Access

Author manuscript

Int Rev Neurobiol. Author manuscript; available in PMC 2019 September 16.

Published in final edited form as:

Int Rev Neurobiol. 2016 ; 126: 157–177. doi:10.1016/bs.irn.2016.02.006.

An Animal Model of Alcohol Dependence to Screen Medications for Treating Alcoholism

H.C. Becker[*,†,‡,1], **M.F. Lopez**[*]

[*]Charleston Alcohol Research Center, Charleston, SC, United States

[†]Medical University of South Carolina, Charleston, SC, United States

[‡]RHJ Department of Veterans Affairs Medical Center, Charleston, SC, United States

Abstract

Despite the high prevalence of alcohol use disorders in the United States, only a relatively small percentage of those afflicted seek treatment. This is further compounded by the fact that there are too few medications available to effectively treat this significant public health problem. The need for identifying and evaluating more effective treatments that aid in preventing relapse and/or tempering risky and harmful alcohol consumption cannot be overstated. Use of animal models represents a critical step in the process of screening, identifying, and informing plans for prioritizing the most promising candidate medications that can be advanced to the next stage of evaluation (clinical laboratory paradigms and controlled clinical trials). Numerous animal models have been developed to study excessive levels of alcohol self-administration. In recent years, a large literature has amassed of studies in which rodent models of dependence have been linked with alcohol self-administration procedures. This chapter focuses on studies employing a dependence model that involves chronic exposure to alcohol vapor by inhalation, which yields in both mice and rats significant escalation of voluntary alcohol consumption. These animal models of dependence and alcohol self-administration have revealed valuable insights about underlying mechanisms that drive excessive drinking. Additionally, this preclinical approach is useful in evaluating the effects of medications on escalated drinking associated with dependence vs more stable levels displayed by nondependent animals.

Alcohol abuse and dependence are serious medical and social problems in the United States and, thus, constitute a major public health concern. In the past decade, alcohol use and abuse has significantly increased in the United States (Dawson, Goldstein, Saha, & Grant, 2015). In a recent epidemiological study, the estimated 12-month prevalence for alcohol use disorder (AUD) indicated that over 32 million Americans met DSM-5 diagnostic criteria spanning the full spectrum of mild to moderate to severe AUD (Grant et al., 2015). Excessive alcohol use has devastating medical consequences, levying a tremendous toll on the health-care industry. Heavy drinking can cause or increase risk for many medical illnesses and accounts for a substantial number of emergency medical admissions related to accidents and violent crime. The economic costs of alcohol abuse and dependence are estimated at 235 billion dollars per year due to health-care expenditures, lost productivity,

[1]Corresponding author: beckerh@musc.edu.

and damage/loss of property (Rehm et al., 2009). In addition to these medical and economic burdens, the cost to society in terms of personal tragedy and loss is enormous. Unfortunately, only a relatively small percentage of those suffering with AUD that would benefit from treatment actually seek treatment. A recent study estimated that less than 10% of those with a history of alcohol abuse seek treatment (Grant et al., 2015). This indicates the need to raise public awareness of the disease and available treatment options and, at the same time, invest resources in developing new and more effective treatments for this major public health problem.

Alcoholism is a chronic relapsing disease, and relapse represents a major challenge to treatment efforts. To date, there is no therapeutic intervention that has proven to be fully satisfactory in preventing relapse, sustaining abstinence, or tempering amount of drinking when a “slip” occurs. For some individuals, heavy and frequent binge-like drinking can lead to general loss of control over regulation of alcohol consumption. In many cases, such drinking patterns can lead to the development of alcohol dependence, rendering these individuals more susceptible to relapse as well as more vulnerable to engaging in drinking behavior that often spirals out of control. Many such individuals make numerous attempts at curtailing their alcohol use, only to find themselves reverting back to patterns of excessive consumption again. The need to provide effective treatments for these individuals suffering from AUDs cannot be overstated.

Significant advancements have been made in our understanding of neurobiological underpinnings and environmental factors that influence motivation to drink as well as consequences of excessive alcohol use. The development of preclinical models has played a central role in expanding our knowledge of the myriad biological, genetic, and environmental forces that influence excessive alcohol consumption. However, despite significant advancements in our understanding of the complexities of the addiction process as well as factors that influence motivation to engage in risky unhealthy drinking, development of new medications for treating AUDs has lagged behind. Thus, a major challenge for the field is to employ established preclinical models to identify and evaluate new therapeutics, which may be added to the armament of treatment strategies that can be advanced to clinical trials and, ultimately, delivered to those suffering from the ravages of alcohol abuse and dependence.

1. ANIMAL MODELS OF EXCESSIVE ALCOHOL DRINKING

Heavy (excessive) levels of drinking and increased vulnerability to relapse represent hallmark features of AUDs and alcoholism. As noted earlier, the development of animal models that incorporate these key behavioral characteristics has played a key role in advancing our knowledge about biological underpinnings and environmental circumstances that engender such maladaptive behavior. These preclinical models also are crucial in providing testing procedures for identifying new potential therapeutic targets and evaluating efficacy and safety of various treatment strategies.

Numerous experimental approaches have been employed in developing rodent models of excessive alcohol self-administration. One of the major obstacles in this work is that rodents

typically do not self-administer alcohol in sufficient amounts to produce overt signs of intoxication. Further, when given the opportunity to voluntarily drink alcohol, even under circumstances when access is unlimited, rodents rarely will consume alcohol in a manner that results in significant elevation in blood alcohol levels (above legal limits). Thus, a major challenge for the field has been to overcome these critical problems so that animal models developed for studying alcohol consumption have greater clinical relevance and, thereby, greater potential for use in elucidating underlying mechanisms as well as identifying and evaluating new and more effective treatment approaches.

In recent years, several new models have been developed, and some older ones have been resurrected and refined that demonstrate excessive and physiologically relevant levels of alcohol consumption (Becker, 2013). In general, these models have incorporated genetic manipulations (eg, selective breeding for high alcohol drinking and preference) or environmental manipulations that involve modifying scheduled access to alcohol, scheduled periods of alcohol deprivation, and linking drinking procedures with dependence models (Becker, 2013). Thus, a variety of experimental approaches have been used to approximate clinical aspects and stages of alcohol addiction. This includes modeling genetic predisposition, binge-like patterns of drinking, relapse vulnerability, and alcohol consumption that reflects motivation related to acquired negative reinforcing effects of alcohol. Not surprisingly, each of these models possesses distinct advantages and disadvantages. Further, all of these models have been used to examine effects of various pharmacological agents (eg, Albrechet-Souza et al., 2015; Anderson, Becker, Adams, Jesudason, & Rorick-Kehn, 2014; Bell et al., 2012; Carnicella, Ron, & Barak, 2014; Crabbe, Harris, & Koob, 2011; Simms, Nielsen, Li, & Bartlett, 2014; Vengeliene, Bilbao, & Spanagel, 2014). This chapter will focus on models of dependence that engender high levels of alcohol self-administration, as well as use of these models for evaluation of medications that may temper excessive drinking associated with dependence.

2. ANIMAL MODELS OF DEPENDENCE AND EXCESSIVE ALCOHOL DRINKING

Alcohol dependence has long been viewed as playing a significant role in promoting and sustaining excessive levels of alcohol consumption, as well as driving increased susceptibility to relapse after periods of attempted abstinence (Cappell & LeBlanc, 1981; Grant, 1995). Indeed, a large literature has amassed of studies in which rodent models of dependence have been linked with alcohol self-administration procedures. Key features of these models that have contributed to their success include first establishing the positive reinforcing effects of alcohol and then presenting alcohol in the context of dependence, but in a manner that facilitates associating consumption of alcohol with the drug's ability to alleviate dysphoric aspects of dependence (withdrawal). This latter feature defines acquisition of the negative reinforcing effects of alcohol, which is thought to play an important role in increasing vulnerability to relapse and then maintaining heavy drinking once a slip occurs (Becker, 2013, 2014).

Over the past decade or so, numerous studies have demonstrated escalation of alcohol consumption using home-cage free-choice drinking models in dependent mice (Becker & Lopez, 2004; Dhaher, Finn, Snelling, & Hitzemann, 2008; Finn et al., 2007; Griffin, Lopez, & Becker, 2009; Lopez & Becker, 2005) and rats (Rimondini, Arlinde, Sommer, & Heilig, 2002; Rimondini, Sommer, & Heilig, 2003; Sommer et al., 2008). Studies have also employed operant conditioning procedures to demonstrate elevated alcohol self-administration in dependent mice (Chu, Koob, Cole, Zorrilla, & Roberts, 2007; Lopez, Anderson, & Becker, 2008) and rats (Funk & Koob, 2007; Funk, O'Dell, Crawford, & Koob, 2006; Funk, Zorrilla, Lee, Rice, & Koob, 2007; Gilpin, Misra, & Koob, 2008; Gilpin, Richardson, & Koob, 2008; Gilpin, Richardson, Lumeng, & Koob, 2008; Gilpin et al., 2009; O'Dell, Roberts, Smith, & Koob, 2004; Richardson et al., 2008; Rimondini, Thorsell, & Heilig, 2005; Roberts, Cole, & Koob, 1996; Roberts, Heyser, Cole, Griffin, & Koob, 2000). In these models, several procedures have been used to induce a state of alcohol dependence. For example, increased alcohol self-administration has been demonstrated in studies where dependence was induced by chronic administration of alcohol in a nutritionally fortified liquid diet (that served as the animals' sole source of calories and fluid) (Brown, Jackson, & Stephens, 1998; Chu et al., 2007; Gilpin et al., 2009; Schulteis, Hyytia, Heinrichs, & Koob, 1996), via intragastric infusions (Cunningham, Fidler, Murphy, Mulgrew, & Smitasin, 2013; Fidler et al., 2011, 2012) and inhalation of alcohol vapors (eg, Becker & Lopez, 2004; Rimondini et al., 2002; Roberts et al., 2000).

Additionally, in many instances these models have provided opportunities to study various withdrawal symptoms. Of particular relevance are symptoms that contribute to a negative emotional and dysphoric state associated with dependence, such as anxiety, heightened stress, anhedonia, and sleep disturbances (Becker, 2014; Heilig, Egli, Crabbe, & Becker, 2010; Koob, 2013). In as much as symptoms related to negative affect that often linger into protracted phases of abstinence contribute to relapse and potential for self-medication with alcohol, these models have proven useful for studying mechanisms underlying motivation to drink in the context of alcohol dependence. Nevertheless, focus on alcohol consumption in these dependence models has been the primary target for evaluation of potential medications.

3. AN ANIMAL MODEL OF DEPENDENCE-RELATED EXCESSIVE ALCOHOL DRINKING

Animal studies linking alcohol dependence and self-administration procedures have predominantly involved administering alcohol vapor in inhalation chambers, with the chronic alcohol exposure delivered in an intermittent fashion such that animals experience multiple withdrawal episodes. Using this experimental approach, escalation of alcohol self-administration has been demonstrated in dependent mice and rats compared to independent groups of animals that display relatively stable and modest levels of alcohol intake (Becker, 2013, 2014; Griffin, 2014; Lopez & Becker, 2014; Vendruscolo & Roberts, 2014). For example, rats exposed to chronic alcohol treatment interspersed with repeated episodes of withdrawal subsequently consumed significantly more alcohol than controls under free-choice unlimited (24 h/day) access conditions (Rimondini et al., 2002, 2003; Sommer et al.,

2008). Similar results have been reported in mice using a dependence model involving repeated cycles of chronic intermittent ethanol vapor exposure and with voluntary alcohol consumption assessed using a limited access (2 h/day) schedule (Becker & Lopez, 2004; Dhaher et al., 2008; Finn et al., 2007; Lopez & Becker, 2005). The intensity of repeated chronic alcohol exposure (producing high and sustained blood alcohol levels) was shown to be critical in favoring escalation of alcohol consumption in the model (Griffin, Lopez, & Becker, 2009). Analysis of the temporal pattern of alcohol consumption revealed that dependent mice not only consumed more alcohol than nondependent animals over the entire 2-h access period, but the rate of consumption was faster and progressively increased over successive withdrawal test periods (Griffin, Lopez, Yanke, Middaugh, & Becker, 2009). Further, the effect appears specific to alcohol because repeated cycles of chronic intermittent alcohol exposure did not produce alterations in water intake or consumption of highly palatable fluids such as sucrose and saccharin (Becker & Lopez, 2004; Lopez, Griffin, Melendez, & Becker, 2012). This suggests that the increase in alcohol consumption is not a nonspecific effect related to a general need to hydrate with fluids or increase caloric intake.

Studies in rodents involving chronic alcohol vapor exposure to induce dependence also have employed operant conditioning procedures to demonstrate increased alcohol self-administration. These studies have been conducted with mice (Chu et al., 2007; Lopez et al., 2008) and rats (Funk & Koob, 2007; Funk et al., 2006, 2007; Gilpin, Misra, et al., 2008; Gilpin, Richardson, & Koob, 2008; Gilpin, Richardson, Lumeng, et al., 2008; Gilpin et al., 2009; O'Dell et al., 2004; Richardson et al., 2008; Rimondini et al., 2005; Roberts et al., 1996, 2000). Use of operant conditioning procedures has enabled the demonstration that chronic intermittent alcohol delivered by inhalation increases both alcohol seeking (responding) as well as consumption components of alcohol self-administration behavior. Further, employing progressive ratio schedules has demonstrated that the amount of work mice (Lopez et al., 2008) and rats (Vendruscolo et al., 2012; Walker & Koob, 2007) are willing to expend in order to gain access to alcohol is significantly increased following repeated cycles of chronic alcohol exposure and withdrawal experience. Recent studies also have shown that dependent animals display compulsive-like responding for alcohol, at least as indexed by relative insensitivity to devaluation of alcohol's rewarding effects (ie, persistent responding for alcohol even after its rewarding value is reduced by adulteration with quinine, or it is associated with lithium chloride-induced aversion; Lopez, Becker, & Chandler, 2014; Vendruscolo et al., 2012).

Regardless of whether free-choice drinking or operant conditioning procedures are used, enhanced alcohol responding/intake in dependent animals has been demonstrated at time points well beyond acute withdrawal (Lopez & Becker, 2005; Rimondini et al., 2003; Roberts et al., 2000; Valdez et al., 2002). For example, increasing the number of chronic alcohol exposure/withdrawal cycles was shown to not only further augment alcohol consumption but also sustain elevated levels of intake for a longer period of time (several weeks) following final withdrawal compared to intake in a separate group of nondependent mice (Lopez & Becker, 2005). Thus, increased alcohol self-administration in these dependence models is not a transient effect, and this provides opportunities for evaluation of medication effects on excessive drinking that occurs at temporally more distal time points relative to acute withdrawal.

Additionally, studies have shown that escalation of alcohol self-administration in these models is especially facilitated when dependence induction involved delivery of chronic alcohol in an intermittent rather than continuous fashion (Lopez & Becker, 2005; O'Dell et al., 2004). Thus, while elevated alcohol self-administration may eventually develop following long-term alcohol exposure, a pattern of chronic intermittent alcohol exposure that involves repeated withdrawal experience (which more closely models typical patterns of alcohol consumption in humans) accelerates the rate at which escalation of drinking is displayed. This suggests that providing an opportunity to consume alcohol in the context of repeated withdrawal experience plays a significant role in promoting enhanced motivation for alcohol.

One procedural difference between studies in rats and mice regards the timing of when animals are given the opportunity to self-administer alcohol in relation to withdrawal from chronic alcohol vapor exposure. Studies in rats have shown that alcohol responding and intake progressively increases when the rats are allowed to self-administer alcohol during repeated acute withdrawal episodes (1–12 h postinhalation exposure) (Roberts et al., 1996). In contrast, mice develop an aversion to alcohol when it is presented for consumption early after vapor exposure. Providing a forced abstinence period of at least 48 h following chronic alcohol vapor exposure enables escalation of self-administration in dependent mice (Lopez & Becker, 2005). However, this effect in mice may be dependent on genotype and the model of chronic alcohol exposure (Cunningham et al., 2013).

Studies in both mice and rats have shown that the escalation of alcohol self-administration following repeated cycles of chronic intermittent alcohol exposure produced significantly higher blood alcohol levels compared to that achieved by more modest and stable levels of intake by nondependent animals (Becker & Lopez, 2004; Roberts et al., 2000). Similar results were obtained in a study involving continuous alcohol vapor exposure and operant oral alcohol self-administration in rats (Gilpin et al., 2009). In another study, microdialysis procedures were used to demonstrate that the faster rate of alcohol intake and greater overall amount consumed by dependent mice produced significantly higher peak and more sustained alcohol concentrations measured in brain compared to levels achieved from consumption of alcohol in nondependent animals (Griffin, Lopez, Yanke, et al., 2009). Moreover, greater voluntary alcohol consumption in dependent mice produced brain alcohol concentrations that approximated those levels experienced during chronic intermittent alcohol exposure that rendered the subjects dependent in the first place. The extent to which achieving a threshold brain alcohol concentration plays a role in promoting as well as perpetuating enhanced alcohol drinking in dependent animals remains to be determined.

In summary, a large number of studies have successfully linked procedures for inducing alcohol dependence with self-administration protocols. Most commonly, induction of dependence has been accomplished by delivery of chronic alcohol exposure via the inhalation route. This route of administration has many advantages (eg, ability to exert rigorous experimental control over variables such as duration, frequency, and intensity of exposure while minimizing compromised health), but a detraction relates to the fact that the inhalation procedure departs from the manner in which humans normally consume alcohol (orally). It is important to note, however, that these models of dependence and relapse

drinking are not designed to examine how dependence develops, but, rather, the focus is on how a history of chronic alcohol exposure that renders subjects dependent alters motivational processes that engender excessive levels of consumption. As previously indicated, with few exceptions, rodents even when given free access to alcohol will not consume sufficient amounts to produce dependence. Thus, in order to study the impact of dependence on continued and sustained alcohol drinking, the dependence state must be experimentally induced. This approach has effectively been adopted in mouse and rat models. Further, incorporating alternating cycles of chronic alcohol exposure interspersed with periods when subjects have the opportunity to self-administer the drug enables evaluation of drinking in the context of both alcohol's positive and negative reinforcing effects. Indeed, a positive feature of this model relates to the ability to contrast relatively stable alcohol consumption in nondependent subjects with escalated drinking exhibited by dependent subjects. This powerful attribute of dependence and relapse drinking models has not only been exploited in studies aimed at elucidating underlying neuroadaptations and motivational mechanisms but also in studies focused on evaluation of pharmacotherapeutics.

4. EVALUATION OF PHARMACOTHERAPEUTICS IN MODELS OF ALCOHOL DEPENDENCE AND RELAPSE DRINKING

In recent years, a large number of studies have employed dependence and relapse drinking models to evaluate the capacity of various pharmacological agents to modulate alcohol consumption (Bell et al., 2015; Meinhardt & Sommer, 2015; Vendruscolo & Roberts, 2014). Table 1 summarizes work conducted evaluating the effects of various pharmacological treatments using these models. All of these studies have been conducted with rats or mice using home-cage drinking or operant self-administration procedures. Of note, all of these studies examined effects of drug treatments on alcohol consumption in dependent and, in most cases, nondependent animals. Thus, studies that evaluated drug effects on operant reinstatement models where effects on alcohol responding were examined under extinction conditions (ie, no alcohol consumption) are not included in Table 1.

In many instances, pharmacological agents were used to probe mechanisms underlying escalated drinking associated with dependence. The development of alcohol dependence is a dynamic process that reflects a complex interplay among many neurobiological, genetic, experiential, and environmental factors. AUD is thought to encompass a composite of brain adaptations that manifest as dysfunctional reward processing, persistent negative affect/emotion along with sensitization of stress systems, and impaired executive function that compromises behavioral control (George & Koob, 2013; Koob, 2013). These adaptations are thought to reflect an allostatic state that is fueled by continued alcohol use (Koob, 2003), and marked by progressive dysregulation of brain mechanisms that mediate motivated behavior (reward circuitry), emotional stability (limbic and stress circuitry), and executive function (cortical circuitry). Thus, it is not surprising that many studies involving alcohol dependence and self-administration models have focused on drug treatments that target neurochemical systems that mediate pharmacological effects of alcohol (eg, GABA, glutamate, opioids, monoamines), as well as neurotransmitter and neuropeptide systems (eg, CRF, NPY) that contribute to adaptations in reward and stress circuitry in the brain

associated with dependence. Such changes in brain function are thought to underlie expression of withdrawal-related symptoms that contribute to enhanced relapse vulnerability as well as promote transition to excessive, uncontrolled drinking (Becker, 2014; Hansson, Rimondini, Neznanova, Sommer, & Heilig, 2008; Koob, 2013).

As previously mentioned, a positive feature of alcohol dependence and self-administration models is that treatment effects may be evaluated in both dependent and nondependent animals. This offers an excellent platform for evaluating efficacy of medications in reducing escalated drinking associated with dependence, more modest and stable levels of intake exhibited by non-dependent animals, or alcohol consumption in both conditions. As shown in Table 1, a large number of drug treatments were shown to be effective in selectively reducing elevated alcohol self-administration in dependent subjects while not altering intake in nondependent animals. This outcome suggests that such drug treatments may be influencing adaptive changes associated with dependence that significantly contribute to enhanced motivation to imbibe. This profile of results is best exemplified by drugs that target CRF1 receptors (CRF1R antagonists).

In several instances, pharmacological agents were shown to reduce alcohol self-administration in both dependent and nondependent animals. Drugs that target monoamine systems are a good example of this scenario. In many of these studies, however, higher doses of the drug treatments were required to reduce alcohol consumption in nondependent animals in comparison to dependent subjects. This was the case for studies testing the effects of the serotonin–norepinephrine reuptake inhibitor milnacipran (Simon O'Brien et al., 2011) and the β-adrenergic receptor antagonist propranolol (Gilpin & Koob, 2010), as well as other drugs such as the GABA-B receptor antagonist baclofen (Walker & Koob, 2007). The greater sensitivity to drug-induced modulation of alcohol consumption in dependent animals would also suggest that the treatment might be targeting brain systems/ processes that have changed as a function of chronic alcohol exposure in these models.

5. CHALLENGES IN DEVELOPING PHARMACOTHERAPIES FOR ALCOHOL DEPENDENCE AND RELAPSE

When one considers the diverse and widespread neuroadaptive changes that are set in motion as a consequence of prolonged excessive alcohol drinking, perhaps it is not surprising that no single pharmacological agent has proven to be fully successful in the treatment of alcoholism. Further, it is plausible that various pharmacological treatments may differ in effectiveness depending on, among several variables, the stage of addiction and motivation for drinking (Koob & Mason, 2016). The challenge of using pharmacotherapies and, perhaps more accurately, choosing the most appropriate drug for treatment of alcoholism is no doubt complicated by the complexity and heterogeneity of this relapsing disease, along with a host of other variables (eg, genotype, comorbidities, treatment regimens, compliance) that must be considered in the context of treatment interventions (eg, Litten et al., 2015; McLellan, Lewis, O'Brien, & Kleber, 2000). This is further compounded by the difficulty and time-consuming, not to mention costly, exercise of moving medications along the path toward FDA approval (Litten et al., 2012; Litten, Falk, Ryan, & Fertig, 2014).

Nevertheless, the alcohol field is at an exciting junction, poised to make inroads in the discovery and development of new medications. In the past two decades, an explosion of new discoveries from studies using molecular biology, neurobiology, neuroimaging, and behavioral neuroscience research has provided new insights about potential novel targets for developing new medications and treatment strategies for alcohol dependence. The burgeoning areas of pharmacogenetics and genomics have highlighted the important role of genotype and endophenotypes in defining differential responsiveness to medications, holding promise for the development of new treatment approaches that are more specifically tailored to subpopulations of individuals battling relapse as well as attempting to moderate their alcohol use and/or sustain abstinence. Unfortunately, despite these advancements, there are too few pharmacotherapeutic agents that have proven to be effective in treating alcohol dependence.

Currently, there are four medications approved by the FDA for treatment of AUD: disulfiram, oral naltrexone, acamprosate, and a long-acting injectable form of naltrexone (O'Malley & O'Connor, 2011). None of these medications have proven to be fully satisfactory with regard to magnitude of effects and uniformity of clinical outcomes. The need for identifying and developing new medications that will be more effective in treating AUDs is of paramount importance from a public health standpoint. No doubt, animal models of dependence and drinking will continue to play a pivotal role in not only the discovery of new and novel targets but also providing a valuable platform for evaluating efficacy of medications in reducing excessive, harmful levels of alcohol consumption. Such preclinical work is a critical step in the process of screening, identifying, and informing plans for prioritizing the most promising candidate medications that will be advanced to the next stage of evaluation—investigation in human laboratory paradigms and controlled clinical trials.

6. SUMMARY

Alcoholism is a complex disease that represents a highly significant public health concern. However, despite remarkable progress in elucidating biological and environmental mechanisms that drive excessive alcohol consumption along with its devastating consequences, few treatments are available for tackling this problem and providing relief for those suffering with the disease. Use of preclinical models that closely resemble the clinical situation plays a critical role in not only screening new test compounds but also identifying the most promising agents to be advanced for further clinical investigation. Numerous animal models have been developed to study underlying mechanisms as well as evaluate potential pharmacotherapeutic effects on excessive levels of drinking. In recent years, a great deal of attention has been focused on models that link alcohol dependence with self-administration procedures. These studies have been conducted in both mice and rats, and they have largely involved chronic intermittent exposure to alcohol vapor by inhalation. After establishing the positive reinforcing effects of alcohol (stable baseline levels of consumption), rodents exposed to chronic intermittent alcohol vapor display an escalation of self-administration behavior in comparison to nondependent animals that maintain a stable level of intake. This dependence-related increase in alcohol consumption has been demonstrated with different drinking models, including home-cage drinking as well as self-administration involving operant conditioning procedures. Further, this alcohol dependence

and drinking model has been widely used to evaluate the effects of medications on self-administration of alcohol in dependent compared to nondependent animals. Thus, studies employing alcohol dependence and self-administration procedures have not only provided critical insights about neuroadaptations that increase susceptibility to relapse and promote excessive drinking, but these models also have served as a valuable platform for identifying novel targets and evaluating new therapeutic strategies for treating AUDs.

ACKNOWLEDGMENTS

This work was supported by NIH grants P50 AA010761, U01 AA014095, and U01 AA020929 from the National Institute on Alcohol Abuse and Alcoholism and grant 2101BX000813 from the Department of Veterans Affairs Medical Research. The views and opinions expressed herein reflect those of the authors and do not necessarily reflect those of the funding agencies. The authors declare no implicit or explicit conflicts of interest with this material.

REFERENCES

Albrechet-Souza L, Hwa LS, Han X, Zhang EY, DeBold JF, & Miczek KA (2015). Corticotropin releasing factor binding protein and CRF2 receptors in the ventral tegmental area: Modulation of ethanol binge drinking in C57BL/6J mice. Alcoholism, Clinical and Experimental Research, 39, 1609–1618.

Anderson RI, Becker HC, Adams BL, Jesudason CD, & Rorick-Kehn LM (2014). Orexin-1 and orexin-2 receptor antagonists reduce ethanol self-administration in high-drinking rodent models. Frontiers in Neuroscience, 8, 33. [PubMed: 24616657]

Becker HC (2013). Animal models of excessive alcohol consumption in rodents. Current Topics in Behavioral Neurosciences, 13, 355–377. [PubMed: 22371267]

Becker HC (2014). Alcohol dependence, withdrawal, and relapse In Noronha ABC, Cui C, Harris RA, & Crabbe JC (Eds.), Neurobiology of alcohol dependence (pp. 377–410). London: Academic Press; Elsevier.

Becker HC, & Lopez MF (2004). Increased ethanol drinking after repeated chronic ethanol exposure and withdrawal experience in C57BL/6 mice. Alcoholism: Clinical and Experimental Research, 28, 1829–1838.

Bell RL, Lopez MF, Cui C, Egli M, Johnson KW, Franklin KM, et al. (2015). Ibudilast reduces alcohol drinking in multiple animal models of alcohol dependence. Addiction Biology, 20, 38–42. [PubMed: 24215262]

Bell RL, Sable HJK, Colombo G, Hyytia P, Rodd ZA, & Lumeng L (2012). Animal models for medications development targeting alcohol abuse using selectively bred rat lines: Neurobiological and pharmacological validity. Pharmacology, Biochemistry, and Behavior, 103, 119–155.

Brown G, Jackson A, & Stephens DN (1998). Effects of repeated withdrawal from chronic ethanol on oral self-administration of ethanol on a progressive ratio schedule. Behavioural Pharmacology, 9, 149–161. [PubMed: 10065934]

Cappell H, & LeBlanc A (1981). Tolerance and physical dependence: Do they play a role in alcohol and drug self-administration? In Israel Y, Glaser FB, Kalant H, Popham RE, Schmidt W, & Smart RG (Eds.), Research advances in alcohol and drug problems (pp. 159–196). New York: Plenum Press.

Carnicella S, Ron D, & Barak S (2014). Intermittent ethanol access schedule in rats as a preclinical model of alcohol abuse. Alcohol, 48, 243–252. [PubMed: 24721195]

Chu K, Koob GF, Cole M, Zorrilla EP, & Roberts AJ (2007). Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF1 receptor antagonist antalarmin and by CRF1 receptor knockout. Pharmacology, Biochemistry, and Behavior, 86, 813–821.

Crabbe JC, Harris RA, & Koob GF (2011). Preclinical studies of alcohol binge drinking. Annals of the New York Academy of Sciences, 1216, 24–40. [PubMed: 21272009]

Cunningham CL, Fidler TL, Murphy KV, Mulgrew JA, & Smitasin PJ (2013). Time-dependent negative reinforcement of ethanol intake by alleviation of acute withdrawal. Biological Psychiatry, 73, 249–255. [PubMed: 22999529]

Dawson DA, Goldstein RB, Saha TD, & Grant BF (2015). Changes in alcohol consumption: United States, 2001–2002 to 2012–2013. Drug and Alcohol Dependence, 148, 56–61. [PubMed: 25620731]

Dhaher R, Finn D, Snelling C, & Hitzemann R (2008). Lesions of the extended amygdala in C57BL/6J mice do not block the intermittent ethanol vapor-induced increase in ethanol consumption. Alcoholism, Clinical and Experimental Research, 32, 197–208.

Edwards S, Guerrero M, Ghoneim OM, Roberts E, & Koob GF (2012). Evidence that vasopressin V1b receptors mediate the transition to excessive drinking in ethanol-dependent rats. Addiction Biology, 17, 76–85. [PubMed: 21309953]

Fidler TL, Dion AM, Powers MS, Ramirez JJ, Mulgrew JA, Smitasin PJ, et al. (2011). Intragastric self-infusion of ethanol in high- and low-drinking mouse genotypes after passive ethanol exposure. Genes, Brain, and Behavior, 10, 264–275.

Fidler TL, Powers MS, Ramirez JJ, Crane A, Mulgrew J, Smitasin P, et al. (2012). Dependence induced increases in intragastric alcohol consumption in mice. Addiction Biology, 17, 13–32. [PubMed: 21955048]

Finn DA, Snelling C, Fretwell AM, Tanchuck MA, Underwood L, Cole M, et al. (2007). Increased drinking during withdrawal from intermittent ethanol exposure is blocked by the CRF receptor antagonist D-Phe-CRF(12–41). Alcoholism, Clinical and Experimental Research, 31, 939–949.

Funk CK, & Koob GF (2007). A CRF(2) agonist administered into the central nucleus of the amygdala decreases ethanol self-administration in ethanol-dependent rats. Brain Research, 1155, 172–178. [PubMed: 17512918]

Funk CK, O'Dell LE, Crawford EF, & Koob GF (2006). Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. The Journal of Neuroscience, 26, 11324–11332. [PubMed: 17079660]

Funk CK, Zorrilla EP, Lee MJ, Rice KC, & Koob GF (2007). Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. Biological Psychiatry, 61, 78–86. [PubMed: 16876134]

Gehlert DR, Cippitelli A, Thorsell A, Le AD, Hipskind PA, Hamdouchi C, et al. (2007). 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethylimidazo [1,2-b]pyridazine: A novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. The Journal of Neuroscience, 27, 2718–2726. [PubMed: 17344409]

George O, & Koob GF (2013). Control of craving by the prefrontal cortex. Proceedings of the National Academy of Sciences of the United States of America, 110, 4165–4166. [PubMed: 23483010]

Gilpin NW, & Koob GF (2010). Effects of beta-adrenoceptor antagonists on alcohol drinking by alcohol-dependent rats. Psychopharmacology, 212, 431–439. [PubMed: 20676608]

Gilpin NW, Misra K, Herman MA, Cruz MT, Koob GF, & Roberto M (2011). Neuropeptide Y opposes alcohol effects on gamma-aminobutyric acid release in amygdala and blocks the transition to alcohol dependence. Biological Psychiatry, 69, 1091–1099. [PubMed: 21459365]

Gilpin NW, Misra K, & Koob GF (2008). Neuropeptide Y in the central nucleus of the amygdala suppresses dependence-induced increases in alcohol drinking. Pharmacology, Biochemistry, and Behavior, 90, 475–480.

Gilpin NW, Richardson HN, & Koob GF (2008). Effects of CRF1-receptor and opioid-receptor antagonists on dependence-induced increases in alcohol drinking by alcohol-preferring (P) rats. Alcoholism, Clinical and Experimental Research, 32, 1535–1542.

Gilpin NW, Richardson HN, Lumeng L, & Koob GF (2008). Dependence-induced alcohol drinking by alcohol-preferring (P) rats and outbred Wistar rats. Alcoholism, Clinical and Experimental Research, 32, 1688–1696.

Gilpin NW, Smith AD, Cole M, Weiss F, Koob GF, & Richardson HN (2009). Operant behavior and alcohol levels in blood and brain of alcohol-dependent rats. Alcoholism, Clinical and Experimental Research, 33, 2113–2123.

Grant K (1995). Animal models of the alcohol addiction process In Kranzler H (Ed.), The pharmacology of alcohol abuse (pp. 185–230). Berlin: Springer-Verlag.

Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. (2015). Epidemiology of DSM-5 alcohol use disorder: Results from the national epidemiologic survey on alcohol and related conditions III. JAMA Psychiatry, 72, 757–766. [PubMed: 26039070]

Griffin WC 3rd (2014). Alcohol dependence and free-choice drinking in mice. Alcohol, 48, 287–293. [PubMed: 24530006]

Griffin WC 3rd, Lopez MF, & Becker HC (2009a). Intensity and duration of chronic ethanol exposure is critical for subsequent escalation of voluntary ethanol drinking in mice. Alcoholism, Clinical and Experimental Research, 33, 1893–1900.

Griffin WC 3rd, Lopez MF, Yanke AB, Middaugh LD, & Becker HC (2009b). Repeated cycles of chronic intermittent ethanol exposure in mice increases voluntary ethanol drinking and ethanol concentrations in the nucleus accumbens. Psychopharmacology, 201, 569–580. [PubMed: 18791704]

Hansson AC, Rimondini R, Neznanova O, Sommer WH, & Heilig M (2008). Neuroplasticity in brain reward circuitry following a history of ethanol dependence. The European Journal of Neuroscience, 27, 1912–1922. [PubMed: 18412612]

Heilig M, Egli M, Crabbe JC, & Becker HC (2010). Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? Addiction Biology, 15, 169–184. [PubMed: 20148778]

Houchi H, Persyn W, Legastelois R, & Naassila M (2013). The adenosine A2A receptor agonist CGS 21680 decreases ethanol self-administration in both non-dependent and dependent animals. Addiction Biology, 18, 812–825. [PubMed: 23301633]

Kallupi M, Vendruscolo LF, Carmichael CY, George O, Koob GF, & Gilpin NW (2014). Neuropeptide YY(2)R blockade in the central amygdala reduces anxiety-like behavior but not alcohol drinking in alcohol-dependent rats. Addiction Biology, 19, 755–757. [PubMed: 23639035]

Kissler JL, Sirohi S, Reis DJ, Jansen HT, Quock RM, Smith DG, et al. (2014). The one-two punch of alcoholism: Role of central amygdala dynorphins/kappa-opioid receptors. Biological Psychiatry, 75, 774–782. [PubMed: 23611261]

Koob GF (2003). Alcoholism: Allostasis and beyond. Alcoholism, Clinical and Experimental Research, 27, 232–243.

Koob GF (2013). Addiction is a reward deficit and stress surfeit disorder. Frontiers in Psychiatry, 4, 72. [PubMed: 23914176]

Koob GF, & Mason BJ (2016). Existing and future drugs for the treatment of the dark side of addiction. Annual Review of Pharmacology and Toxicology, 56, 299–322.

Litten RZ, Egli M, Heilig M, Cui C, Fertig JB, Ryan ML, et al. (2012). Medications development to treat alcohol dependence: A vision for the next decade. Addiction Biology, 17, 513–527. [PubMed: 22458728]

Litten RZ, Falk D, Ryan M, & Fertig J (2014). Research opportunities for medications to treat alcohol dependence: Addressing stakeholders' needs. Alcoholism, Clinical and Experimental Research, 38, 27–32.

Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, & Koob GF (2015). Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. Alcoholism, Clinical and Experimental Research, 39, 579–584.

Lopez MF, Anderson RI, & Becker HC (2008). Repeated cycles of chronic intermittent ethanol exposure increase both self-administration and the reinforcing value of ethanol in C57BL/6J mice. Alcoholism, Clinical and Experimental Research, 32, 163A.

Lopez MF, & Becker HC (2005). Effect of pattern and number of chronic ethanol exposures on subsequent voluntary ethanol intake in C57BL/6J mice. Psychopharmacology, 181, 688–696. [PubMed: 16001125]

Lopez MF, & Becker HC (2014). Operant ethanol self-administration in ethanol dependent mice. Alcohol, 48, 295–299. [PubMed: 24721194]

Lopez MF, Becker HC, & Chandler LJ (2014). Repeated episodes of chronic intermittent ethanol promote insensitivity to devaluation of the reinforcing effect of ethanol. Alcohol, 48, 639–645. [PubMed: 25266936]

Lopez MF, Griffin WC, Melendez RI, & Becker HC (2012). Repeated cycles of chronic intermittent ethanol exposure leads to the development of tolerance to aversive effects of ethanol in C57BL/6J mice. Alcoholism: Clinical and Experimental Research, 36, 1180–1187.

McLellan AT, Lewis DC, O'Brien CP, & Kleber HD (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. JAMA, 284, 1689–1695. [PubMed: 11015800]

Meinhardt MW, & Sommer WH (2015). Postdependent state in rats as a model for medication development in alcoholism. Addiction Biology, 20, 1–21. [PubMed: 25403107]

Nealey KA, Smith AW, Davis SM, Smith DG, & Walker BM (2011). kappa-opioid receptors are implicated in the increased potency of intra-accumbens nalmefene in ethanol-dependent rats. Neuropharmacology, 61, 35–42. [PubMed: 21338616]

O'Dell LE, Roberts AJ, Smith RT, & Koob GF (2004). Enhanced alcohol self-administration after intermittent versus continuous alcohol vapor exposure. Alcoholism, Clinical and Experimental Research, 28, 1676–1682.

O'Malley SS, & O'Connor PG (2011). Medications for unhealthy alcohol use: Across the spectrum. Alcohol Research & Health, 33, 300–312. [PubMed: 23580015]

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, & Patra J (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet, 373, 2223–2233. [PubMed: 19560604]

Richardson HN, Zhao Y, Fekete EM, Funk CK, Wirsching P, Janda KD, et al. (2008). MPZP: A novel small molecule corticotropin-releasing factor type 1 receptor (CRF1) antagonist. Pharmacology, Biochemistry, and Behavior, 88, 497–510.

Rimondini R, Arlinde C, Sommer W, & Heilig M (2002). Long-lasting increase in voluntary ethanol consumption and transcriptional regulation in the rat brain after intermittent exposure to alcohol. The FASEB Journal, 16, 27–35. [PubMed: 11772933]

Rimondini R, Sommer W, & Heilig M (2003). A temporal threshold for induction of persistent alcohol preference: Behavioral evidence in a rat model of intermittent intoxication. Journal of Studies on Alcohol, 64, 445–449. [PubMed: 12921185]

Rimondini R, Thorsell A, & Heilig M (2005). Suppression of ethanol self-administration by the neuropeptide Y (NPY) Y2 receptor antagonist BIIE0246: Evidence for sensitization in rats with a history of dependence. Neuroscience Letters, 375, 129–133. [PubMed: 15670655]

Roberto M, Cruz MT, Gilpin NW, Sabino V, Schweitzer P, Bajo M, et al. (2010). Corticotropin releasing factor-induced amygdala gamma-aminobutyric acid release plays a key role in alcohol dependence. Biological Psychiatry, 67, 831–839. [PubMed: 20060104]

Roberto M, Gilpin NW, O'Dell LE, Cruz MT, Morse AC, Siggins GR, et al. (2008). Cellular and behavioral interactions of gabapentin with alcohol dependence. The Journal of Neuroscience, 28, 5762–5771. [PubMed: 18509038]

Roberts AJ, Cole M, & Koob GF (1996). Intra-amygdala muscimol decreases operant ethanol self-administration in dependent rats. Alcoholism, Clinical and Experimental Research, 20, 1289–1298.

Roberts AJ, Heyser CJ, Cole M, Griffin P, & Koob GF (2000). Excessive ethanol drinking following a history of dependence: Animal model of allostasis. Neuropsychopharmacology, 22, 581–594. [PubMed: 10788758]

Rodriguez de Fonseca F, Roberts AJ, Bilbao A, Koob GF, & Navarro M (1999). Cannabinoid receptor antagonist SR141716A decreases operant ethanol self administration in rats exposed to ethanol-vapor chambers. Zhongguo Yao Li Xue Bao, 20, 1109–1114. [PubMed: 11189201]

Sabino V, Cottone P, Zhao Y, Iyer MR, Steardo L Jr., Steardo L, et al. (2009). The sigma-receptor antagonist BD-1063 decreases ethanol intake and reinforcement in animal models of excessive drinking. Neuropsychopharmacology, 34, 1482–1493. [PubMed: 18946467]

Schulteis G, Hyytia P, Heinrichs SC, & Koob GF (1996). Effects of chronic ethanol exposure on oral self-administration of ethanol or saccharin by Wistar rats. Alcoholism, Clinical and Experimental Research, 20, 164–171.

Sidhpura N, Weiss F, & Martin-Fardon R (2010). Effects of the mGlu2/3 agonist LY379268 and the mGlu5 antagonist MTEP on ethanol seeking and reinforcement are differentially altered in rats with a history of ethanol dependence. Biological Psychiatry, 67, 804–811. [PubMed: 20189165]

Simms JA, Nielsen CK, Li R, & Bartlett SE (2014). Intermittent access ethanol consumption dysregulates CRF function in the hypothalamus and is attenuated by the CRF-R1 antagonist, CP-376395. Addiction Biology, 19, 606–611. [PubMed: 23362976]

Simon O'Brien E, Legastelois R, Houchi H, Vilpoux C, Alaux-Cantin S, Pierrefiche O, et al. (2011). Fluoxetine, desipramine, and the dual antidepressant milnacipran reduce alcohol self-administration and/or relapse in dependent rats. Neuropsychopharmacology, 36, 1518–1530. [PubMed: 21430652]

Smith AW, Nealey KA, Wright JW, & Walker BM (2011). Plasticity associated with escalated operant ethanol self-administration during acute withdrawal in ethanol-dependent rats requires intact matrix metalloproteinase systems. Neurobiology of Learning and Memory, 96, 199–206. [PubMed: 21530666]

Sommer WH, Rimondini R, Hansson AC, Hipskind PA, Gehlert DR, Barr CS, et al. (2008). Upregulation of voluntary alcohol intake, behavioral sensitivity to stress, and amygdala crhr1 expression following a history of dependence. Biological Psychiatry, 63, 139–145. [PubMed: 17585886]

Sommer WH, Rimondini R, Marquitz M, Lidstrom J, Siems WE, Bader M, et al. (2007). Plasticity and impact of the central renin-angiotensin system during development of ethanol dependence. Journal of Molecular Medicine (Berlin, Germany), 85, 1089–1097.

Suchankova P, Yan J, Schwandt ML, Stangl BL, Caparelli EC, Momenan R, et al. (2015). The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: Evidence from human genetic association studies and a mouse model of alcohol dependence. Translational Psychiatry, 5, e583. [PubMed: 26080318]

Thorsell A, Slawecki CJ, & Ehlers CL (2005). Effects of neuropeptide Y on appetitive and consummatory behaviors associated with alcohol drinking in wistar rats with a history of ethanol exposure. Alcoholism, Clinical and Experimental Research, 29, 584–590.

Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP, et al. (2002). Increased ethanol self-administration and anxiety-like behavior during acute ethanol withdrawal and protracted abstinence: Regulation by corticotropin-releasing factor. Alcoholism, Clinical and Experimental Research, 26, 1494–1501.

Vendruscolo LF, Barbier E, Schlosburg JE, Misra KK, Whitfield TW Jr., Logrip ML, et al. (2012). Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. The Journal of Neuroscience, 32, 7563–7571. [PubMed: 22649234]

Vendruscolo LF, & Roberts AJ (2014). Operant alcohol self-administration in dependent rats: Focus on the vapor model. Alcohol, 48, 277–286. [PubMed: 24290310]

Vengeliene V, Bilbao A, & Spanagel R (2014). The alcohol deprivation effect model for studying relapse behavior: A comparison between rats and mice. Alcohol, 48, 313–320. [PubMed: 24811155]

Walker BM, & Koob GF (2007). The gamma-aminobutyric acid-B receptor agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. Alcoholism, Clinical and Experimental Research, 31, 11–18.

Walker BM, & Koob GF (2008). Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. Neuropsychopharmacology, 33, 643–652. [PubMed: 17473837]

Walker BM, Rasmussen DD, Raskind MA, & Koob GF (2008). alpha1-Noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol, 42, 91–97. [PubMed: 18358987]

Walker BM, Zorrilla EP, & Koob GF (2011). Systemic kappa-opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. Addiction Biology, 16, 116–119. [PubMed: 20579007]

Table 1

Effect of Medication Treatments Evaluated in Rodent Models of Alcohol Dependence and Drinking

			Effect		
Target System	**Medication**	**Mode of Action**	**Nondep.**	**Dep.**	**Reference**
GABA	Baclofen	GABA-B agonist	→	↓	Walker and Koob (2007)
	Muscimol	GABA-A agonist	→	↓	Roberts et al. (1996)
	Gabapentin	GABA modulator	→	↓	Roberto et al. (2008)
Glutamate	Acamprosate	Modulator	→	↓	Rimondini et al. (2002)
	LY379268	mGluR2/3 agonist	↓	↓	Sidhpura, Weiss, and Martin-Fardon (2010)
	MTEP	mGluR1/5 antagonist	↓	↓	Sidhpura etal. (2010)
Opiates	Naltrexone	Nonselect antagonist	↓	↓	Gilpin, Richardson, and Koob (2008) and Walker and Koob (2008)
	Nalmefene	MOR/KOR antagonist	↓	↓	Kissler et al. (2014) and Nealey, Smith, Davis, Smith, and Walker (2011)
	BD–1063	DOR antagonist	→	↓	Sabino et al. (2009)
	CTOP + naltrindole	MOR/DOR antagonist	↓	→	Kissler et al. (2014) and Nealey et al. (2011)
	Nor-BNI	KOR antagonist	→	↓	Kissler et al. (2014), Nealey etal. (2011), Walker, Rasmussen, Raskind, and Koob (2008), and Walker, Zorrilla, and Koob (2011)
Monoamines	Desipramine	SNRI	↓	↓	Simon O'Brien et al. (2011)
	Fluoxetine	SSRI	↓	↓	Simon O'Brien et al. (2011)
	Milnacipran	SNRI	→	↓	Simon O'Brien et al. (2011)
	Prazosin	α1–NE antagonist	↓	↓	Walker et al. (2008)
	Propranolol	β–NE antagonist	↓	↓	Gilpin and Koob (2010)
Neuropeptides	Antalarmin	CRF1R antagonist	→	↓	Funk et al. (2007)
	D-Phe-$CRF_{12–41}$	CRF1R antagonist	→	↓	Funk et al. (2006) and Valdez et al. (2002)
	MJL-1-109- 2	CRF1R antagonist	→	↓	Funk et al. (2007)
	MTIP	CRF1R antagonist	→	↓	Gehlert et al. (2007)
	MPZP	CRF1R antagonist	→	↓	Gilpin, Richardson, and Koob (2008) and Richardson et al. (2008)
	R121919	CRF1R antagonist	→	↓	Funk et al. (2007) and Roberto et al. (2010)
	Urocortin3	CRF2R agonist	→	↓	Funk and Koob (2007)
	NPY	NPYR agonist	↓	↓	Gilpin etal. (2011) and Thorsell, Slawecki, and Ehlers (2005)
	BIIE0246	NPY2R antagonist	→	→	Kallupi et al. (2014)
	JNJ-31020028	NPY2R antagonist	→	→	Kallupi et al. (2014)
	SSR149415	AVP V_{1b} antagonist	→	→	Edwards, Guerrero, Ghoneim, Roberts, and Koob (2012)
Others	AC3174	Glucagon-1 agonist	→	↓	Suchankova et al. (2015)
	CGS 21680	Adenosine A2a agonist	→	↓	Houchi, Persyn, Legastelois, and Naassila (2013)
	FN-439	MP protease	-	↓	Smith, Nealey, Wright, and Walker (2011)
	Ibudilast	Nonselect PDE inhibitor	↓	↓	Bell et al. (2015)
	Mifepristone	GR antagonist	→	↓	Vendruscolo et al. (2012)

Target System	Medication	Mode of Action	Effect		Reference
			Nondep.	Dep.	
	SR141716A	CB1 antagonist	→	↓	Rodriguez de Fonseca, Roberts, Bilbao, Koob, and Navarro (1999)
	Spirapril	ACE inhibitor	↓	↓	Sommer et al. (2007)