Rat Animal Models for Screening Medications to Treat Alcohol Use Disorders

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The purpose of this review is to present animal research models that can be used to screen and/or repurpose medications for the treatment of alcohol abuse and dependence. The focus will be on rats and in particular selectively bred rats. Brief introductions discuss various aspects of the clinical picture, which provide characteristics of individuals with alcohol use disorders (AUDs) to model in animals. Following this, multiple selectively bred rat lines will be described and evaluated in the context of animal models used to screen medications to treat AUDs. Next, common behavioral tests for drug efficacy will be discussed particularly as they relate to stages in the addiction cycle. Tables highlighting studies that have tested the effects of compounds using the respective techniques are included. Wherever possible the Tables are organized chronologically in ascending order to describe changes in the focus of research on AUDs over time. In general, high ethanol-consuming selectively bred rats have been used to test a wide range of compounds. Older studies usually followed neurobiological findings in the selected lines that supported an association with a propensity for high ethanol intake. Most of these tests evaluated the compound's effects on the maintenance of ethanol drinking. Very few compounds have been tested during ethanol-seeking and/or relapse and fewer still have assessed their effects during the acquisition of AUDs. Overall, while a substantial number of neurotransmitter and neuromodulatory system targets have been assessed; the roles of sex- and age-of-animal, as well as the acquisition of AUDs, ethanol-seeking and relapse continue to be factors and behaviors needing further study.

1. Background from a Clinical Perspective

1.1. Societal Burden of Alcohol Abuse and Dependence

Approximately half of all Americans have at least one relative with an alcohol use disorders (AUD), with some of these individuals having this trait across multiple generations (Research Society on Alcoholism [RSA], 2011, 2015). Half of individuals meeting a life-time diagnosis for an AUD do so by age 21 with two-thirds doing so by age 25 (Hingson et al., 2006). This is especially troubling given between 15% and 25% of individuals in the military have AUDs (Bray & Hourani, 2007; Bray et al., 2006; RSA, 2011, 2015). There has been a narrowing of the gender gap recently, especially among youth and the elderly (Brienza and Stein, 2002; Nelson et al., 1998; Substance Abuse and Mental Health Services Administration (SAMHSA), 2012; Wilsnack et al., 1991). In the US, the cost of AUDs approaches a quarter of a trillion dollars each year (Harwood et al., 2000; RSA, 2015), with close to 100,000 people dying due to alcohol-related causes every year (RSA, 2011, 2015). The Centers for Disease Control and Prevention (CDC) considers AUDs the third leading cause of preventable death (Mokdad et al., 2004) and is a major factor in the top three leading medical causes of death (RSA, 2011, 2015). Moreover, a direct association has been found between alcohol (ethanol, the primary form of alcohol abused, will be used instead of alcohol in the rest of the paper) use and 50 different medical conditions (Reed et al., 1996; Rehm et al., 2003).

1.2. (Endo)Phenotypic Associations with Ethanol Abuse and Dependence

For the present discussion, an endophenotype (sometimes called intermediate phenotype) is defined as a characterisitic (a) having relative specificity for the psychiatric disorder being studied, (b) a trait vs state characteristic such that it predates overt expression of symptoms, (c) having significant heritability and is associated with familial density of the disorder, and (d) has biological and clinical plausibility (e.g., Ray and Heilig, 2013). Preclinical and clinical research indicates the following endophenotypes are directly related to the development of ethanol dependence (a) lower initial sensitivity to ethanol's aversive effects (c.f., Bell et al., 2006b, 2012; Colombo et al., 2006; Draski and Deitrich, 1996; Le et al., 2001; Schuckit and Gold, 1988), (b) greater levels and/or quicker development of ethanol-induced tolerance (c.f., Costin and Miles, 2014; Lê and Mayer, 1996), (c) anxiety-like and/or depressive behavior including during ethanol withdrawal (c.f., Ciccocioppo et al., 2006; Heilig et al., 2010; Kirby et al., 2011; Overstreet et al., 2006; Pautassi et al., 2010; Sjoerds et al., 2014; Thorsell, 2010), (d) stress reactivity (c.f., Barr and Goldman, 2006), and (e) sweet liking/preference (c.f., de Wit and Richards, 2004; Kampov-Polevoy et al., 2014; Lange et al., 2010; Pepino and Mennella, 2007; Perry and Carroll, 2008).

Endophenotypes also include ethanol-associated physiological and behavioral stimulation (Trim et al., 2010) [which is modeled in rodents by increased motor activity and/or approach behavior (Chappell and Weiner, 2008; Faria et al., 2008; Wise and Bozarth, 1987), aggression (Chiavegatto et al., 2010), and social facilitation (Varlinskaya and Spear, 2009, 2010)]. Interestingly, there appears to be pharmacological validity for ethanol-associated stimulation as well as reward, with histaminergic (Panula and Nuutinen, 2011 and references therein) and ghrelin (Jerlhag et al., 2011 and references therein) systems implicated in ethanol-induced motor activation, ethanol-induced conditioned place preference,

ethanol-preference and excessive ethanol intake. Nevertheless, there are concerns with establishing consilience and translatability of ethanol-induced stimulation between the preclinical and clinical literature (c.f., Crabbe et al., 2010). For instance, other than lower dose effects on self-report (Morzorati et al., 2002; Viken et al., 2003), heart rate (Finn and Justus, 1997; Peterson et al., 1996), and brain activity (Lukas et al., 1986; Sorbel et al., 1996; Trim et al., 2010) the stimulating effects of ethanol are not as readily seen in humans compared with rodents.

1.3. Adolescence

Adolescence is a crucial stage of development during which addiction becomes a prominent public health concern (c.f., Dahl and Spear, 2004; Essau, 2008; Liddle and Rowe, 2006; Monti et al., 2001; Romer and Walker, 2007; Rosner, 2013; Spear, 2010; Wagner and Waldron, 2001). Today's youth are initiating ethanol use earlier (e.g., grade school) and experiencing more ethanol-related problems before leaving high school (Bava and Tapert, 2010; Gore et al., 2011; Kandel et al., 1997; Miller et al., 2001; Nelson et al., 1998; Pitkanen et al., 2005; Quine and Stephenson, 1990; Winters, 2001). Three-quarter of high school seniors in the United States have consumed ethanol with half of them initiating drinking before the eighth grade (Johnston et al., 1999). This is alarming since early onset of ethanol use along with binge drinking are strong predictors of future ethanol dependence (Anthony and Petronis, 1995; Capaldi et al., 2013; Chou and Pickering, 1992; Grant and Dawson, 1997; Hawkins et al., 1997; Rossow and Kuntsche, 2013). Moreover, adolescent onset of ethanol use is associated with a more rapid progression to dependence, compared with individuals who initiated use as adults (Clark et al., 1998). Regarding binge drinking, a quarter of high school seniors report binge drinking, with approximately three-quarters of college students reporting binge drinking during high school (Dawson et al., 2004; Johnston et al., 1991, 1993, 2008; Kuntsche et al., 2004; Presley et al., 1994; Wechsler et al., 2000; White et al., 2006). It is estimated that greater than 1 out of 3 male college students engage in binge drinking in the United States and many of these consume at least 2 to 3 times the binge definition threshold (e.g., Wechsler et al., 2000; White et al., 2006). However, in some United Kingdom locales adolescent girls may actually engage in binge drinking more than adolescent boys (c.f., Plant and Plant, 2006). Regarding younger individuals, the seriousness of this problem is underscored by the fact that adolescents between 12 and 20 years of age drink 11 percent of all ethanol consumed in the United States, with more than 90 percent of it consumed in the form of binge drinking (NIAAA, 2012). Essentially, binge ethanol drinking has been defined as an escalation in self-administration (c.f., Covington and Miczek, 2011), achieving BACs associated with intoxication and an important step in the development of ethanol dependence (c.f., Koob, 2013; Koob et al., 2014a; Noronha et al., 2014).

1.3.1. Binge Drinking as a Developmental Phenomenon

Clinical evidence indicates that binge drinking behavior is engaged by adolescents and young adults more often and to a greater magnitude than older (>24 years old) adults (c.f., Courtney and Polich, 2009; Marczinski et al., 2009; Martinic and Measham, 2008; Plant and Plant, 2006). Earlier studies reporting contrary findings may be due to changes in the definition of binge drinking over time. The fact that binge ethanol drinking occurs mostly in adolescents and young adults is due, at least in part, to the fact that younger subjects are less affected by ethanol than older individuals. Most of the literature evaluating

this observation has been done in rodent models (see discussion by Spear, 2010), with some evidence for this from clinical observations as well. The most obvious clinical observation is that adolescents tend to drink substantially more ethanol per occasion than adults (NIAAA, 2012; SAMHSA, 2012) even though they can achieve similar BACs with fewer drinks (Donovan, 2009; NIAAA, 2012; SAMHSA, 2012). Regarding insensitivity to ethanol's effects, Rohsenow and colleagues (2012) found that hangover insensitivity was significantly correlated with intoxication insensitivity and future ethanol-related problems. Another recent study (Gilman et al., 2012) examined the effects of ethanol in heavy and light social drinkers. The study examined individual subjective and objective, the latter measured by fMRI to emotional stimuli, responses while BACs were clamped at 80 mg%. These authors reported that heavy, relative to light, drinking individuals had both reduced sensitivity to ethanol's subjective effects and reduced activation of the nucleus accumbens (Acb) and amygdala (Amyg) to emotional stimuli.

There also is evidence suggesting that young heavy drinkers, relative to young light drinkers, experience greater stimulation on the rising limb of the BAC-curve and lower sedation on the descending limb of the BAC-curve (e.g., Holdstock et al., 2000; King et al., 2002). King and colleagues (2011) replicated their previous findings that weekly binge drinkers experience greater stimulation and less sedation following ethanol consumption than young light drinkers. These authors also reported that greater stimulation and lower sedation predicted escalated binge drinking over the next 2 years. In turn, escalated binge drinking predicted an increased likelihood of meeting diagnostic criteria for an AUD (King et al., 2011). This parallels findings that Family History Positive (FHP) for AUD individuals experience greater stimulation on the ascending limb and less sedation on the descending limb of the BAC-curve than family history negative (FHN) for AUD controls (e.g., Brunelle et al., 2004, 2007; Newlin and Thomson, 1990, 1999; c.f., Sher, 1991; Windle and Searles, 1990).

The difficulty with evaluating whether adolescent and young adult binge drinkers experience greater reward (e.g., stimulation) and less aversion (e.g., sedation) than light drinkers or older drinkers is the role of positive outcome expectancies from drinking to intoxication, such that young binge-drinkers expect increased peer affiliation as well as feelings of euphoria and excitement (c.f., Duka et al., 1998; Marczinski et al., 2009; Martinic and Measham, 2008; Plant and Plant, 2006). Note that these are not expectancies associated with drinking in general but specifically "drinking to intoxication". This parallels the BAC requirement (greater than 0.08 gram percent; i.e., 80 mg%) found in NIAAA's definition of binge ethanol-drinking (NIAAA, 2004). There is preclinical evidence (e.g., Bell et al., 2000, 2001) indicating that ethanol-exposure approximating these BAC levels can induce tolerance to ethanol-induced motor impairment (i.e., ataxia). As noted in the discussion on the addiction process, escalation of intake is associated with tolerance to effects induced by ethanol which, in turn, may lead to abuse and dependence. However, as noted by (Ahmed, 2011), escalation in ethanol drinking, or the intake of substances of abuse, does not necessarily stem from the development of neuronal tolerance in humans. Although, it also should be noted that these other possible explanations for the development of tolerance in humans (Ahmed, 2011), such as social and economic factors, are not easily amenable to examination when using animal models.

1.4. Polysubstance Abuse

As with ethanol, initiation of drug use and abuse generally occurs during adolescence and young adulthood (Kandel and Logan, 1984). Moreover, abuse of one drug is positively associated with initiating use of another drug of abuse (Yamaguchi and Kandel, 1984). Thus, again as with ethanol, the developmental periods of adolescence and young adulthood represent the peak times for initiating and using multiple substances of abuse (c.f., Dean et al., 2014). A recent meta-analysis/literature review addressed whether respondent subclassifications of substance use could be determined from published studies on adolescent and young adults (Tomczyk et al., 2016). Twenty-three studies (~a half million subjects) met inclusion criteria. Overall, these authors reported that none to low use were the largest "latent" classes, moderate to high single substance use (e.g., ethanol) were intermediate in size, and polysubstance use had the least respondents. However, approximately 32% of the respondents, across all of the analyzed studies, endorsed use of at least 2 substances, usually ethanol and smoking (Tomczyk et al., 2016). Given the above, Connor and colleagues (2014) make some important points about diagnostic and research challenges as they relate to changes introduced by the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5) (American Psychiatric Association, 2013). In particular, the DSM-5 removed the diagnostic category "Polysubstance dependence" along with the terms "Abuse" and "Dependence". This may result in underestimating polysubstance dependence, since each drug class an individual abuses can be scaled separately on the severity index.

1.5. Stages in the Development of Alcohol Use Disorders

AUDs represent a chronic, progressive, relapsing disorder that advances from experimentation to dependence (Heilig and Egli, 2006; Jupp and Lawrence, 2010; Koob, 2009; Koob and LeMoal, 2008; Koob and Volkow, 2010; Spanagel, 2009; Volkow and Li, 2005). During experimentation, the individual experiences the rewarding, euphoric and positive-reinforcing effects of ethanol consumption. Moreover, experimentation includes binge-like drinking and acute increases in motor, such as pro-social behavior, and autonomic, such as heart rate, activity which are generally perceived as euphoric and pleasant. The experimentation and binge-drinking stages are associated with positive reinforcement; which increases the probability, frequency and magnitude of subsequent drinking behavior. After chronic use, there is an increase in dysphoria (as opposed to euphoria), such as anxiety, during ethanol withdrawal. These dysphoric effects can be physiological in nature (e.g., hangover, hyperthermia, tachycardia, etc.) or associated with negative behavioral sequelae, such as getting arrested. With this increase in dysphoria, the individual often seeks to relieve this state by relapsing to ethanol drinking. Essentially, during the early stages of AUDs positive reinforcement predominates, whereas during later stages of AUDs negative reinforcement tends to predominate (Koob et al., 2014a, 2014b; Koob & Le Moal, 2006, 2008).

Addiction-related positive- vs negative-reinforcement can also be characterized in terms of impulsive vs compulsive ethanol drinking (Garbusow et al., 2014; Hagele et al., 2014; Koob et al., 2014a, 2014b; Koob & Le Moal, 2006, 2008; Spanagel, 2009). Within these constructs, impulsive drinking is associated with binge drinking and intoxication, during which an individual putatively has some volitional control, and subsequently there is the maintenance of ethanol drinking (Gray & MacKillop, 2014; Hamilton et al., 2014; but see Irimia et al., 2013). Chronic usage leads to the development of tolerance to ethanol's effects (Kippin, 2014). Following the development of tolerance there is the development of dependence as indicated by withdrawal signs once ethanol use is terminated and chronic relapsing to mitigate

associated dysphoria (Edwards et al., 2015). This negative reinforcement to mitigate physical and behavioral withdrawal leads in turn to compulsive/habitual drinking (Koob, 2014; Potgieter et al., 1999). It is during this transition from impulsive to compulsive drinking that the individual appears to "lose control" of their drinking. This, in turn, leads to a preoccupation with, and an anticipation of, future ethanol consumption during periods of acute and chronic ethanol withdrawal (Burnett et al., 2016; Koob et al., 2014a, 2014b; Koob & Le Moal, 2006, 2008). Nevertheless, it should be noted that AUDs do not necessarily progress in a linear fashion, such that the frequency and/or duration a person experiences these cycles of drinking, abstaining, seeking, and relapsing can differ substantially across individuals (e.g., Barker & Taylor, 2014; Mackenzie et al., 2014; Sartor et al., 2014; van Rizen & Dishion, 2014).

1.6. Genetics of Alcohol Use Disorders

The well-documented familial incidence of alcoholism as well as findings from twin and adoption studies indicate that ethanol dependence is a highly heritable disease (Cloninger, 1987; Cotton, 1979; Schuckit, 1986). For instance, FHP individuals are at a 3-7 fold increased risk to develop alcoholism compared with FHN controls (Reich et al., 1998). Furthermore, this genetic proposal has been micro-dissected by multiple gene studies [for example the Collaborative Study On the Genetics of Alcoholism (COGA), the Study of Addiction: Genes and Environment (SAGE) and the European research project on risk taking behavior in teenagers (IMAGEN)] examining the association between diagnostic criteria for ethanol dependence, or related phenotypes, and the presence of single nucleotide polymorphisms (SNPs) in ethanol-dependent individuals (Agrawal et al., 2008; Chen et al., 2012; Dick, 2013; Edenberg, 2012; Edenberg and Foroud, 2013; Enoch, 2013; Kapoor et al., 2013; Levey et al., 2014; MacKillop and Acker, 2013; Ray and Heilig, 2013; Rietschel and Treutlein, 2013; Wall et al., 2013; Wong and Schumann, 2008; Yan et al., 2014).

1.7. Summary of Human Characteristics for Animal Model Development

This first section provided an overview of characteristics observed in individuals suffering from AUDs and the second section of this paper will discuss how well selectively bred rats can display these same characteristics. It is clear that AUDs continue to be a major public health concern and despite some inroads made into identifying molecular targets for the treatment of ethanol dependence considerable more research is needed. Some of the key characteristics often displayed by individuals with AUDs include, an early onset of drinking, engaging in binge-like drinking, reduced sensitivity to the aversive and perhaps greater sensitivity to the stimulating effects of ethanol, the development of tolerance to ethanol's effects, anhedonia associated with ethanol withdrawal, increased stress reactivity, greater sweet-liking, pursuance of novelty-seeking, certain electrophysiological measures, and key gene and/or protein differences from controls. It is believed that an animal model of AUD should display many of these characteristics and as the number of characteristics observed increases so too does the face validity of the animal model.

2. Background from an Animal Model Perspective

2.1. Pros and Cons of Animal Model Research

While drug development relies heavily on in vitro assays early in the process, subsequent studies in vivo are required in the pathway to FDA regulation and clinical use (Blass, 2015). In vivo assays are required to evaluate a compound in a highly complex biological system as opposed to in vitro assays, which are constrained by their limited macromolecular environment (Blass, 2015). Essentially, the outcome measures of an in vivo assay are greater than the sum of its multiple constituent measures or presumable endpoints initially measured using in vitro assays. The role of animals in research on human diseases continues to be debated (e.g., Cattaneo et al., 2015; Doke and Dhawale, 2015; Fiester, 2008; Gupta, 2014; Helms et al., 2015; Lynch et al., 2010). Regarding this debate, a major premise for arguments against animal research is the claim that no animal model recapitulates the entire disease state of humans, especially as it relates to psychiatric disorders (e.g., Hayes and Delgado, 2006; but see Humby and Wilkinson, 2006 for a discussion on examining endophenotypes/intermediate phenotypes as a compromise). The polygenic nature of mental health disorders (e.g., Nurnberger and Berrettini, 2012) indicates that often times psychiatric genetics and epidemiology must use endophenotypes to parse the genetics associated with symptomology of these disorders (Chen et al., 2012; MacKillop and Munafo, 2013). Thus, the term intermediate phenotype, instead of endophenotype, is often used to convey that an observed genetic, behavioral or physiological characteristic bridges the gap between the disease process and diagnostic criteria. An example is prepulse inhibition (PPI) of the acoustic startle response (ASR) and schizophrenia. Rudimentary screening for the disorder doesn't include testing for altered PPI, yet preclinical PPI assays have strong predictive validity for detecting the efficacy of antipsychotics. These endophenotypes and biomarkers can be identified by findings from next generation RNA and/or DNA sequencing (Barrera and Sebat, 2016; Gupta and Gupta, 2014), pharmacogenomics (Perlis, 2016), gene networks (Parikshak and Geschwind, 2016), and genetic epidemiology (Merikangas and Meirkangas, 2016). Two examples are the mu-opioid receptor (MOR) variant, OPRM1, and the long and short variants of the serotonin transporter (SERT) (Berretini, 2013; Johnson, 2004, 2010; Johnson et al., 2003). More recent recent endophenotype identification has used advanced imaging techniques (Greicius, 2016; c.f., Self and Staley, 2010; Zahr and Peterson, 2016) or a combination of the above (e.g., Muller et al., 2010). Thus, with an increased focus on precision medicine and progress in identifying endophenotypes animal models, especially those used to determine treatment efficacy, need to incorporate biomarkers associated with AUDs and their development (e.g., Miczek, 2008; Millan, 2008; Winsky et al., 2008).

2.2. Validity, Reliability and Reproducibility

By displaying characteristics observed in the clinical setting, animal models are considered to have significant validity (e.g., Egli et al., 2016; Heilig and Egli, 2006; Litten et al., 2012). In basic terms, validity refers to the ability of an experimental method or measurement to accurately and precisely portray the construct, being examined, under "real-world" conditions. The three primary constructs of validity pertaining to medications discovery or screening are internal, external, and predictive validity. A test or method is considered to have *internal validity* if the causal inferences that Factor A influences Factor B observed in the test or method are appropriate. This generally requires (1) Factor A preceding Factor B, (2) there is a significant association between Factor A and Factor B, and (3) the results obtained are not due to confounding factors. A number of confounding factors interfere with internal validity including

variable selection, repeated testing, instrumentation (i.e., test equipment), sample selection bias, statistical regression to the mean, attrition of subjects, etc. *External validity* is the generalizability of findings from a test or method across situations and/or across subjects/samples, which requires efforts to limit multiple types of selection bias. Thus, replication is the best confirmation of external validity with meta-analytic techniques serving a similar purpose. *Predictive validity*, as it relates to animal models for drug discovery and screening, refers to the ability of a method or test (i.e., animal model) to correctly identify medications that interfere with the development and/or expression of AUDs.

It is important to recognize that, when pursuing the identification of medications to treat mental health disorders, deficits in external or face validity do not necessarily negate predictive validity. For instance, the Porsolt forced swim test and PPI of ASR have high predictive validity for medications to treat depression and schizophrenia, yet have poor face validity for these disorders. Finally, *reliability* refers to consistency of findings across experiments, such that the relevance of a model is determined by *experimental reliability* and *extrapolation reliability* (e.g., Rohra and Qazi, 2008). The former refers, essentially, to test-retest reliability such that the model will yield similar results across multiple tests, while controlling for within-subject effects. The latter refers to the ability of an animal model to yield results similar to those found in the clinical population. However, experimental and extrapolation reliability are based implicitly on the presence of sound validity. Thus, if a model has high reliability but low validity then the model will have minimal relevance.

2.3. Animal Models

Animal models attempt to parallel the human condition and many of these models have provided important information about mediating factors for medical and psychiatric disorders (c.f., Adan and Kaye, 2011; Buccafusco, 2001; Conn, 2008; Griffin, 2002; Kalueff, 2006; Kobeissy, 2012; McArthur and Borsini, 2008a,b,c; McKinney, 1988, 2001; Pankevich et al., 2013; Siegel, 2005; Verma and Singh, 2014; Warnick and Kalueff, 2010), including dual-diagnosis (Edwards and Koob, 2012). Particularly germane to the present topic, animal models have led to important findings on neural substrates mediating addiction to multiple substances of abuse (c.f., Bell and Rahman, 2016; DeBiasi, 2015; Dwoskin, 2014; Ekhtiari and Paulus, 2016a, 2016b; Koob et al., 2014; McArthur and Borsini, 2008c; Olmstead, 2011) and ethanol in particular (Bell et al., 2005, 2006b, 2012, 2013, 2014, 2016; Knapp and Breese, 2012; Maldonado-Devincci et al., 2012; McBride and Li, 1998; McBride et al., 2014b). As indicated above, advanced neuroimaging techniques including resting state functional connectivity are being used to develop endophenotypes for medications development targeting AUDs (e.g., Brown et al., 2015; Cui et al., 2015; Ernst et al., 2015; Fedota and Stein, 2015; Gowin et al., 2015; Moeller et al., 2016; Muller-Oehring et al., 2015a, 2015b; Schuckit et al., 2016; Squeglia et al., 2014). In general, an animal model has the advantage of allowing the experimenter to control factors such as the animal's genetic background, environment, and drug exposure. In addition, an animal model allows for the examination of neurobehavioral, neurochemical and neurophysiological correlates associated with the behavioral, physiological and/or neurological state that is modeled. These correlates in turn facilitate the development of pharmacological and/or behavioral treatments for the disorder in question.

2.4. Criteria for an Animal Model of AUD

There have been reservations as to whether a valid animal model of AUD could be developed (Cicero, 1979; Dole, 1986). These concerns stemmed from the fact that, in general, animals lower on the evolutionary scale, including rodents, do not readily consume sufficient amounts of ethanol to achieve pharmacologically relevant blood alcohol concentrations (BACs). In order to get a rodent to consume sufficient amounts of ethanol, experimental manipulations are required. These experimental/environmental manipulations include fluid deprivation (Sandi et al., 1990), schedule-induced polydipsia (Ford, 2014; Meisch, 1975, 2001), scheduled availability (Holloway et al., 1984) including intermittent every-other-day access (Carnicella et al., 2014), sucrose-fading (Samson, 1986), and/or forced induction of dependence (Deutsch & Eisner, 1977); which can be achieved intragastrically (Crews, 2008; French, 2001), intraperitoneally (Pascual et al., 2009, 2014), by ethanol-vapor exposure (Roberts et al., 2000; Vendruscolo and Roberts, 2014), chronic drinking of a liquid ethanol diet (Brown et al., 2004; Lieber and DeCarli, 1989), or long-term drinking with water and food concurrently available (Vengeliene et al., 2009). Most of these methods include an integral stress factor, which does have some face validity with the clinical condition (Al'Absi, 2007).

Despite the above reservations, certain criteria for an animal model of AUD have been put forth (Cicero, 1979; Dole, 1986; Lester & Freed, 1973). Briefly, these criteria include 1) the animal should orally self-administer ethanol, 2) the amount of ethanol consumed should result in pharmacologically relevant BACs, 3) ethanol should be consumed for its post-ingestive pharmacological effects, and not strictly for its caloric value or taste, 4) ethanol should be positively reinforcing, such that animals will work for access to ethanol, 5) chronic ethanol consumption should lead to the expression of metabolic and/or functional tolerance, and 6) chronic consumption of ethanol leads to dependence, as indicated by withdrawal symptoms after access to ethanol is terminated. Other criteria have been posited as well. A 7th proposed criterion is the animals should express relapse-like behavior, which manifests as a loss-of-control (McBride & Li, 1998; Rodd et al., 2004b). Additional criteria might be the ability to display binge-like drinking, as well as the expression of excessive ethanol consumption during the juvenile, adolescent and emerging adult stages of development (e.g., Bell et al., 2013; 2014). Finally, with a substantial minority of alcoholics engaging in polysubstance use and abuse, perhaps it is time to include this behavior in criteria for an animal model of AUD (e.g., Bell et al., 2016) as well.

2.5. Adolescence and Emerging Adulthood in the Rat Model

Ethanol use and abuse during adolescence is relatively common around the world (World Health Organization, 2011). Undoubtedly, some of the reasons may be associated with "rites of passage" such as graduating high school, entering college, joining the military etc. All of these institutions (high school, college, military) often give tacit support for the use and abuse of ethanol. There also is substantial evidence that adolescent mammals have decreased sensitivity to ethanol's perceived negative (e.g., ataxia) effects and increased sensitivity to its perceived positive effects (e.g., behavioral and autonomic activation) (Spear, 2010, 2013, 2014). Therefore, it is not surprising that adolescent rodents often consume significantly more ethanol than their adult counterparts (Bell et al., 2006c, 2011, 2013, 2014; Dhaher et al., 2012a; Spear, 2014). Research over the years has led to hypothesized parallel ages between humans and rats. These putative time periods (Table 1 adapted from Bell et al., 2013, 2014) have been based on neurobiological, sexual, foraging, and social characteristics that have been

evolutionarily conserved across species (e.g., Spear, 2000, 2010). Table 1 includes relative rat body weights which are the averages of Sprague-Dawley, Wistar, and Long-Evans Hooded rats at their respective ages. Body weights are included because many studies do not list the age of the subjects but do provide body weights. There is still substantial discussion on what constitutes an adolescent or adult rat. For example, Spear (2015) has noted significant differences in the long-term effects of ethanol following early- vs late-adolescent exposure. This parsing of the adolescent window results in some overlap with the juvenile and emerging adulthood stages of development, at least as depicted in Table 1. Despite this ongoing debate, it is clear that rat models of adolescent substance use and abuse have revealed important information on the behavioral, neurobiological, and genetic consequences of ethanol and/or drug exposure (Adriani and Laviola, 2004; Andersen, 2003; Bell et al., 2013, 2014, 2016; Chambers et al., 2003; Smith, 2003; Spear, 2000, 2010, 2014, 2015; Spear and Varlinskaya, 2006; Witt, 1994, 2010).

Table 1. Approximate parallel ages between the human and rat equivalent

Human Ages (Years)							
-3 to 0 Months	0 to 6	6	7 to 12	13 to 18	18 to 21	21 to 24	25 to 28
Neonate	Prejuvenile	Weaning	Juvenile	Adolescent	Emerging Adulthood	Early Young Adult	Young Adult
Rat Ages [Post-Natal Days (PNDs)]							
1 to 7	8 to 21	21	22 to 27	28 to 42	43 to 60	61 to 75	76 to 90
Rat Body Weights (g)							
Male: 6 to 15	16 to 40	40	40 to 70	70-155	155-260	260-335	335-390
Female: 6 to 15	16 to 38	38	38 to 65	65-130	130-180	180-210	210-250

2.6. Binge-Drinking in Rat Models

The primary binge-like drinking criteria that can be modeled in the rat are the requirements of (a) BACs greater than 80 mg% and (b) clear signs of intoxication, usually in the form of locomotor impairment. Our laboratory has used three primary behavioral models of binge-like drinking. These are (a) the alcohol deprivation effect (ADE), (b) episodic access, and (c) drinking-in-the-dark—multiple-scheduled-access (DID-MSA) procedures. The ADE results in both of these parameters being met. The ADE is basically the phenomenon that, after chronic access to ethanol usually 24h/day, when ethanol access is terminated and the subjects are re-exposed to ethanol access they tend to increase their ethanol intake relative to levels observed before the deprivation interval. However, because the ADE requires extended periods of deprivation before the animal is re-exposed to ethanol access, it probably models relapse-like behavior (Martin-Fardon and Weiss, 2013; Rodd et al., 2004b; Spanagel and Holter, 1999) to a greater extent than binge-like drinking. The episodic access procedure is similar to the ADE but incorporates shorter periods of ethanol access and forced abstinence. With the episodic access procedure, rats are given free-choice access to ethanol for an initial 8 days followed by cycles of 4 days of deprivation from and 4 days of re-exposure to ethanol access. Our laboratory has examined the effects of episodic access and found that whereas both high alcohol-drinking 1 and 2, HAD1 and HAD2 replicate lines, rats displayed an escalation of intake (an ADE), alcohol-preferring (P) rats did not (Bell et al., 2008).

Moreover, this did not appear to be a sex-dependent effect. This episodic protocol has been modified to examine changes in glutamatergic-associated protein levels in the extended Amyg and Acb of adult P rats (Obara et al., 2009). Overall, these authors reported that expression levels of N-methyl-D-aspartate receptor (GRIN) subunits and Homer proteins were differentially affected by episodic vs continuous access and whether tissue was harvested after a 24h vs 4-week deprivation period.

The most recent model of binge-like drinking used by our laboratory is the DID-MSA procedure (e.g., Bell et al., 2006b, 2006c, 2009, 2011; McBride et al., 2010). This procedure parallels the DID procedure used in mice (e.g., Boehm et al., 2008; Crabbe et al., 2009; Lyons et al., 2008; Moore and Boehm, 2009; Navarro et al., 2009; Rhodes et al., 2005). However, initial access to ethanol during the dark-cycle must occur immediately upon lights out to maximize intake in rats, whereas initial access for mice must occur after three or fours into the dark cycle (Bell et al., 2006c, Rhodes et al., 2005; but see Colombo et al., 2014). As with all of the drinking protocols used by our laboratory, water and food are freely available ad libitum. The rats experience between two and four 1h access periods across the 12h dark cycle with each access period separated by two or more hours. The rats experience a two day deprivation period each weekend. Selectively bred rats experiencing the DID-MSA procedure readily display BACs in excess of 80 mg%, usually in excess of 100 mg%, with clear signs of motor impairment (e.g., Bell et al., 2011). When this procedure was adapted for use in operant chambers, P rats displayed BACs in excess of 250 mg% (McBride et al., 2010). Finally, it should be noted that limited access scheduling during the rats' active-period (i.e., dark-cycle) has been a procedure used for many years and itself often results in BACs in excess of 80 mg% (See Bell et al., 2014 for a discussion of scheduled ethanol access procedures across 20+ rat lines/strains).

3. Selective Breeding

Bi-directional selective breeding is a powerful genetic tool that has been employed to study the genetics of many ethanol-associated phenotypes (Crabbe, 2008). Compared to pure association studies such as genome-wide association studies (GWAS) and studies using recombinant inbred lines (RILs) panels, selective breeding from a heterogeneous outbred stock can make low frequency/rare alleles more common. Selective breeding involves establishing a distribution of scores for the phenotype of interest. Then, subjects are selected from the extremes of this distribution. Subjects from the same extreme are mated together and this cycle of selection and breeding occurs over multiple generations. This results in the high and low off-spring displaying phenotypic extremes that far exceed the range found in the original foundation stock. Heuristically, as relevant genes are segregated correlated traits of the primary selected phenotype (presumably due to pleiotropic actions of genes: Crabbe et al., 1990) can be identified and studied.

3.1. Selectively Bred High Ethanol-Consuming Rat Lines

There are primarily seven bi-directionally selected bred high ethanol-consuming rat lines used globally. The alcohol-preferring AA and alcohol-avoiding [ALKO Non-Alcohol-Accepting (ANA)] rats were developed from a Wistar-Sprague-Dawley cross foundation stock in Helsinki, Finland (Eriksson, 1968). The lines were revitalized with Brown-Norway and Lewis rat lines in the late 1980's (Sommer et al.,

2006). The high alcohol-drinking HAD and low alcohol-drinking LAD lines of rats were developed from N/NIH heterogeneous stock rats at Indiana University School of Medicine in Indianapolis, Indiana, USA (Li et al., 1993). The N/NIH line of rats was derived from an eight inbred strain cross (ACI, BN, BUF, F344, M520, MR, WKY and WN), with each strain displaying different phenotypes including ethanol intake, at the National Institutes of Health (Hansen and Spuhler, 1984). Two separate colonies were used to breed HAD and LAD lines of rats, such that replicate (HAD1 vs. LAD1 and HAD2 vs. LAD2) lines are available. The alcohol-preferring, P, and alcohol-nonpreferring, NP, rat lines were developed from closed-colony Wistar foundation stock at the Walter Reed Army Hospital and transferred to the Indiana University School of Medicine in Indianapolis, Indiana, USA (Lumeng et al., 1977). The Sardinian alcohol-preferring, sP, and alcohol-nonpreferring, sNP, rats were developed from a Wistar foundation stock at the University of Cagliari, Italy (Colombo et al., 2006). The alcohol-preferring UChB and alcohol-nonpreferring [University of Chile A (UChA)] lines of rats were developed from a Wistar foundation stock at the University of Chile, Santiago, Chile (Mardones and Segovia-Riquelme, 1983). The Marchigian sP (msP) line does not have a non-preferring counterpart, although an outbred Wistar is often used as a control, and was derived from the sP line from the University of Cagliari, Italy (Ciccocioppo et al., 2006). All of the above lines were selected for 24h ethanol intake. A selective breeding program for limited access ethanol intake has also been undertaken yielding the High vs Low Addiction Research Foundation (HARF vs LARF) rat lines (e.g., Le et al., 2001).

The 24h selective breeding programs had two primary selection criteria. First, the high ethanol-consuming rat lines needed to drink at least 5 grams (g) of ethanol/kilogram (kg) bodyweight/day. Five g/kg/day, in a clinical sense, is equivalent to a 165 pound man consuming approximately a fifth of 90-proof whiskey per day. The second criterion is that the animals had to prefer 10% ethanol over water by at least a 2:1 ratio. As seen in Table 2, all seven high ethanol-consuming rat lines meet the selection criteria and achieve intoxicating BAC levels after free-choice ethanol drinking. Six of the rat lines display an ADE indicating relapse behavior. Six of the rat lines will operantly self-administer ethanol indicating these rat lines find ethanol reinforcing. In addition, six of the lines display behavioral and/or physiological measures (i.e., generally activation or approach behavior) of ethanol reward. Five of the rat lines display tolerance to ethanol-associated effects. In addition, the high drinking lines generally develop quicker, or greater, tolerance to ethanol-associated effects than their low drinking counterparts. Only a few of the rat lines have demonstrated excessive ethanol-intake during adolescence, nicotine and/or cocaine self-administration. Importantly, all seven of the rat lines have published gene differences relative to their low drinking counterparts, or Wistar controls in the case of msP rats.

3.2. Other Bi-directionally Selectively Bred Rat Lines

Other rat lines have undergone selective breeding for endophenotypes associated with AUDs, but were not selected for the high ethanol preference or intake phenotypes. The High Alcohol vs Low Sensitivity (HAS vs LAS) rat lines were selected for ethanol-induced sedation and show alterations in ethanol-induced conditioned taste aversion and nicotine-induced locomotor activity (e.g., de Fiebre et al., 2002; Kuljosky et al., 1995). The Alcohol Tolerant (AT) and Alcohol Non-Tolerant (ANT) rats were selected for sensitivity to ethanol-induced motor impairment and the development of tolerance to this effect, with

non-tolerance being mediated by a mutation of the GABRA-alpha 6 subunit (Wong et al., 1996). The High Saccharin Consumption (HiS) and Low Saccharin Consumption (LoS) Rats were selected for different propensities to consume a sweet, saccharin solution with the former consuming significantly more ethanol than the latter (c.f., Carroll et al., 2008). The Taste Aversion Prone (TAP) and Taste Aversion Resistant (TAR) rats were bidirectionally selected for cyclophosphamide conditioned taste aversion (CTA) to a saccharin solution, with the latter showing lower ethanol-induced CTA and greater ethanol intake than the former (e.g., Elkins et al., 1992; Orr et al., 2004). The Swim Test Susceptible (SUS) and Swim Test Resistant (RES) rats were bidirectionally selected for decreased swimming (SUS) activity when the test was preceded by a stressor, with the latter showing greater ethanol intake than the former (e.g., Weiss et al., 2008).

----------Insert Table 2 About Here----------

4. Behavioral Models for Screening Treatment Compounds and/or Targets

4.1. The Home-Cage and Operant Environments

Home-cage drinking is relatively self-explanatory, such that the rat has access to ethanol in its home-cage environment. There are pros and cons to this test environment and there continues to be a debate as to its face validity with the clinical condition. However, home-cage drinking is positively associated with both the reinforcing and rewarding aspects of ethanol (e.g., Green and Grahame, 2008). On the other hand, operant self-administration requires removing the rat from its home-cage and transporting them to an operant test chamber, which has its own inherent cues, usually in an adjacent room. It is the role of these cues that make operant testing so attractive for compound testing. However, operant testing is resource-intense with greater costs in time, materials, and technicians compared with home-cage testing. Many reviews have been written on operant procedures (June and Gilpin, 2010; Lopez and Becker, 2014; Ostroumov et al., 2015; O'Tousa and Grahame, 2014; Rodd et al., 2004; Samson and Czachowski, 2003; Vendruscolo and Roberts, 2014; Weiss, 2011), so only the basics will be covered here. The removal of the animal from their home-cage environment, transport to a test room, and placing the animal in the operant chamber results in many opportunities for the animal to form associations between environmental stimuli and learning the reinforcement value of ethanol. Reinforcement refers to the ability of a stimulus to increase the probability of a response occurring in the future, when the stimulus and response have been successfully associated with each other. Positive reinforcement refers to an increased probability of a response, in the presence of a stimulus, in order to receive a "positive" stimulus or reinforcer. Note: that reinforcer is more appropriate than reward because reward is not, in general, dependent upon a trained or conditioned response. Negative reinforcement refers to an increased probability of a response, in the presence of a stimulus, in order to avoid a negative/noxious stimulus. Operant self-administration is conducted in operant chambers, sometimes called Skinner boxes, where a subject is placed in the chamber and allowed to bar press on a lever in order to receive ethanol (the reinforcer). Cues such as lights or sounds, in the chamber, are programmed to alert the animal to different phases of an experiment, such as an anticipation phase before the bar press levers are extend into the chamber.

In general, there are two types of schedules-of-reinforcement: ratio which controls the number of responses (usually bar presses) required for reinforcement and interval which controls the period of time at which point the reinforcement is presented following the required response. Fixed-ratio (FR) reinforcement refers to a subject receiving reinforcement after a set number of bar presses. Variable-ratio (VR) reinforcement refers to a subject receiving reinforcement after a random number of responses, with the distribution of these numbers of responses covering a range centered on an average number (i.e., in general this average would be associated with the FR requirement). For instance, an FR-1 schedule would be used to initiate training where the subject receives reinforcement after each bar press. This is also called continuous reinforcement. Similalrly, an FR-3 schedule would result in the subject receiving reinforcement after each set of 3 bar presses. Finally, most experimenters include a time-out period following each reinforcement where responses are not counted towards the next reinforcement until the time-out period is over. The time-out is used to control for purely stereotypical behavior (e.g., self-administration of amphetamine which results in stereotypic motor responses that are not explicitly tied to the drug's reinforcement value). Similar to ethanol drinking in the home cage, outbred rats, those not selectively bred for high drinking, require different types of training or shaping regimens in order for the animal to acquire self-administration behavior. This is primarily for the oral route of administration. However, in selectively bred high ethanol-consuming rats this training is minimal or not needed at all indicating these lines find ethanol reinforcing and rewarding (see Table 2).

4.2. Modeling the Stages of the Addiction Cycle

In general, an ethanol dependent individual develops addiction to ethanol through multiple stages, progressing from impulsive drinking to compulsive drinking (Feltenstein and See, 2013; Koob, 2013; Koob et al., 2014; Little et al., 2008; Noronha et al., 2014; Olmstead, 2011; Pierce and Kenny, 2013; Scofield et al., 2016; Vanderschuren and Ahmed, 2013). These stages include acquisition (Carroll and Meisch, 2011), escalation (Ahmed, 2011), binge-like behavior (Covington and Miczek, 2011; Stephens et al., 2013), habit formation and compulsion (Belin et al., 2011; Everitt et al., 2010), withdrawal (Barr et al., 2011; Koob, 2008; Koob and LeMoal, 2010), relapse (Erb and Placenza, 2011; Martin-Fardon and Weiss, 2013; Meyerhoff et al., 2013; Stewart, 2010), craving (Grimm, 2011), as well as ethanol seeking and a pre-occupation with future use (Lasseter et al., 2010).

4.3. Acquisition of Alcohol Use Disorders

Delaying the onset of ethanol abuse during adolescence and/or emerging adulthood may reduce the risk of developing AUDs later in life. Thefore, treating an individual while they are still engaging in impulsive drinking and before compulsive drinking has been established may prevent the development of ethanol dependence. The closest selectively bred animal model of this would be testing the efficacy of a compound to disrupt acquisition of ethanol intake. This is done by administering the compound concurrently with initial ethanol access, or by pretreating the animal before initial ethanol access. Therefore, disrupting the acquisition of ethanol abuse in today's youth is an important consideration. This would be prophylactic in nature similar to fortifying flour with thiamine to prevent deficiencies and subsequent brain damage and probably restricted to "captive" samples such as those in chemical dependency treatment. Pharmacological studies evaluating the acquisition of ethanol intake have been

conducted under both home-cage drinking and operant self-administration conditions. As seen in Table 3, roles for the adrenergic (Froehlich et al., 2013), cannabinoid (Gessa et al., 2005; Serra et al., 2001), GABAergic (GABRB: Colombo et al., 2002a; Orru et al., 2005), opioid (Dhaher et al., 2012b; Sable et al., 2006), and serotonergic (Rodd et al., 2010; Rodd-Henricks et al., 2000a) systems have been implicated in the acquisition of ethanol intake. Of the selectively bred rat lines discussed here, only the P and sP rat lines have been used to examine acquisition of ethanol intake. However, only naltrexone has been tested in both P and sP rats. Unfortunately, all of these treatments had a modest effect on ethanol intake and intake levels increased to control levels after cessation of treatment.

----------Insert Table 3 About Here----------

4.4. Binge-Like Drinking

The number of reports documenting pharmacological disruption of binge-like drinking is limited. As discussed above, binge-like drinking is associated with repeated sessions of intoxicated drinking per day (e.g., Bell et al., 2011). Given this, repeated testing sessions per day precludes controlling for carryover effects. However, most published binge-drinking studies tested the compound either acutely (i.e., once or twice) or chronically on a once-a-day basis. Examples of neurotransmitter systems mediating binge-like intake include the cholinergic (Katner et al., 1997), dopaminergic (Ingman et al., 2006), GABAergic (GABRA: Liu et al., 2011), noradrenergic (Warnock et al., 2012), and serotonergic (Ingman et al., 2006) systems (Table 4). Of the selectively bred rat lines discussed here, only the AA and P rat lines have been used to examine binge-like drinking, with no compounds being tested in both lines. Unfortunately, since BACs in general were not reported it is difficult to determine if the ethanol intake levels truly met the definition for binge drinking (i.e., > 80 mg%).

----------Insert Table 4 About Here----------

4.5. Maintenance of Ethanol Drinking

Pharmacological studies examining the maintenance of ethanol drinking have been the test of choice in the ethanol research field. Usually, the assumption is that the maintenance of ethanol intake reflects habitual or compulsive use. In fact, habitual or compulsive use models have been posited as preclinical models for medications testing (Carnicella et al., 2014; O'Tousa and Grahame, 2014). Similar to acquisition, studies on maintenance have been performed under both home-cage drinking and operant self-administration conditions. Free-choice access refers to tests during which the animal can choose between ethanol, usually water and food. Sometimes, multiple choices of ethanol solutions are given, which tends to increase the overall volume of intake (Bell et al., 2003, 2004; Rodd-Henricks et al., 2001). The home-cage environment is more amenable to this than the operant chamber. For instance, food is very rarely available in the operant chamber although this could be a control over prandial-associated intake. When assessing the maintenance of ethanol drinking the investigator administers the compound during ongoing drinking. Usually this is done under limited access conditions. The compound is administered and then after a set period of time, usually associated with absorption and the compound's transit of the blood-brain-barrier (BBB), the subject is given access to ethanol for a discrete period-of-time. Limited access is used to assess the acute effects of the compound, especially if tested

across days. Although when conducting a study under 24h access conditions, ethanol intake can be recorded post-treatment at different time-points during the day. This allows the experimenter to measure both the acute (e.g., first 1h or 4h post-administration) and more chronic effects of the compound. A benefit of 24h access tests is the ability to detect the effects of a compound relative to its temporal bioavailability (e.g., absorption, transit across the BBB, and metabolism).

An interpretative difficulty of 24h access testing is the inability to disentangle the interactional post-acute compound effects from continuous ethanol intake effects, although limited access tests also have this problem but to a lesser degree. Major concurrent measures would include body weight as well as food and water intake to detect secondary effects. Examples of neurotransmitters modulating the maintenance of ethanol intake include the adrenergic (alpha: Froehlich et al., 2013a), cannabinoid (Dyr et al., 2008; Gessa et al., 2005; Hansson et al., 2007), cholinergic (Bell et al., 2009; Sotomayor-Zarate et al., 2013), dopaminergic (Dyr et al., 1993; Thanos et al., 2005), GABAergic (GABRA: Agabio et al., 1998; GABRA-BDZ complex: June et al., 1998b; McKay et al., 2004; GABRB: Maccioni et al., 2012; Quintanilla et al., 2008), glutamatergic (Bilbeny et al., 2005; Cowen et al., 2005b; Sari et al., 2013a), histaminergic (Lintunen et al., 2001), opioid (pan-opioid: Hyytia and Sinclair, 1993; June et al., 1998d; MOR: Honkanen et a., 1996; Krishnan-Sarin et al., 1998; DOR: Hyytia and Kiianmaa, 2001; sigma: Sabino et al., 2009a), and serotonergic (Long et al., 1996; Overstreet et al., 1997; Panocka et al., 1995b; West et al., 2011) systems (Table 5). Overall, the neurotransmitter systems most often tested across the lines have been the (a) cannabinoid system in six of the selectively bred rat lines, (b) GABAergic system in five of the selectively bred lines as well as Sprague-Dawley and Long-Evans Hooded outbred lines, and (c) opioid system in six of the selectively bred rat lines as well as Sprague-Dawley and Wistar outbred lines. Across the rat lines, the CB1R antagonist, SR-141716, has been tested in six of the selectively bred rat lines as well as Wistar rats with consistent reductions in ethanol intake. Across rat lines, naloxone/naltrexone has been tested in, and consistently reduced ethanol intake by, five of the selectively bred rat lines as well as Sprague-Dawley and Wistar rats.

----------Insert Table 5 About Here----------

4.6. Relapse Behavior

Ethanol abuse and dependence are considered chronic relapsing disorders, such that 60-80 percent of abstinent alcoholics will relapse during their lifetime (Barrick and Connors, 2002; Chiauzzi, 1991; Jaffe, 2002; Weiss et al., 2001). Thus, an animal model of AUD ought to demonstrate this feature of the clinical picture as well (McBride and Li, 1998). Although a number of criteria for relapse have been put forth (Barrick and Connors, 2002; Chiauzzi, 1991; Jaffe, 2002; Weiss et al., 2001), the primary criterion holds that a return to levels of ethanol consumption equal to or greater than that observed prior to abstinence constitutes a relapse. A common model of AUD relapse is the alcohol deprivation effect (ADE). The ADE is a temporary increase in ethanol intake and/or preference over water upon re-exposure to ethanol access compared with levels observed prior to ethanol withdrawal (Brown et al., 1998; Burish et al., 1981; Heyser et al., 1997, 2003; Kornet et al., 1990; McKinzie et al., 1998; Mello and Mendelson, 1972; Rodd et al., 2003a, Rodd-Henricks et al., 2000a, 2001; Sinclair, 1971; Sinclair and Li, 1989; Sinclair and Senter, 1967; Sinclair et al., 1973; Wolfgramm and Heyne, 1995).

Thus, by definition the ADE usually reflects an escalation of intake. Moreover, the ADE is not simply an effect of withdrawal, because it can be observed before an animal becomes phycically dependent upon ethanol (Bell et al., 2008; McKinzie et al., 1998; Sinclair and Senter, 1967; Rodd-Henricks et al., 2000a, 2001) or after overt withdrawal signs have passed (Rodd-Henricks et al., 2002a; Rodd et al., 2003). While most studies have relied upon a single period of abstinence, this does not parallel the clinical condition because most individuals seeking treatment have experienced multiple cycles of abstinence and relapse. Finally, as seen in Table 2, different selectively bred rat lines display different ADE profiles (e.g., time-dependent) under particular conditions. Given the multiple genes, each contributing a relatively small effect-size, mediating the genetic risk for developing AUD; it is not surprising that there are different drinking, including relapse, profiles among the selected lines (Table 2). Examples of neurotransmitters and neuromodulators modulating relapse to ethanol intake include the adrenergic (alpha: Froehlich et al., 2013a), cannabinoid (Dyr et al., 2008; Gessa et al., 2005; Hansson et al., 2007), cholinergic (Bell et al., 2009; Sotomayor-Zarate et al., 2013), dopaminergic (Dyr et al., 1993; Thanos et al., 2005), GABAergic (GABRA: Agabio et al., 1998; GABRA-BDZ complex: June et al., 1998b; McKay et al., 2004; GABRB: Maccioni et al., 2012; Quintanilla et al., 2008), glutamatergic (Bilbeny et al., 2005; Cowen et al., 2005b; Sari et al., 2013a), histaminergic (Lintunen et al., 2001), opioid (pan-opioid: Hyytia and Sinclair, 1993; June et al., 1998d; MOR: Honkanen et a., 1996; Krishnan-Sarin et al., 1998; DOR: Hyytia and Kiianmaa, 2001; Sigma: Sabino et al., 2009a), and serotonergic (Long et al., 1996; Overstreet et al., 1997; Panocka et al., 1995b; West et al., 2011) systems (Table 6). Unfortunately, only the P, HAD1, HAD2, and sP rat lines have been consistently used to assess compound efficacy in disrupting relapse-like behavior. Moreover, no single compound has been tested across three or more selectively bred rat lines. Thus, more research is needed to address the validity of findings across selectively bred rat lines and/or mouse lines.

----------Insert Table 6 About Here----------

4.7. Ethanol-Seeking (Craving) Behavior

For the present discussion, craving and ethanol-seeking will be considered similar constructs on a behavioral continuum from a more visceral response to an overt behavioral response, respectively. To test for ethanol-seeking behavior, an animal is trained to operantly self-administer ethanol, this operant response is then extinguished, such that the animal no longer responds on the lever previously associated with ethanol reinforcement, with changes in response rate across time reflecting seeking behavior. This can also be determined by comparing response numbers between the lever previously associated with ethanol and the control lever (i.e., is the animal able to distinguish between the two). Or, another method would be to compare the response rate with a baseline rate recorded prior to extinction. It has been suggested that the rate of extinction can be a measure of ethanol-seeking, because the animal continues to manifest an overt behavior directed toward the lever previously associated with ethanol reinforcement in the absence of reinforcement (Koob, 2000; Littleton, 2000). In a clinical sense, this would be similar to an individual displaying approach behavior (i.e., going to the liquor store) and being frustrated by the fact that the liquor store is closed.

Responses on the operant lever, previously associated with ethanol reinforcement, in the absence of reinforcement can be elicited several ways. Here we will examine (a) *drug-induced "priming"* of the response, (b) *cue-induced "priming"* of the response, and (c) *"Pavlovian Spontaneous Recovery" (PSR)* of the response. Essentially, PSR stems from the work of Pavlov who showed that simply returning the animal to the environment previously associated with reinforcement "recovered" the response, even if the response was absent (i.e., extinguished) at the end of the previous session (c.f., Rodd et al., 2004). All of these methods have been reviewed by others as noted in sections 4.1 and 4.2 and the present discussion will only present an overview. The word priming is used because these three methods essentially prepare/prime the animal to make the response. These three forms of reinstatement of responding can be arranged on a continuum from the most overt (drug-induced priming) to the least overt (PSR), in the sense that all three use cues to elicit the response. Drug-induced priming automatically incorporates environmental cues associated with (a) drug self-administration as well as (b) drug-induced physiological responses. The drug-induced priming dose is usually too small to induce behavioral activation. Nevertheless, most drugs-of-abuse, including ethanol, do sensitize behavioral activation (i.e., shift the dose-response curve to the left) and; therefore, this remains a critique of this model/procedure.

Cue-induced priming of the response uses discrete cues from the environment that were previously associated with ethanol self-administration (Koob, 2000). Therefore, the environmental cues recruited in drug-induced priming are also present in cue-induced priming but overt physiological responses to the drug are absent. The role of environmental cues in drug- vs cue-induced priming can, to some degree, be dissociated by administering the drug priming in a different environment. However, absolute dissociation is impossible. Finally, PSR of responding incorporates the environmental cues used in cue-induced priming. One method to dissociate the more subtle cues in the environment from the more overt, discrete cues used in cue-induced priming is to employ positive (+), negative (-) and neutral cues in the methodology. (+)-cues are stimuli previously associated with ethanol/drug availability, (-)-cues are stimuli previously associated with ethanol/drug "non"-availability, and neutral cues are environmental cues present in both circumstances (e.g., Knight et al., 2016). As seen in Table 7, roles for the adrenergic (alpha: Bertholomey et al., 2013), cannabinoid (Cippitelli et al., 2005), cholinergic (Hauser et al., 2014a; Le et al., 2003), dopaminergic (Hauser et al., 2014b; Vengeliee etal., 2006), GABAergic (GABRB: Maccioni et al., 2008b), glutamatergic (Backstrom and Hyytia, 2004; Rodd et al., 2006; von der Glotz et al., 2009), neuropeptide Y (Bertholomey et al., 2011), nociceptin-orphanin (Ciccocioppo et al., 2004), opioid (pan-opioid: Le et al., 1999; MOR: Giuliano et al., 2015; DOR: Henderson-Redmond and Czachowski, 2014; KOR: Deehan et al., 2012), and serotonergic (Hauser et al., 2014a) systems have been implicated in ethanol-seeking and -craving behavior. Also as seen in Table 7, outbred rat lines are used more consistently than selectively bred rat lines when investigating the efficacy of compounds to disrupt ethanol-craving and –seeking behavior.

----------Insert Table 7 About Here----------

4.8. Dependence and Withdrawal-Associated Effects

The research on dependence and withdrawal in rats has been limited, at least as it pertains to medications screening for the treatment of AUD. Early work examined the GABAergic system, due to the fact that agonists of this system were, and still are, used to treat the danger of ethanol-withdrawal associated seizures. Subsequent work examined the role of the glutamatergic system and its hyperexcitability in the dependent state. This paralleled work examining neurosteroids and their modulation of the GABAergic system. Peptide systems such as cotricotrophin releasing factor (CRF) and neuropeptide Y (NPY) have also received attention because of their recognized role in anxiety and their activity in the extended amygdala. More recent research has recognized that stress-associated systems play a key role in the development and maintenance of AUD and addiction in which withdrawal plays an important part (See Griffin, 2014). Therefore, stress-associated seeking and/or craving behavior has received research interest but mostly in non-selectively bred (i.e., outbred) rat lines. Table 8 describes some of the neurotransmitters and neuromodulators mediating stress-associated findings from selectively bred and outbred rats. These include the adrenergic (Rasmussen et al., 2014), corticotrophin (Overstreet et al., 2007), dopaminergic (Overstreet et al., 2007), GABAergic (GABRA-BDZ: Knapp et al., 2007a, 2007b), neuroimmune (Breese et al., 2008), neuropeptide Y (Cippitelli et al., 2011), and serotonergic (Overstreet et al., 2007) systems.

----------Insert Table 8 About Here----------

4.9. Summary

The research presented in Tables 3 through 8 highlights compounds and rat lines used to assess disruption of different stages in the addiction cycle. The tables were tabulated to provide a historical perspective on the evolution of (a) neurotransmitter/ neuromodulatory targets examined as well as (b) stages in the addiction cycle being investigated. Although this paper has focused primarily on selectively bred rat lines, it has included some of the findings garnered from research using outbred rat lines. This provides some context into which the results from selectively bred rat research can be placed. This also highlights some areas of medications screening that have been dominated by the use of outbred rat lines. A very clear example of this is the dependence/ withdrawal/ stress areas of research. This is due, at least in part, to the fact that the active selection process has resulted in high ethanol-consuming rats that can consume ethanol with limited adverse effects. From the data presented herein and a previous paper (Bell et al., 2012), it is clear that not all neurotransmitter/ neuromodulatory systems have received the same level of scrutiny in all of the rat lines. For instance, the vast majority of the research examining the alcohol dehydrogenase and aldehyde dehydrogenase systems has been performed in the UChB and UChA rat lines. Similarly, histaminergic research has been limited to the AA and ANA rat lines. Another example is the cannabinoid system, such that most of the research in these selected rat lines has been conducted in the sP and sNP rat lines, with the AA and ANA rat lines also receiving substantial focus.

This uneven focus, across the rat lines, on particular neurotransmitter systems creates difficulty with interpreting validity. Exacerbating this is the fact that the present publishing environment places low priority on negative findings and if a particular compound is found to be effective in one rat line it is rarely tested in the other rat lines. Reasoning for the latter is that studies following the first one are not

novel. In order to increase the validity of animal research targeting treatment of AUDs, the field needs to understand both the positive and negative findings for particular compound classes (e.g., neurotransmitter, neuromodulator, transcription factor, etc.) and/or compounds within a class. Finally, the present review makes it clear that the single neurotransmitter/ neuromodulatory-system research approach that characterized early work has progressed to a more thorough understanding of intracellular cascades that are involved in multiple neuromodulatory systems. In addition, it also is now recognized, with some of these findings presented in their respective Tables, that neurotransmitter/ neuromodulatory systems involved in one stage of the addiction cycle do not necessarily mediate another stage of the addiction cycle.

5. Caveats, Challenges, and Conclusions

A few caveats need to be mentioned before summarizing this review. First, the mouse ethanol research literature was not discussed. This was done due to space limitations and in no way minimizes the substantial literature that is associated with it. Second, transgenic ethanol research was not discussed. Similar to the first caveat, especially since most of the transgenic work has involved mice, this was done due to space limitations. For excellent discussions on both of these subjects see Barkley-Levenson and Crabbe (2014), Crabbe et al. (2006), Fisch and Flint (2006), Greenberg and Crabbe (2016), Kalueff and Bergner (2010), Mayfield et al. (2016), as well as Oberlin et al. (2011). Third, models of withdrawal, and to some degree dependence, as well as stress and its associated medications screening received limited review. To a great extent this is also related to the first caveat, in the sense that most of the ethanol withdrawal research has been conducted in mice. We noted some of the rat research, often using outbred rat lines, in section 4.8 and table 8; for other work and discussion see Al'Absi (2007), Becker (2013), Burke and Miczek (2014), Greenberg and Crabbe (2016), Lopez and Becker (2014), Metten et al. (2014), Phillips et al. (2015), Spanagel et al. (2014), Vendruscolo and Roberts (2014), as well as Zorrilla et al. (2014).

This review highlights the fact that most of the medications research conducted thus far has sought to delineate the role and importance of different neuromodulatory and neuroanatomical systems in the maintenance of ethanol intake. This is especially obvious from the early ethanol research focus on the role of the opioid, dopaminergic, and serotonergic systems in ethanol abuse and dependence. Of these systems, the most effective FDA-approved medication (naltrexone) targets the opioid system. As outlined elsewhere (e.g., Bell et al., 2012), the bi-directional selection for high vs low ethanol-consuming rat lines has resulted in dopaminergic and serotonergic deficits in many, but not all of the high ethanol-consuming rat lines. Therefore, it is not surprising that much of the earlier research focused on these neurotransmitter systems. However, much of this earlier, and later, work did not result in readily translatable treatment strategies. Recognition of the difficulty in translating preclinical findings into clinical treatments has been recognized by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH). To facilitate testing compound efficacy, NIAAA and NIDA have created programs, in partnership with the pharmaceutical industry, to screen compounds that have either received FDA-approval for other indications or have gone through significant clinical trials. Essentially, the objective is to assess the ability to "repurpose" drugs to treat AUDs that have already received considerable regulatory scrutiny.

The National Institute on Mental Health (NIMH) of NIH has also recognized this modest translatability of preclinical research to clinical practice and has developed, as well as incorporated, the Research Domain Criteria (RDoC) program into their preclinical funding strategies. RDoC incorporates examination of the psychobiological and neuroscientific causation into translational research models. Put another way, RDoC focuses on dimensional/ valence constructs observed across multiple mental disorders rather than strict diagnostic symptomology related to a single disorder (Cuthbert, 2016; Kozak and Cuthbert, 2016; MacNamara and Phan, 2016). This focus on systems, rather than clinical diagnostic symptoms, has seemingly pitted the RDoC project against the Diagnostic and Statistical Manual of Mental Disorders system (e.g., Pritchard, 2015), such that a binary (i.e., one-or-the-other) system approach is generally discouraged (Shorter, 2015). As noted by Kaffman and Krystal (2012) and from the work of Hyman and colleagues (Hyman, 2010; Casey et al., 2013), the DSM and ICD classification systems were developed to achieve the highest inter-rater reliability *based on diagnostic symptomology*. Therefore, animal models of psychiatric disorders have generally focused on recapitulating many if not all of the DSM- and ICD-defined symptoms as separate models. However, this focus on diagnostic symptomology has, to some degree, interfered with recognizing that there are *domains of symptomology* stretching across different diagnostic categories. NIMH, NIAAA, and NIDA have recognized this and have developed several joint funding programs that recognize that, for instance, ethanol, nicotine, and stimulant addiction are not unitary phenomenon with minimal overlap. Rather, ethanol dependence has to be examined within its neurobiological, physiological, developmental, behavioral, and social context (c.f., Kaffman and Krystal, 2012; Kobeissy, 2012; Nestler and Hyman, 2010).

With these considerations in mind, the present paper first presented a background from a clinical perspective in order to provide an overview of the constellation of factors influencing the development of ethanol dependence in humans. Section two provided some background on the rat and how the above clinical factors can be examined within the rat's developmental context. For instance, rats also go through developmental stages and physiological as well as behavioral milestones point to adolescence as a critical stage of development for rats just as it is for humans. Also, binge eating and drinking are observed in adolescent rats just as they are in humans. Moreover, rats display physiological characteristics of lower sensitivity to ethanol's aversive, but not necessarily deleterious, effects and higher sensitivity to ethanol's stimulating effects similar to observations in the clinical setting. Thus through experimental manipulations, it has been shown that binge ethanol intake by adolescent rats is not purely to satisfy increased caloric demand associated with the adolescent growth spurt. The third section highlighted behavioral characteristics of the seven dominant selectively bred high, vs low, ethanol-consuming rat lines in the world. As shown in Table 2, all of the lines display many of the characteristics observed in individuals caught in the ethanol addiction cycle.

The fourth section discussed common pharmacological test procedures as they relate to stages of the addiction cycle. Each of these stages is accompanied by a table highlighting associated findings from the seven, international selectively bred high ethanol-consuming rat lines as well as some findings from other selectively bred rat lines and outbred rats. Overall, the literature reviewed herein indicates that all of these high ethanol-consuming rat lines have face validity displaying many, but not necessarily all, of the characteristics observed in the ethanol-dependent individual. In addition, each of the lines has

tested various neurotransmitter and neuromodulator compounds in the procedures outlined in the fourth section. Nevertheless, these animal models need to be expanded into more holistic models. For instance, binge-drinking with an adolescent age-of-onset is a crucial factor in the development of AUDs that has received limited attention. In addition, most individuals addicted to ethanol are also addicted to other substances-of-abuse and discussions regarding animal models of polysubstance dependence are limited. Therefore, despite making progress in determining the neurobiological systems mediating ethanol dependence, further work using more holistic models needs to be undertaken in both the preclinical and clinical areas to determine molecular targets for pharmacological treatment of AUDs.

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Statement of Conflict

All authors declare they have no perceived or real conflicts of interest associated with any part of this work.

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Table 1. Approximate Parallel Ages Between the Human and Rat Equivalents							
Human Ages (Years)							
-3 to 0 Months	0 to 6	6	7 to 12	13 to 18	18 to 21	21 to 24	25 to 28
Neonate	Prejuvenile	Weaning	Juvenile	Adolescent	Emerging Adulthood	Early Young Adult	Young Adult
Rat Ages [Post-Natal Days (PNDs)]							
1 to 7	8 to 21	21	22 to 27	28 to 42	43 to 60	61 to 75	76 to 90
Rat Body Weights (g)							
Male: 6 to 15	16 to 40	40	40 to 70	70-155	155-260	260-335	335-390
Female: 6 to 15	16 to 38	38	38 to 65	65-130	130-180	180-210	210-250

Table 2. Criteria for an animal model of alcoholism that each of the high alcohol-consuming selected lines successfully meets.

		Rat Line					
	AA	HAD	P	sP	UChB	msP	WHP
1) Ethanol is orally self-administered under free-choice conditions (>5 g of ethanol/kg bodyweight/day)	Yes[1]	Yes[9]	Yes[16]	Yes[31]	Yes[39]	Yes[45]	Yes[54]
2) Pharmacologically relevant BACs are achieved with self-administration (50 to 200 mg%)	Yes[2]	Yes[10]	Yes[17]	Yes[32]	Yes[40]	Yes[46]	Yes[55]
3) Ethanol is consumed for its post-ingestive effects and not for taste or calories only (administered by non-oral routes of administration)	NK	NK	Yes[18]	NK	NK	Yes[47]	NK
4a) Ethanol is rewarding as indicated by behavioral and/or autonomic activation	Yes[3]	Yes[11]	Yes[19]	Yes[33]	NK	Yes[48]	NK
4b) Ethanol is rewarding as indicated by a conditioned place preference (CPP)	NK	NK	No[20]	NK	Yes[41]	Yes[49]	NK
5) Ethanol is positively reinforcing (the animal operantly works for access)	Yes[4]	Yes[12]	Yes[21]	Yes[34]	NK	Yes[50]	Yes[56]
6a) Chronic consumption leads to metabolic tolerance	Yes[5]	NK	Yes[22]	NK	NK	NK	Yes[57]
6b) Chronic consumption leads to functional tolerance	NK	NK	Yes[23]	Yes[35]	Yes[42]	NK	Yes[58]
7) Chronic consumption leads to dependence (withdrawal-like signs seen)	NK	NK	Yes[24]	Yes[36]	NK	NK	Yes[59]
8) Relapse behavior is displayed	Yes[6]	Yes[13]	Yes[25]	Yes[37]	Yes[43]	Yes[51]	NK
9) Serve as an animal model of adolescent alcohol abuse	NK	Yes[14]	Yes[26]	NK	NK	NK	NK
10a) Self-administer or consume other drugs of abuse—nicotine, including line differences in self-administration	NK	NK	Yes[27]	NK	NK	Yes[52]	NK

10a) Self-administer or consume other drugs of abuse—cocaine, including line differences in self-administration	Yes[7]	NK	Yes[28]	NK	NK	NK	Yes[60]
11a) Gene expression differences between high and low consuming lines	Yes[8] Acb, VTA, CeA Advillin NFkB signaling	Yes[15] Acb, VTA, CeA Glu, ILK signal Ankrd12 NFkB signaling Gsta4	Yes[29] Acb, VTA, CeA DA, GABA, Glu, NPY, CRF NFkB signaling Gsta4	Yes[38] Acb, VTA, CeA Glu, NPY Ankrd12 Gsta4	Yes[44] VTA ALDH2, ADH1B	Yes[53] Extended Amyg CRFR1, GABA	Yes[61] mPFC, Hipp, Acb Gabra4, DA
11a) Gene and protein expression differences expressed after ethanol intake	NK	NK	Yes[30] Acb, VTA, CeA DA, GABA, Glu, 5HT, peptides	NK	Yes[44]	Yes[53]	NK

AA = ALKO Alcohol-Accepting rat lines; HAD (HAD1 and HAD2) = High Alcohol Drinking rat lines; P = Alcohol-Preferring rat line; sP = Sardinian Alcohol-Preferring rat line; UChB = University of Chile B, high ethanol-consuming, rat line; msP = Marchigian Sardinian Alcohol-Preferring rat line; WHP = Warsaw High Preferring, high ethanol-consuming, rat line; NK = Not Known; BACs = Blood Alcohol Concentrations; Acb = Nucleus Accumbens; VTA = Ventral Tegmental Area; CeA = Central Amygdala; Glu = Glutamate; NF-κB = Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells ; ILK = Interleukin; Ankrd12 = Ankyrin Repeat Domain 12; Gsta4 = Glutathione S-Transferase A4; DA = Dopamine; GABA = Gamma Amino Butyric Acid; NPY = Neuropeptide Y; CRF = Corticotrophin Releasing Factor; ALDH2 = Aldehyde Dehydrogenase 2; ADH1B = Alcohol Dehydrogenase 1B; CRFR1 = CRF Receptor1; mPFC = Medial Prefrontal Cortex; Hipp = Hippocampus; Gabra4 = GABA-A Receptor containing alpha-4 subunit; 5HT = Serotonin; [1]Ritz et al., 1986; [2]Aalto, 1986; [3]Paivarinta and Korpi, 1993; [4]Files et al., 1997, 1998; Samson et al., 1998; [5]Forsander and Sinclair, 1992; [6]Sinclair and Li, 1989; [7]Hyytia and Sinclair, 1993; [8]McBride et al., 2012, 2013b; [9]Rodd-Henricks et al., 2000a; [10]Bell et al., 2008; Murphy et al., 2002; Oster et al., 2006; [11]Rodd et al., 2004; [12]Files et al., 1998; Oster et al., 2006; Samson et al., 1998; [13]Oster et al., 2006; Rodd et al., 2009; Rodd-Henricks et al., 2000b; [14]Bell et al., 2004; [15]McBride et al., 2012, 2013b; [16]Li et al., 1987; [17]Bell et al., 2006a, 2008a, 2011; Murphy et al., 1986, 2002; Rodd et al., 2003; [18]Murphy et al., 1988; Waller et al., 1984; [19]Bell et al., 2002, 2008b; Melendez et al., 2002; Rodd et al., 2004a; [20]Schechter et al., 1992; [21]Files et al., 1998; Murphy et al., 1989; Rodd et al., 2003; Rodd-Henricks et al., 2002a, 2002b; Samson et al., 1998; Toalston et al., 2008; [22]Lumeng and Li, 1986; [23]Gatto et al., 1987; Stewart et al., 1991; [24]Kampov-Polevoy et al., 2000; Waller et al., 1982; [25]Rodd et al., 2003; Rodd-Henricks et al., 2000a, 2000b, 2001; [26]Bell et al., 2003, 2011, 2013; Toalston et al., 2014, 2015; [27]Hauser et al., 2012, 2014a; Le et al., 2006; Rezvani et al., 2010; [28]Katner et al., 2011; Hauser et al., 2014b; Rodd et al., 2007; [29]Bell et al., 2016; McBride et al., 2012, 2013b; [30]Bell et al., 2006a, 2009, 2016; McBride et al., 2010, 2013a, 2014a; McClintick et al., 2015, 2016; Obara et al., 2009; Rodd et al., 2008; Sari et al., 2006; [31]Agabio et al., 1996; [32]Colombo et al., 2006 ; Lobina et al., 1997; [33]Agabio et al., 2001; Colombo et al., 1998b; [34]Vacca et al., 2002; [35]Colombo et al., 2006; [36]Loi et al., 2010; [37]Agabio et al., 2000; Serra et al., 2003; [38]McBride et al., 2012, 2013b; [39]Mardones and Segovia-Riquelme, 1983; Quintanilla et al., 2006; [40]Quintanilla et al., 2008; [41]Quintanilla and Tampier, 2011; [42]Quintanilla and Tampier, 2011; Tampier et al., 2008; [43]Tampier and Quintanilla, 2011; [44]Israel et al., 2006; Ocaranza et al., 2008; Quintanilla et al., 2005a, 2005b, 2006, 2012; Rivera-Meza et al., 2010; [45]Ciccocioppo et al., 2006; [46]Ciccocioppo et al., 2006; [47]Ciccocioppo et al., 1999a; [48]Ciccocioppo et al., 1999b; [49]Ciccocioppo et al., 1999a; [50]Cannella et al, 2016; Ciccocioppo et al., 2004; Cippitelli et al., 2005; Rorick-Kehn et al., 2016; [51]Ciccocioppo et al., 2006; [52]Scuppa et al., 2015; [53]Ayanwuyi et al., 2013; Cannella et al, 2016; Ciccocioppo et al., 2006; [54]Dyr and Kostowski, 2000, 2004, 2008; [55]Dyr and Kostowski, 2004; [56]Dyr and Kostowski, 2008; Rok-Bujko et al., 2006; [57]Dyr and Taracha, 2012; [58]Dyr and Taracha, 2012; [59]Dyr and Taracha, 2012; [60]Acewicz et al., 2012; [61]Stankiewicz et al., 2015. See Table 1 for other abbreviations.

Table 3. Rat Studies on the Acquisition of Alcohol Intake and Its Pharmacological Disruption.

Ethanol Access Procedures	Sex	Line/Strain	Age	Drug	Treatment Site	Molecular Target	Findings	Citation
24h 2BFC 15% LA OFC 15%	F	P	Adolescent PND 30 In Adulthood PND 75	Pre-exposure			Readily acquired drinking during adolescence Increased operant acquisition rate in adulthood	Rodd-Henricks et al., 2002a
Adrenergic								
LA 2BFC 15% (2h)	M	P	Adult >PND 90	Prazosin Antagonist	Systemic	Alpha1Rs	Reduced acquisition	Froehlich et al., 2013a
Cannabinoid								
24h 2BFC 10%	M	sP	Adult >PND 75	SR 141716 Antagonist	Systemic	CB1R	Reduced acquisition	Serra et al., 2001
24h 2BFC 10%	M	sP	Adult >PND 75	SR147778 Antagonist	Systemic	CB1R	Reduced acquisition	Gessa et al., 2005
GABAergic								
24h 2BFC 10%	M	sP	Adult >PND 75	Baclofen Agonist CGP44532 Agonist	Systemic	GABRB	Both reduced acquisition	Colombo et al., 2002
24h 2BFC 10%	M	sP	Adult >PND 75	CGP7930 PAM GS39783 PAM	Systemic	GABRB	Both reduced acquisition	Orru et al., 2005
Glutamatergic								
24h 3BFC 15%, 30%	F	P	Adolescent PND 30 Adult PND 75	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF reduced acquisition in both adolescents and adults	Sari et al., 2013a
Opioid								
LA 2BFC 10%		P	Adult	Naloxone Antagonist	Systemic	MOR, DOR, KOR	Dose-dependently reduced acquisition	Badia-Elder et al., 1999
24h 2BFC 15%	M&F	P	Adolescent PND 30	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Dose-dependently reduced acquisition	Sable et al., 2006
24h 2BFC 15%	M&F	P	Adult >PND 75	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Dose-dependently reduced acquisition	Sable et al., 2006
Serotonergic								
24h 2BFC 15%	M	P	Adult >PND 90	MDL 72222 Antagonist ICS205-930 Antagonist	Systemic	HTR3	Both reduced acquisition	Rodd-Henricks et al., 2000a
LA OFC 15 %	F	P	Adult >PND 90	ICS 205-930 Antagonist	pVTA	HTR3	Dose-dependently and acutely reduced acquisition	Rodd et al., 2010
24h 2BFC 15%	M	P	Adolescent Postnatal Day	MDL 72222 Antagonist	Systemic	HTR3	Both reduced acquisition	c.f., Bell et al., 2012

Table 3. Rat Studies on the Acquisition of Alcohol Intake and Its Pharmacological Disruption.

			(PND) 30	ICS205-930 Antagonist				
Multiple Neurotransmitter and Neuromodulator Studies								
24h 2BFC 10%	M	sP	Adult >PND 75	Naltrexone Antagonist Baclofen Agonist	Systemic	MOR, DOR, KOR GABRB	Low doses of each had no effect; The combination reduced acquisition	Colombo et al., 2005

2BFC = 2-Bottle Free-Choice; LA OFC = Limited Access Operant Frontal Choice; F = Female; P = Alcohol-Preferring rat line; PND = Post-Natal Day; M = Male; sP = Sardinian Alcohol-Preferring rat line; GABRB = Gamma Amino Butyric Acid-B Receptor; PAM = Positive Allosteric Modulator; 3BFC = 3 Bottle Free-Choice; GLT1 = Glutamate Transporter1; EAAT2 = Excitatory Amino Acid Transporter2; CEF = Ceftriaxone; MOR = Mu Opioid Receptor; DOR = Delta Opioid Receptor; KOR = Kappa Opioid Receptor; HTR3 = Serotonin-3 Receptor; See Tables 1 and 2 for other abbreviations.

Table 4. Rat Studies of Binge-Like (Most Rely on Original Authors' Interpretation) Behavior and Its Pharmacological Disruption

Ethanol Access Procedures	Sex	Line/Strain	Age	Drug	Region	Molecular Target	Findings	Citation
Cholinergic								
LA 2BFC 10%	F	P	Adult >PND 90	Carbachol Agonist Methylscopola-mine-bromide Antagonist	PPN VTA	AChRs mAChRs	Both compounds in both regions decreased intake	Katner et al., 1997
Dopaminergic								
LA 2BFC 10%	F	P	Adult >PND 90	SCH 23390 Antagonist Sulpiride Antagonist	Acb	D1R D2R, D3R, GHBR	SCH in Acb did not affect intake; Sulpiride in Acb reduced intake	Levy et al., 1991
LA 2BFC 10%	M	AA	Adult >PND 90	Clozapine Antagonist, partial agonist Olanzapine Inverse agonist, antagonist	Systemic	D2R, HTR2, GRIN, GLT1 HTR2, H1R, mAChR4/5, D2R	Clozapine did not alter intake; Olanzapine nonselectively reduced intake	Ingman and Korpi, 2006
LA 2BFC 10%	M	AA	Adult >PND 75	Aripiprazole Partial agonist	Systemic	D2R, D3R, D4R, HTR1A, HTR2C, HTR7	Aripiprazole reduced intake at doses that also suppressed locomotor activity	Ingman et al., 2006
GABAergic								
LA Drinking-in-the-dark (DID) 10%	?	P	Adult >PND 90	GABRA α2 siRNA GABRA α1 siRNA TLR4-siRNA	CeA VP CeA	GABRA α2 GABAR α1R TLR4	GABA-A α2R and TLR4 viral vector in CeA reduced intake; GABAA α1R siRNA in VP reduced intake	Liu et al., 2011
Monoamine Reuptake Inhibitor								
LA DID 10%	M	P	Adult >PND 90	Amitifadine Inhibitor Imipramine Inhibitor, antagonist	Systemic	SERT, NET, DAT SERT, NET, D2R, mAChR2, H1R, MOR?	Amitifadine reduced intake; Imipramine nonselectively reduced intake	Warnock et al., 2012

PPN = Pedunculopontine Nucleus; mAChRs = Muscarinic Acetylcholine Receptors; D1R = Dopamine-1 Receptor; GHBR = Gamma Hydroxybutyrate Receptor; GRIN = Glutamate Ionotropic Receptor—N-Methyl-D-Asparate subtype; TLR4 = Toll-Like Receptor 4; VP = Ventral Pallidum; H1R = Histamine-1 Receptor; See Tables 1 through 3 for other abbreviations.

Ethanol Access Procedures	Sex	Line/Strain	Age	Drug	Region	Molecular Target	Findings	Citation
Continuous access (24h) 2 bottle free-choice (2BFC: water and 10% ethanol); 4h limited access (LA) 2BFC 10%; 1h LA every 3h 2BFC 10% 1h LA every 3h 2BFC multiple concentrations (MC: 5%, 10%, 15%)	M	P	Adult >PND 90				Blood alcohol concentrations (BACs) limit intake; Scheduled LA increases intake per access session	Murphy et al., 1986
LA operant free-choice (OFC: water and 5%-30% with increasing concentration across days)	M	P & NP	Adult >PND 90				NP rats fail to self-administer any concentration; P rats readily self-administer all concentrations; Even when adulterated with a non-preferred flavor	Murphy et al., 1986
24h 2BFC 3%-30% vs water 24h 2BFC Nutrasweet vs 10% 24h 2BFC Slender (chocolate drink) vs 10%	M	P & NP	Adult >PND 90				NP rats consume more 3% ethanol than P rats, but the reverse is true for all other concentrations; P rats maintain high intake even in the presence of other palatable solutions	Lankford et al., 1991
LA OFC 8%	M	P vs NP HAD vs LAD	Adult >PND 120				P > HAD > LAD > NP responding	Ritz et al., 1994
24h 2BFC 10% LA OFC 10%, 15%, 30%	M	sP vs sNP	Adult >PND 90				sP self-administered all concentrations; But sNP did not self-administer the different concentrations	Vacca et al., 2002b
24h 2BFC 10% 24h 3BFC 0.2% saccharin	F	UChB	?				A third solution of saccharin reduces intake	Tampier & Quintanilla, 2009
Adrenergic								
24h 2BFC 10%	M	AA	Adult >PND 90	Medetomidine Agonist Atipamezole Antagonist	Systemic	Alpha2Rs	Atipamezole increased drinking; medetomidine did not alter drinking	Korpi, 1990
24h 2BFC 10%	M	P & HAD1	Adult >PND 90	Uncontrollable stress		HPA activity Adrenergic activity	Stress moderately decreased intake by Ps and HAD1s; Post-stress increased intake in P, but not HAD1, rats	Chester et al., 2004
LA OFC 10%	M	P	Adult >PND 90	Prazosin Antagonist	Systemic	Alpha1Rs	Prazosin reduced responding	Verplaetse et al., 2012

LA OFC 10% Appetitive vs Consummatory Responding	M	P & HAD2	Adult >PND 90	Yohimbine Antagonist	Systemic	Alpha1Rs, Alpha2Rs	Yohimbine enhanced self-administration	Bertholomey et al., 2013
LA 2BFC 15%	M	P	Adult >PND 90	Prazosin Antagonist	Systemic	Alpha1Rs	Lack of tolerance to chronic prazosin-induced reductions in drinking	Froehlich et al., 2013a
LA 2BFC 15%	M	P	Adult >PND 90	Doxazosin Antagonist	Systemic	Alpha1Rs	Doxazosin reduced drinking	O'Neil et al., 2013
Cannabinoid								
LA 2BFC 10%	M	sP	Adult >PND 90	SR-141716 Antagonist	Systemic	CB1R	SR-141716 dose-dependently reduced intake	Colombo et al., 1998a
LA OFC 10%	M	msP & Wistar	Adult >PND 90	SR141716 Antagonist	Systemic	CB1R	SR141716A reduced responding in both lines	Cippitelli et al., 2005
24h 2BFC 10%	M	sP	Adult >PND 75	SR147778 Antagonist	Systemic	CB1R	SR147778 reduced intake	Gessa et al., 2005
LA OFC 10%	F	AA & Wistar	Adult >PND 90	SR141716 Antagonist URB597- fatty acid amido-hydrolase FAAH Inhibitor	Systemic PFC striatum	CB1R CBRs	SR141716A systemically and in the PFC, but not striatum, decreased responding; URB597 increased operant responding	Hansson et al., 2007
LA 2BFC 10%	M	WHP	Adult >PND 180	SR141716 Antagonist	Systemic	CB1R	SR141716A reduced intake	Dyr et al., 2008
LA OFC 10%	M	AA	Adult >PND 90	SR141716A Antagonist WIN55,212-2 Agonist	Systemic VTA Acb	CB1R	Systemic administration exerted biphasic change in responding; Only SR141716A was effective in VTA and Acb	Malinen & Hyytia 2008
LA OFC 15%		P	Adult >PND 90	SR141716A Antagonist	Systemic	CB1R	SR141716A transiently reduced responding	Getachew et al., 2011
24h 2BFC 10%	M	sP & snP	Adult >PND 70	SR141716A Antagonist	Systemic	CB1R	SR141716A reduced intake	Vinod et al., 2012
Cholinergic								
24h 2BFC 10%	M	P & NP	Adult >PND 90	Scopolamine Antagonist Methscopola-	Systemic	mAChRs	Scopolamine and methscopolamine reduced intake and preference in P; Scopolamine did not alter	Rezvani et al., 1990

				mine Antagonist			intake in NP; Methscopolamine nonselectively reduced intake in NP	
LA 2BFC 10%	F	P	Adult >PND 90	Carbachol Agonist Methylscopola-mine bromide Antagonist Oxotremorine Agonist	PPN VTA	Cholinergic Rs AChR mAChRs	Carbachol in VTA and scopolamine in PPN decreased intake; Carbachol in PPN and methylscopolamine in VTA nonselectively decreased intake	Katner et al., 1997
24h 3BFC 15% & 30%	M	HAD-2	Adult >PND 90	Cytisine Partial agonist Lobeline Mixed agonist-antagonist	Systemic	Alpha4beta2 subunit containing nAChRs nAChR	Cytisine and lobeline dose-dependently reduced intake	Bell et al., 2009
24h 2BFC 10%	M	P	Adult >PND 90	Sazetidine-A Desensitizer	Systemic	Alpha4beta2 subunit containing nAChRs	Sazetidine-A reduced intake	Rezvani et al., 2010
24h 2BFC 10%	M	UChB	Young-Adult >PND 60	Varenicline Cytisine Partial agonists	Systemic	Alpha4beta2 subunit containing nAChRs	Both partial agonists reduced intake	Sotomayor-Zarate et al., 2013
Dopaminergic								
LA 2BFC 10%	M	AA	Adult >PND 90	SCH 23390 Antagonist Sulpiride Antagonist	Acb	D1R D2R	SCH23390 did not alter intake; Sulpiride decreased intake	Levy et al., 1991
LA 2BFC 10%	F	HAD	Adult >PND 90	SKF-38393 agonist SCH-23390 Antagonist Quinpirole Agonist Spiperone Antagonist	Systemic	D1R D2R	D1 and D2 agonists as well as D1 antagonist reduced intake; D2 antagonist increased intake	Dyr et al., 1993
24h 2BFC 10%	M	sP	Adult >PND 90	SCH 39166 Antagonist	Systemic	D1R	SCH 39166 non-specifically reduced intake	Panocka et al., 1995a

LA 2BFC 15%	F	P	Adult >PND 90	Quinpirole Agonist Quinelorane Agonist Sulpiride Antagonist	aVTA pVTA	D2R	Quinpirole and quinelorane, but not sulpiride, in aVTA reduced intake; Quinpirole in pVTA had nonspecific effects	Nowak et al., 2000
LA 2BFC 15%	F	P	Adult >PND 90	SCH-23390 Antagonist Sulpiride Antagonist	VP	D1R D2R	Sulpiride increased intake; SCH-23390 did not alter intake	Melendez et al., 2005
24h 2BFC 15%	M	P & NP	Adult >PND 90	SB-277011-A Antagonist	Systemic	D3R	SB-277011-A reduced intake and lick responses	Thanos et al., 2005
GABAergic								
LA 2BFC 10%	M	sP	Adult >PND 90	Ro19-4603 Partial inverse agonist	Systemic	GABRA-BDZ complex	Ro19-4603 (3 x daily) reduced intake	Balakleevsky et al., 1990
LA 2BFC 10%	M	Sprague-Dawley	Adult >PND 90	Ro15-4513 Partial inverse BDZ agonist	Systemic	GABRA-BDZ complex	Ro15-4513 reduced intake	June et al., 1991
LA 2BFC 10%	M	Sprague-Dawley	Adult >PND 90	Ro15-4513 Partial inverse agonist Ro15-1788 Antagonist	Systemic	GABRA-BDZ complex	Ro15-4513 reduced intake and the antagonist Ro15-1788 (Flumazenil) blocked these effects	June et al., 1992
24h 2BFC 10%	M	AA	Adult >PND 90	Gamma-vinyl GABA Agonist	Systemic	GABRA	Gamma-vinyl GABA decreased intake	Wegelius et al., 1993
LA 2BFC 10%	F	P	Adult >PND 90	Ro19-4603 Inverse agonist	Systemic	GABRA-BDZ complex	Ro19-4603 reduced intake	June et al., 1994b
LA 2BFC (2-11%)	M	Sprague-Dawley	Adult >PND 90	Ro15-4513 Partial inverse agonist Ro15-1788 Partial inverse agonist	Systemic	GABRA-BDZ complex	Both Ro15-4513 and Ro15-1788 reduced self-administration	June et al., 1994a
LA 2BFC 10%	M	NP	Adult >PND 90	Ro19-4603 Inverse agonist FG 7142 Inverse agonist DMCM	Systemic	GABRA-BDZ complex	RO19-4603 reduced intake; FG 7142 and DMCM had non-selective effects; Bretazenil increased intake at higher doses	June et al., 1996b

				Inverse agonist Bretazenil (R016-6028) Partial agonist				
LA 2BFC 10%	M	P	Adult >PND 90	RO19-4603- Inverse agonist CGS 8216- Antagonist Flumazenil- Antagonist ZK 93426- Antagonist	Systemic	GABRA-BDZ complex	RO19-4603 reduced intake and CGS 8216 reversed these effects; Neither flumazenil nor ZK 93426 reversed RO19-4603's effects	June et al., 1996a
24h 2BFC 10%	M	sP	Adult >PND 180	Gamma-hydroxybutyric acid (GHB) Agonist	Systemic	GABRA GHBR	GHB reduced intake	Agabio et al., 1998
LA OFC 10%	M&F	P & NP	Adult >PND 90	RO19-4603 Inverse agonist	Systemic Acb, CPU, VTA	GABRA-BDZ complex	Systemic and Acb infusions of Ro-19-4603 reduced self-administration; Ro19-4603 in the VTA or CPu did not alter responding	June et al., 1998e
LA 2BFC 10%	F	P & NP	Adult >PND 90	CGS 8216 Antagonist ZK 93426 Antagonist	Systemic	GABRA-BDZ complex	CGS 8216 and ZK 93426 dose-dependently reduced drinking with some specificity over saccharin	June et al., 1998b
LA OFC 10%	M	P	Adult >PND 75	Ru 34000 Inverse agonist Flumazenil Antagonist Ru 40410 Antagonist	Systemic VTA	GABRA-BDZ complex	Ru 34000 via sc, ip, oral, VTA nonselectively decreased responding; Flumazenil, but not Ru40410, reversed the effects of Ru34000	June et al., 1998c
LA OFC 10%	M	P	Adult >PND 90	Flumazenil Antagonist CGS 8216 Antagonist ZK 93426 Antagonist	Systemic	GABRA-BDZ complex	All antagonists reduced self-administration	June et al., 1998f
LA 2BFC 15% LA OFC 15%	F	P	Adult >PND 90	Picrotoxin Antagonist Muscimol	aVTA	GABRA-BDZ complex GABRA	Picrotoxin and bicuculline into the aVTA reduced intake and responding;	Nowak et al., 1998

				Agonist Bicuculline Antagonist		GABRA	Muscimol reversed the effects of picrotoxin	
LA OFC 10%	M	P	Adult >PND 90	RY023 Inverse agonist ZK 93426 Antagonist	Hipp, Acb, VTA	GABRA5-BDZ complex	RY023 dose-dependently reduced responding; ZK93426 reversed these effects	June et al., 2001; Cook et al., 2005
LA OFC 10%	M	P	Adult >PND 90	3-propoxy-beta-carboline hydro-chloride (3-PBC) Mixed agonist-antagonist	VP, Acb, CPU	GABRA1-BDZ complex	3-PBC in aVP and mVP, but not Acb or CPU, reduced responding	Harvey et al., 2002
LA OFC 10%	F	P & HAD1	Adult >PND 90	bCCt Mixed agonist–antagonist Chlordiazepox-ide PAM	Systemic VP AcbShell AcbCore CPU	GABRA1-BDZ complex GABRA-BDZ complex	bCCt systemic or VP reduced responding; bCCt into the Acb or CPU did not alter responding; bCCt reversed chlordiazepoxide-induced sedation	June et al., 2003
LA OFC 10%	M	Long-Evans	Adult >PND 90	RY024 Inverse agonist	Systemic	GABRA5-BDZ complex	RY024 reduced responding, antagonized motor impairment, and sedative effects	McKay et al., 2004
LA OFC 10%	M	P	Adult >PND 90	RY023 Inverse agonist	Systemic Hipp	GABRA5	RY023 dose-dependently reduced responding	Cook et al., 2005
24h 2BFC 10%	M	sP	Adult >PND 75	CGP7930 PAM GS39783 PAM	Systemic	GABRB	Both positive allosteric modulators reduced intake	Orru et al., 2005
LA OFC 15%	M	sP	Adult >PND 75	Baclofen Agonist	Systemic	GABRB	Baclofen dose-dependently reduced responding	Maccioni et al., 2005
LA OFC 10%	M	iP	Adult >PND 90	CGP7930 Allosteric modulator Baclofen Agonist	Systemic	GABRB	CGP7930 and baclofen reduced responding; Combination of substhreshold doses reduced responding	Liang et al., 2006
LA OFC 15%	M	sP	Adult >PND 75	GS39783 PAM	Systemic	GABRB	GS39,783 dose-dependently reduced responding	Maccioni et al., 2007b

24h 2BFC 10%	M&F	UChB	Early-Adult >PND 60	Baclofen Agonist	Systemic	GABRB	Baclofen reduced intake	Quintanilla et al., 2008
24h 2BFC 10% LA OFC 10%	M	sP	Adult >PND 75	BHF177 PAM	Systemic	GABRB	BHF177 reduced self-administration	Maccioni et al., 2009
24h 2BFC 10% LA OFC 10%	M	sP	Adult >PND 75	rac-BHFF [(R,S)-5,7-di-tert-butyl-3-hy-droxy-3-tri-fluor omethyl-3H-benzofuran-2-one]-PAM	Systemic	GABRB	rac-BHFF reduced self-administration	Maccioni et al., 2010
LA OFC 10%	M	P & sP & AA	Adult >PND 90	GS39783 PAM Baclofen Agonist	Systemic	GABRB	Baclofen and GS39783 reduced FR and PR responding; Rank of potency for both drugs P>sP>AA rats	Maccioni et al., 2012
LA OFC 15%	M	sP	Adult >PND 90	GS39783 PAM BHFF PAM	Systemic	GABRB	Both GABRB positive allosteric modulators reduced responding without tolerance and potentiated baclofen's effects	Maccioni et al., 2015
Glutamatergic								
LA OFC 10%	M	Long-Evans	Adult >PND 90	LY379268 Agonist (S)-3,4- DCPG [(S)-3,4-dicar-boxyphenylglycine]-agonist	Systemic	GRM2/3 GRM8	LY379268 and (S)-3, 4- DCPG reduced responding	Backstrom & Hyytia 2005
LA OFC 10%	M	iP & AA & Fawn-Hooded	Adult >PND 90	MTEP Antagonist	Systemic	GRM5	MTEP reduced responding in all strains/lines; Sedation seen in iP rats	Cowen et al.,2005b
LA OFC 10%	M	P	Adult >PND 90	2-methyl-6-(phenylethyl)-pyridine (MPEP) Antagonist LY-341495	Systemic	GRM5 GRM2/3	MPEP and LY341495 reduced responding	Schroeder et al., 2005a

				Antagonist CPCCOEt Antagonist		GRM1		
24h 2BFC 10%	M&F	UChB	Adult >PND 120	DCD Synthetic polyamine	Systemic	GRIN1/GRIN2	DCD reduced intake with lack of tolerance; absence of disulfiram effect	Bilbeny et al., 2005
24h 2BFC 10%	M&F	UChB	Adult >PND 90	DCD Synthetic polyamine	Systemic	GRIN1/GRIN2	DCD reduced intake with lack of tolerance; absence of disulfiram effect	Font et al., 2005
LA OFC 15%	M	P	Adult >PND 90	LY404039 Agonist	Systemic	GRM2/3	LY404039 did not alter responding	Rodd et al., 2006
LA OFC 15%	M	iP	Adult >PND 90	JNJ16259685 Antagonist MPEP Antagonist	Systemic	GRM1 GRM5	Both JNJ16259685 and MPEP reduced self-administration	Besheer et al., 2008a, 2008b
LA OFC 15%	M	P	Adult >PND 90	MPEP Antagonist LY379268 Agonist	Acb	GRM5 GRM2/3	MPEP in Acb reduced responding but not activity; LY379268 in Acb reduced responding and motor activity	Besheer et al., 2010b
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF reduced intake; CEF increased GLT1 in Acb and PFC	Sari et al., 2011
24h 3BFC 15% & 30%	M	P	Adult >PND 90	GPI-1046 Up-regulator	Systemic	GLT1 (EAAT2)	GPI-1046 reduced intake: GPI-1046 increased GLT1 in AcbCo and PFC	Sari & Sreemantula, 2012
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	Ethanol reduced GLT1 and increased ENT1 in the AcbSh and AcbCo; CEF reversed these effects as well as reducing intake	Sari et al., 2013b
24h 3BFC 15% & 30%	F	P	Adult >PND 90 Initiated PND 30 or PND 75	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF reduced intake as adults in both rats initiating intake at PND 30 or PND 75; CEF increased GLT1 in Acb and PFC of both groups as well	Sari et al., 2013a
24h 3BFC 15% & 30%	M	P	Adult >PND90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF reduced chronic intake; CEF increased GLT1 and xCT	Rao & Sari, 2014b

							in Acb, PFC, and Amyg	
24h 3BFC 15% & 30%	M	P	Adult >PND 90	MS-153 Up-regulator	Systemic	GLT1 (EAAT2)	MS-153 increased GLT1, NFkB-65 and pAKT; but reduced IkBalpha in Acb; MS-153 reduced intake	Alhaddad et al., 2014b
24h 3BFC 15% & 30%	M	P	Adult >PND 90	MS-153 Up-regulator	Systemic	GLT1 (EAAT2) xCT	Ethanol reduced GLT1a, GLT1b and xCT in Amyg and Hipp; MS-153 increased GLT1a, GLT1b and xCT in Amyg and Hipp; MS-153 reduced intake	Aal-Aaboda et al., 2015
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ampicillin Up-regulator	Systemic	GLT1 (EAAT2) xCT	AMP increased GLT1 and xCT in Acb and PFC; AMP reduced intake	Alasmari et al., 2015
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator Dihydrokainic acid (DHK) Blocker	Systemic	GLT1 (EAAT2)	Ethanol reduced GLT1 and increased extra-cellular glutamate in Acb; CEF increased GLT1, and glutamine synthetase activity while reducing extra-cellular glutamate in Acb; DHK reversed CEF's effects on GLT1 levels and extra-cellular glutamate; Ceftriaxone reduced intake	Das et al., 2015
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Amoxicillin Up-regulator Amoxicillin/ Clavulanate (Augmentin) Up-regulator	Systemic	GLT1 (EAAT2)	AUG increased GLT1 and pAKT in Acb and mPFC; AMOX increased GLT1 and pAKT in Acb; Aug and AMOX reduced intake	Goodwani et al., 2015
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ampicillin, Cefazolin, and Cefoperazone Up-regulator	Systemic	GLT1 (EAAT2)	AMP, CEFA, and CEFO reduced intake and increased both GLT1 and pAKT in Acb and PFC	Rao et al., 2015a
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF increased GLT1, GLT1a, GLT1b and xCT in the Acb and PFC	Rao et al., 2015b

(a) 24h 3BFC 15% & 30%; (b) 24h 3BFC (10 % sucrose + 0.07mg/ml nicotine and 10% sucrose + 0.14mg/ml nicotine); (c) 24h 3BFC (15% ethanol + 0.07 mg/ml nicotine and 30% ethanol + 0.14 mg/ml nicotine); (d) 24h 3BFC (10% sucrose + 10% sucrose)	F	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF reduced ethanol, ethanol + nicotine, nicotine + sucrose, and sucrose intake to varying degrees	Sari et al., 2016
Histaminergic								
LA OFC 10%	M	AA & ANA	Adult >PND 90	clobenpropit Antagonist Thioperamide Antagonist R-α- methyl Agonist Mepyramine Antagonist	Systemic	Histamine H3R and H1R	H3 antagonists reduced responding; H3 agonists increased responding; H1 antagonist did not alter responding	Lintunen et al., 2001
Opioid								
LA 2BFC 10%	M	HAD	Adult >PND 90	Naloxone Antagonist	Systemic	MOR, DOR, KOR	Naloxone dose-dependently decreased intake	Froehlich et al., 1990
24h 2BFC 10%	M	HAD	Adult >PND 90	Naloxone Antagonist ICI 174864 Antagonist Thiorphan Inhibitor Hydrocinnamic acid Inhibitor	Systemic	MOR, DOR, KOR DOR Enkephalinase	Naloxone and ICI 174864 reduced intake; Thiorphan increased intake; Hydrocinnamic acid did not alter intake	Froehlich et al., 1991
LA OFC 10%	M	AA	Adult >PND 90	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Acute and repeated Naltrexone reduced responding	Hyytia & Sinclair 1993
24h 2BFC ?%	M&F	AA	Adult >PND 90	CTOP Antagonist ICI 174,864 Antagonist	ICV	MOR DOR	CTOP decreased intake; ICI 174,864 did not alter drinking	Hyytia, 1993
LA 2BFC 10%	M	AA	Adult >PND 90	Naloxonazine	Systemic	MOR-mu1	Naloxonazine had non-specific	Honkanen et al.,

				Naltrindole		DOR	effects Naltrindole had no effect on intake	1996
LA 2BFC (2-11%)	M	Sprague-Dawley	Adult >PND 90	Buprenorphine Partial agonist	Systemic	MOR & KOR	Buprenorphine reduced intake	June et al., 1998a
LA OFC 10%	M&F	P & Wistar	Early Adulthood >PND 60	Nalmefene, Naltrexone	Systemic	MOR, DOR, KOR	Nalmefene was more potent than naltrexone; The SC route was extremely more potent than the PO; Nalmefene's effects were greater in P than Wistar rats	June et al., 1998d
LA 2BFC 10%	M	HAD	Adult >PND 90	Beta-FNA Antagonist	Systemic	MOR-specific	Beta-FNA dose-dependently reduced intake	Krishnan-Sarin et al., 1998
LA OFC 10%	F	P	Adult >PND 90	Naltriben Antagonist Naloxone Antagonist	Systemic	DOR-δ2 MOR, DOR, KOR	Both naltriben and naloxone reduced responding	June et al., 1999
LA 2BFC 10%	M	AA	Adult >PND 90	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Naltrexone reduced intake	Parkes & Sinclair, 2000
LA OFC 10%	M	AA & Wistar	Adult >PND 90	Naloxone Antagonist CTOP- Antagonist Naltrindole Antagonist	Systemic ICV Acb BLA VTA	MOR, DOR, KOR MOR DOR	Subcutaneous naloxone and ICV CTOP and naltrindole reduced self-administration equally in AA and Wistar rats; Naltrindole administered ICV, Acb, or BLA reduced Wistar responding, whereas CTOP was effective only in the BLA	Hyytia & Kiianmaa, 2001
24h 2BFC 10%	M	AA & P	Adult >PND 90	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	High doses of naltrexone reduced palatability for AA, but not P, rats; Reduced intake by both lines	Coonfield et al., 2004
LA OFC 10%		P	Adult >PND 90	Nalmefene Antagonist	Hipp Acb VTA	MOR, DOR, KOR	Nalmefene in the Acb and VTA reduced responding; Higher doses required for effects in VTA; Non-specific effects after nalmefene in Hipp	June et al., 2004
24h 2BFC 15%	M&F	P	Adolescent >PND 30	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Lower doses of naltrexone more effective in adolescents	Sable et al., 2006

			Adult >PND 90				vs adults; Adult rats displayed greater tolerance to naltrexone's effects vs periadolescent	
24h 2BFC 10%	M	sP	Adult >PND 90	14-methoxy-metopon- Agonist Naltrexone Antagonist	Systemic ICV	MOR MOR, DOR, KOR	14-MM dose-dependently, and time-dependently affected intake; 14-MM decreased intake at 30 min but increased intake at 60-240 min; naltrexone blocked 14-MM enhancing effects on intake	Sabino et al., 2007
24h 2BFC 10%	F	WHP	Adult >PND 90	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Naltrexone reduced intake	Zalewska-Kaszubska et al., 2008
LA OFC 15%	F	P	Adult >PND 90	Naltrexone Antagonist LY255582 Antagonist	Systemic	MOR, DOR, KOR MOR	Both naltrexone and LY reduced responding	Dhaher et al., 2012a
24h 2BFC 10% LA OFC 10%	M	P & HAD	Adult >PND 90	Naltrexone Antagonist GSK1521498 Antagonist	Systemic	MOR, DOR, KOR MOR	Naltrexone and GSK1521498 reduced intake & responding; GSK1521498 was more effective	Giuliano et al., 2015
LA 2BFC 10%	M	AA	Emerging adulthood >PND 60	CTOP Antagonist DAMGO Agonist Morphine Agonist U50488H Antagonist	AcbSh	MOR MOR MOR, DOR, KOR KOR	CTOP increased intake; DAMGO had a trend to decrease intake; Morphine and U50488H had no effect	Uhari-Vaananen et al., 2016
Serotonergic								
Intragastric (IG) FC 20%	M	P	Adult >PND 90	Fluoxetine Inhibitor	Systemic	SERT	Fluoxetine reduced IG self-administration	Murphy et al., 1988
LA 2BFC 10%	F	P	Adult >PND 90	Spiroxatrine Antagonist Fluoxetine Inhibitor 8-hydroxy-2(di-N-propyl-amino)	Systemic	HTR1A SERT	Fluoxetine reduced intake; Spiroxatrine had a modest effect on intake; Fluoxetine and spiroxatrine had a synergistic reduction; DPAT also augmented	McBride et al., 1989

				tetralin (DPAT) Agonist		HTR1A	fluoxetine's effects on intake	
LA 2BFC 10%	F	sP	Adult >PND 85	MDL 72222 Antagonist	Systemic	HTR3	MDL 72222 reduced intake	Fadda et al., 1991
LA 2BFC 10%	M	sP	Adult >PND 90	GR113808 Antagonist	Systemic	HTR4	GR113808 reduced intake	Panocka et al., 1995b
24h 3BFC (3-30%)	M	P	Adult >PND 90	Amperozide Antagonist FG5893 Mixed antagonist FG5974 Mixed antagonist	Systemic	HTR2A HTR1A	Amperozide and FG5974 reduced intake	Lankford et al., 1996a
24h 3BFC (3%-30%)	M	HAD	Adult >PND 90	FG5865 Mixed agonist/ antagonist	Systemic	HTR1A/2	FG5865 reduced intake	Long et al., 1996
24h 2BFC (3%-30%)	M	P	Adult >PND 90	FG5865 Mixed agonist/ antagonist	Systemic	HTR1A/2	FG5938 reduced intake	Piercy et al., 1996
24h 2BFC 10% LA 2BFC 10%	?	P & AA & Fawn-Hooded	Adult >PND 70	Amperozide Antagonist FG 5974 Mixed antagonist/ agonist	Systemic	HTR2A HTR1A/2A	Amperozide dose-dependently reduced 24h and LA intake; FG 5974 modestly reduced 24h intake but increased LA intake with non-specific effects	Overstreet et al., 1997
24h 2BFC 10%	F	P	Adult >PND 90	WAY 100635 Antagonist Fluoxetine Inhibitor	Systemic	HTR1A SERT	WAY and fluoxetine alone and together additively reduced intake	Zhou et al., 1998
24h 2BFC 15%	M	P	Adult >PND 90	MDL 72222 Antagonist ICS205-930 Antagonist	Systemic	HTR3	Both MDL and ICS reduced drinking	Rodd-Henricks et al., 2000a
LA OFC 15%	F	P	Adult >PND 90	ICS 205-930 Antagonist	pVTA aVTA	HTR3	ICS in the pVTA, but not aVTA, increased responding	Rodd et al., 2010
LA 1B Test ?%	M	Swim Test Susceptible (SUS) Rat	Adult >PND 90	Fenfluramine Agonist 8-OH-DPAT Agonist	Systemic	SERT SERT, HTR1A, HTR7	Fenfluramine dose-dependently reduced intake; Biphasic effects of 8-OH-DPAT lower doses increased and higher doses decreased	West et al., 2011

							intake	
24h 2BFC 12%	F	P	Adult >PND 90	Lorcaserin Agonist	Systemic	HTR2C	Lorcaserin reduced intake, with some non-specificity	Rezvani et al., 2014
Neuropeptidergic								
24h 2BFC 10%	M	sP	Adult >PND 90	SSR149415 Antagonist	Systemic	Arginine vasopressin (AVP) V1bR	SSR149415 reduced intake	Zhou et al., 2011
24h 2BFC 10%	F	AA	Adult >PND 90	HS014 Antagonist MTII Agonist	ICV	Melanocortin MC4R MC3/4Rs	HS014 did not alter intake; MTII non-specifically reduced intake	Ploj et al., 2002
LA 2BFC 10%	M	msP	Adult >PND 90	AgRP Antagonist SHU9119 Antagonist MTII Agonist	ICV	MCRs MC3/4Rs MC3/4Rs	AgRP did not affect intake; SHU9119 did not affect intake; MTII nonselectively reduced intake, although tolerance developed to this effect	Polidori et al., 2006
LA 2BFC 8%	M	sP	Adult >PND 90	NH,-SENK Agonist SENK Agonist [MePhe7]NKB Agonist Sar9 Met(02)]SP Agonist GR64349 Agonist	ICV	Neurokinin Rs NK3R NK3R NK3R NK1R NK2R	NK3R, but not NK1R or NK2R, agonists reduced intake	Ciccocioppo et al., 1994
LA 2BFC (2-11%)	M	P & NP & Wistars	Adult >PND 90	NPY Agonist	ICV	NPYRs	NPY reduced intake in P but not NP or Wistars	Badia-Elder et al., 2001
LA 2BFC (2-11%)	F	HAD & LAD	Adult >PND 90	NPY Agonist	ICV	NPYRs	NPY reduced intake in HAD but not LAD	Badia-Elder et al., 2003
LA OFC 10%	M	Long Evans	Adult >PND 90	BIBP 3226 Antagonist	CeA	NPY-Y1R	BIBP 3226 reduced self-administration	Schroeder et al., 2003
24h 2BFC 15%	F	HAD1	Adult >PND 90	NPY Agonist	PVN-Hyp	NPYRs	NPY dose-dependently increased intake	Gilpin et al., 2004
24h 2BFC 10% LA OFC 10%	M	iP	Adult >PND 90	L-152,804 Antagonist	Systemic	NPY-Y5R	L-152,804 reduced intake and self-administration	Schroeder et al., 2005b

24h 2BFC 15%	F	P	Adult >PND 90	NPY Agonist	CeA	NPYRs	NPY did not affect intake	Gilpin et al., 2008
24h 2BFC 10%	M	P	Adult >PND 90	NPY Agonist	CeA	NPYRs	NPY reduced intake	Zhang et al., 2010
24h 2BFC 15%	F	P	Adult >PND 90	NPS Agonist	ICV	NPSRs	NPS reduced intake	Badia-Elder et al., 2008
LA OFC 10%	M	msP	Adult >PND 90	N/OFQ Agonist	Systemic	Nociceptin/ orphanin FQ; N/OFQ & NOPR	N/OFQ reduced intake and progressive ratio (PR) responding	Ciccocioppo et al., 2004
24h 2BFC 10%	M	P	Adult >PND 90	TA-0910 Agonist	Systemic	TRHR	TA-0910 dose-dependently reduced intake	Rezvani et al., 1992
Other Systems								
24h 2BFC 10%	F	UChB	Early Adult >PND 60	Disulfiram Inhibitor Cyanamide Inhibitor	Systemic	ALDH2	Chronic ethanol induced tolerance to effects of ALDH2 inhibitors	Tampier et al., 2008
24h 2BFC 10%	F	UChB	Early Adult >PND 60	Anti-*Aldh2* Antisense gene	IV	ALDH2	Antisense induced a long-term reduction in intake	Ocaranza et al., 2008
24h 2BFC 10% LA OFC 10%	M	iP & Fawn-Hooded & Long-Evans	Adult >PND 90	CVT-10216 Inhibitor	Systemic	ALDH2	CVT-10216 reduced intake in FH; CVT-10216 reduced responding in FH, iP, and LE	Arolfo et al., 2009
24h 2BFC 10%	F	WHP	Adult >PND 90	Levetiracetam Inhibitor	Systemic	Synaptic vesicle glycoprotein SV2A Ca+	Levetiracetam reduced intake	Zalewska-Kaszubska et al., 2011
24h 2BFC 5%	F	UChB	Adult >PND 120	HCN-2 Lenti virus overexpression	Intra-VTA	Hyperpolarization activated cyclic nucleotide-gated (HCN-2)	HCN increased intake; HCN increased CPP; HCN increased LMA	Rivera-Meza et al., 2014
24h 2BFC 10%	M	UChB	Young-Adult >PND 60	Fenofibrate PPAR agonist	Systemic	Peroxisome proliferator-activated receptor (PPAR)	Fenofibrate reduced intake	Karahanian et al., 2014
24h 2BFC 15%	M&F	HAD1 & HAD2	Adult >PND 90	Ivermectin PAM *P2rx4* shRNA lentivirus	Systemic ICV pVTA	Purinergic P2X4 receptor P2RX4	Ivermectin reduced intake in both; *P2rx4* knockdown in pVTA reduced intake by HAD1	Franklin et al., 2015a

Multiple Neurotransmitter/Neuromodulator System Studies								
LA 2BFC 15%	M	P	Adult >PND 90	Prazosin Antagonist Naltrexone Antagonist	Systemic	Alpha1Rs MOR, DOR, KOR	Combination of threshold doses of naltrexone and prazosin reduced drinking	Froehlich et al., 2013b
LA 2BFC 20%	M	P	Adult >PND 270	Prazosin Antagonist Naltrexone Antagonist	Systemic	Alpha1Rs MOR, DOR, KOR	Combination of Prazosin and naltrexone was more effective than each alone in reducing drinking	Rasmussen et al., 2015
24h 2BFC 10%	M	sP	Adult >PND 180	WIN 55,212-2 Agonist CP 55,940 Agonist SR 141716 Antagonist Naloxone Antagonist	Systemic	CB1R MOR, DOR, KOR	CB1 agonists increased drinking; CB1 and MOR/DOR/KOR antagonists reduced CB1 agonist effects	Colombo et al., 2002b
LA 2BFC 10%	M	P & HAD	Adult >PND 90	Apomorphine Agonist, Antagonist 7-OH-DPAT Agonist	Systemic	D1R, D2R HTR2, AlphaRs D3R, HTRs	Apomorphine and 7-OH-DPAT reduced intake in Ps and HADs	Russell et al., 1996
24h 2BFC 10%	M	P	Adult >PND 90	7-OH-DPAT Agonist	Systemic	D3R, HTRs	7-OH-DPAT reduced intake	Mason et al., 1997
24h 2BFC 10%	?	P	Adult >PND 90	GBR 12909 Antagonist Amphetamine DAT modulator Homocryptine- Agonist Ro 15-4513 Inverse agonist	Systemic	D2R DAT D2R GABRA-BDZ complex	All DA modulators and Ro 15-4513 reduced intake	McBride et al., 1990
LA OFC 10%		P	Adult >PND 90	SCH 23390 Antagonist Eticlopride Antagonist Naltrexone Antagonist	BNST	D1R D2R MOR, DOR, KOR	SCH23390 reduced responding but nonspecifically; Eticlopride and naltrexone did not alter responding	Eiler et al., 2003

LA OFC 10%	M&F	P	Adult >PND 90	Eticlopride Antagonist SR95531 Antagonist	VTA-BNST VTA-Acb	D2R GABRAs	Eticlopride in the VTA reduced responding; SR95531 in the Acb, but not BNST, reduced responding; The combination had no effect on responding	Eiler & June, 2007
LA OFC 10%	M	Wistar	Adult >PND 90	sodium-N-acetyl-homotaurinate (Na-AOTA) calcium-bis(N-acetylhomotaurinate)- (Ca-AOTA) Partial agonists	Systemic	GABRA/GABRB GRIN, GRM1, GRM5	Ca-AOTA, but not NA-AOTA, reduced responding; Suggesting calcium salt effects of acamprosate	Spanagel et al., 2014
LA 2BFC 10%	M	AA	Adult >PND 90	ZK 91296 PAM CGS 9895 PAM Ro 15-4513 Inverse agonist Ro 19-4603 Inverse agonist Bretazenil Agonist Naloxone Antagonist	Systemic	GABRA-BDZ complex GABRA-BDZ complex GABRA-BDZ complex GABRA-BDZ complex GABRA-BDZ complex MOR, DOR, KOR	ZK 91296 and CGS 9895 modestly reduced intake; Ro15-4513 and Ro19-4603 reduced intake; Bretazenil modestly reduced intake; Naloxone decreased intake	Wegelius et al., 1994
LA OFC 10% 24h 2BFC 5% 24h 3BFC 5% & 20%	M	iP & AA & Fawn-Hooded	Adult >PND 90	Acamprosate Modulator	Systemic	GABA/Glu Ca2+ channel	Acamprosate decreased iP and FH responding, tolerance developed to these effects; Acamprosate decreased AA and FH intake, tolerance developed to these effects	Cowen et al., 2005a
24h 2BFC 10%	F	WHP	Adult >PND 90	Acamprosate Modulator	Systemic	GABA/Glu Ca2+ channel	Acamprosate decreased intake	Zalewska-Kaszubska et al., 2008a
LA OFC 15%	M	sP	Adult >PND 75	Baclofen Agonist Naloxone Antagonist	Systemic	GABRB MOR, DOR, KOR	Both baclofen and naloxone reduced responding; Baclofen had non-specific effects	Maccioni et al., 2005
LA OFC 15%	M	iP	Adult >PND 90	Ganaxolone Neurosteroid	Systemic	GABRA GRIN	Pregnenolone reduced responding but not activity;	Besheer et al., 2010a

				analog Pregnenolone Precursor of neurosteroids		Sigma-1R	Ganaxolone reduced responding and activity	
24h 2BFC 10%		P & Wistar	Adult >PND 90	Topiramate Modulator	Systemic	GABRA Ca^{2+} channels GRIA/GRIK	Topiramate modestly, but persistently reduced intake in P but not Wistar rats	Breslin et al., 2010
LA OFC 10%		P & Wistar	Adult >PND 90	Naloxone Antagonist Bromocriptine Agonist Methysergide Partial agonist, antagonist	Systemic	MOR, DOR, KOR D2R HTR1A HTR2B, HTR2C	Naloxone reduced responding but not preference in P; Bromocriptine reduced responding & preference in P; Naloxone and bromocriptine produced smaller reductions in Wistar; Methysergide did not affect responding in either strain	Weiss et al., 1990
24h 2BFC 10%	M	P & AA & Fawn-Hooded	Adult >PND 90	Ibogaine-indole alkaloid Agonist, partial agonist	Systemic	MOR, KOR, GRIN, HTR3, sigma1R, sigma2R	SC ibogaine altered intake; IP ibogaine reduced intake in all lines; IG ibogaine reduced intake in FH	Rezvani et al., 1995
24h 2BFC 3-30%	M	HAD	Adult >PND 90	Naltrexone Antagonist Amperozide Antagonist	Systemic	MOR, DOR, KOR HTR2A	Dose-dependent reductions in intake by both amperozide and naltrexone	Lankford & Myers 1996
LA OFC 10%	M	Wistar	Adult >PND 90	Naltrexone Antagonist Fluoxetine Blocker	Systemic	MOR, DOR, KOR; 5HT-transporter (SERT)	Naltrexone and fluoxetine reduced responding	Le et al., 1999
24h 2BFC 10%		P & HAD & Fawn-Hooded	Adult >PND 90	Naltrexone antagonist Fluoxetine inhibitor TA-0910 Agonist	Systemic	MOR, DOR, KOR SERT TRH R	Low doses of naltrexone, fluoxetine, and TA-0910 alone did not alter intake; A combination of these compounds reduced intake	Rezvani et al., 2000
24h 2BFC 10% LA 2BFC 10%	M	AA	Adult >PND 180	6-OHDA lesions of dorsal & ventral Striatum Naltrexone Antagonist	Systemic	Catechol-aminergic nerve terminals MOR, DOR, KOR	Naltrexone reduced 24h and LA intake in both the 6-OHDA–treated and the control groups	Koistinen et al., 2001

24h 2BFC 10%	M	sP	Adult >PND 90	Morphine Agonist Naloxone Antagonist SR 141716 Antagonist	Systemic	MOR, DOR, KOR CB1R	Low dose morphine increased drinking; high dose decreased drinking; naloxone blocked morphine's effects; SR 141716 was only effective against low dose morphine	Vacca et al., 2002a
LA OFC 10%	M&F	P & HAD1	Adult >PND 90	Naltrexone Antagonist betaCCt, mixed BDZ agonist–antagonist	CeA CPU	MOR, DOR, KOR GABRA1-BDZ complex	betaCCt and naltrexone in the CeA reduced responding; whereas betaCCt and naltrexone in the CPU did not alter responding	Foster et al., 2004
LA OFC 10%	M	sP	Adult >PND 90	DTG Agonist BD-1063 Antagonist	Systemic	Sigma1R, GRIN Sigma1R, GRIN	DTG increased fixed and progressive ratio BACs; BD-1063 blocked the effects of DTG	Sabino et al., 2011
LA OFC 10%	M	sP & Wistar	Adult >PND 90	BD-1063 Antagonist	Systemic	Sigma1R, GRIN	BD-1063 dose dependently reduced responding by sP and Wistars	Sabino et al., 2009a
24h 2BFC 10%	M	sP	Adult >PND 90	NE-100 Antagonist	Systemic	Sigma1R, GRIN	NE-100 dose-dependently reduced intake	Sabino et al., 2009b
24h 2BFC 8%	M	sP	Adult >PND 90	Ritanserin Antagonist Risperidone Mixed antagonist	Systemic	HTR2 HTR1C/D2R	Risperidone, but not ritanserin, dose-dependently reduced preference	Panocka et al., 1993b
LA 2BFC 10%	M	AA	Adult >PND 90	Risperidone Antagonist	Systemic	D1R, D2R, HTR2C	Risperidone reduced intake	Ingman et al., 2003a
24h 2BFC 10%	M	P	Adult >PND 90	Fluoxetine Inhibitor Fluvoxamine Inhibitor Desipramine Inhibitor	Systemic	SERT SERT SERT/NET	Fluoxetine, fluvoxamine and desipramine reduced intake	Murphy et al., 1985
LA 2BFC 10%	M	P	Adult >PND 90	Fluoxetine Inhibitor Desipramine Inhibitor Ro 15-4513 Partial inverse	Systemic	SERT SERT/NET GABRA-BDZ complex	Fluoxetine, desipramine, and Ro15-4513 reduced intake; Ro15-1788 did not alter intake;	McBride et al., 1988

				agonist Ro 15-1788 Antagonist		GABRA-BDZ complex	Ro15-1788 blocked Ro15-4513's effects	
24h 2BFC 10%	?	P & HAD	Adult >PND 90	Fluoxetine Inhibitor Fenfluramine Reverser D,L-5-hydroxy-tryptophan Agonist 8-OH DPAT Agonist TFMPP Agonist DOI Agonist GBR 12909 Inhibitor Amphetamine Reverser Bromocryptine Agonist	Systemic	SERT SERT HTRs HTR1A HTR1A HTR2 DAT DAT D2R	5-HT and DA agents reduced intake in both P and HADs	McBride et al., 1990
24h 2BFC 3%	M	sP, Wistar	Adult >PND 90	Risperidone Antagonist Ritanserin Antagonist Haloperidol Antagonist	Systemic	HTR2/D2R HTR1C D2R	Risperidone, ritanserin, and haloperidol reduced preference; Only lowest dose of risperidone reduced intake	Panocka et al., 1993a, 1993b, 1993c
LA 2BFC 10%	M	AA	Adult >PND 90	Deramciclane Antagonist Midazolam Agonist	Systemic	HTR2 GABRA-BDZ complex	Deramciclane did not alter intake; Midazolam increased intake	Ingman et al., 2004
24h 2BFC 10%	M	P & Wistar	Adult >PND 90	Ondansetron Antagonist Topiramate Modulator	Systemic	HT3R GABA/Glu	Topiramate modestly but persistently decreased intake alone and in combination with ondansetron	Lynch et al., 2011
LA OFC 10%	M	P & NP	Adult >PND 90	DOV 102,677 (DOV) Uptake inhibitor	Systemic	SERT, NET, DAT	DOV reduced responding	Yang et al., 2012

24h 2BFC 10%	M	P	Adult >PND 90	TA-0910 Agonist 7-OH-DPAT Antagonist R(+)-SCH23390 Antagonist s(-)-eticlopride Antagonist	Systemic	TRHR D3R D1R D2R	TA-0910 reduced intake; 7-OH-DPAT reduced intake; SCH23390 modestly reduced intake; Eticlopride reduced intake; Eticlopride, but not SCH23390 or 7-OH-DPAT, reduced TA-0910's effects	Mason et al., 1997
24h 2BFC 10%	M	P	Adult >PND 90	TA-0910 Agonist Bromocriptine Agonist	Systemic	TRHR D2R	TA-0910 reduced intake with tolerance to these effects; TA-0910 reduced bromocriptine's effects	Mason et al., 1994
LA 3BFC 15%, 30% 24h 3BFC 15%, 30%	M&F	P & HAD1	Adult >PND 90	Rolipram Inhibitor Ro 20-1724- Inhibitor *Il-22ra2* shRNA lentivirus	Systemic AcbShell	Phosphodie-sterase-4 (PDE4) Interleukin 22 R alpha2 gene	Rolipram and Ro20-1724 reduced intake in both lines; Il22ra2 knockdown in AcbSh reduced intake in P	Franklin et al., 2015b
24h 2BFC 10%	M	iP	Adult >PND 90	Carisbamate Inhibitor Naltrexone Antagonist	Systemic	VGSCs for Glu activity MOR, DOR, KOR	Carisbamate selectively reduced intake and was more effective than naltrexone	Rezvani et al., 2009

NP = Alcohol-Non-Preferring rat line; LAD = Low Alcohol Drinking (LAD1 and LAD2) rat lines; sNP = Sardinian Alcohol-Non-Preferring rat line; ANA = ALKO Alcohol-Non-Accepting rat line; iP = Inbred P; HPA = Hypothalamic Pituitary-Adrenal axis; GABRA-BDZ = GABA-A Receptor—Benzodiazepine Receptor complex; sc = subcutaneous; ip = intraperitoneal; CPU = Caudate Putamen; Grm2/3 = Glutamate Metabotropic Receptor 2/3; pAKT = also called Protein Kinase B (PKB); xCT = Cystine/Glutamate Antiporter; ICV = Intra-Cerebro-Ventricular admission; BLA = Basolateral Amygdala; SERT = Serotonin Transporter; NET = Norepinephrine Transporter; DAT = Dopamine Transporter; TRH = Thyrotrophin Releasing Hormone; BNST = Bed Nucleus Stria Terminalis; GRIA = Glutamate Ionotropic Receptor-AMPA (quisqualate) subtype; GRIK = Glutamate Ionotropic Receptor-Kainate subtype. See Tables 1 through 4 for other abbreviations.

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

Ethanol Access Procedures	Sex	Line	Age	Drug	Region	Molecular Target	Findings	Citations
24h 2BFC 10%	M&F	AA	Adult >PND 90	Ethanol re-exposure			Absence of alcohol deprivation effect (ADE) after long-term deprivation interval	Hilakivi et al., 1984
24h 2BFC 10%	?	AA	Adult >PND 300	Ethanol re-exposure			Re-exposure did not lead to ADE	Sinclair & Tiihonen 1988
24h 2BFC ?%	?	AA	Adult PND?	Ethanol re-exposure			Re-exposure led to ADE after 12h and 24h, but not longer, deprivations	Sinclair and Li, 1989
LA OFC 10% 24h 2BFC 10%	M	Wistar	Adult >PND 90	Ethanol re-instatement Ethanol re-exposure			Re-instatement led to ADE after 5, 7, 14, 28 days deprivation; Re-exposure led to ADE after 5 days	Heyser et al., 1997
LA OFC 15% 24h 2BFC 10%	M&F	P	Adult >PND 75 Juvenile >PND 22	Ethanol re-instatement Ethanol re-exposure			ADE expressed after extended deprivation following ethanol after juvenile or adult initiation	McKinzie et al., 1998
24h 4BFC 5%, 10%, 20%	M	Wistar	Adult ?PND	Ethanol re-exposure			Repeated short-term deprivations increased ADE	Holter et al. 1998
24h 2BFC 10%	M	sP	Adult >PND 75	Ethanol re-exposure			Absence of ADE during initial 24h of re-exposure after 3 to 30 days of deprivation	Agabio et al., 2000
Vapor exposure then LA OFC 10%	M	Wistars	Adult > PND 90	Ethanol re-instatement			Increased responding after re-instatement; Increased responding remained elevated for 4-8 weeks	Roberts et al., 2000
24h 2BFC 10%	F	P	Adult >PND 90	Ethanol re-exposure			Single concentration (10%) induced ADE and there was prolonged expression for 4 consecutive days	Rodd-Henricks et al., 2000a
24h 2BFC 10%	M	HAD1 & HAD2	Adult >PND 90	Ethanol re-exposure			Only repeated cycles of deprivation resulted in ADE	Rodd-Henricks et al., 2000b
24h 4BFC 10%, 20%, 30%	F	P	Adult >PND 90	Ethanol re-exposure			Multiple concentrations increased ADE over 10% only; induced ADE with higher ethanol intakes there was prolonged expression for 6 consecutive days.	Rodd-Henricks et al., 2001
24h 2BFC 15% LA OFC 15%	F	P	Adolescent PND 30-60 Adult >PND 75	After pre-exposure Ethanol re-instatement			Expression of ADE during reacquisition in adulthood	Rodd-Henricks et al., 2002a
24h 2BFC 15%	F	P	Adult PND 75-	After pre-			Absence of ADE during	Rodd-Henricks

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LA OFC 15%			105 ≥PND 135	exposure Ethanol re-instatement			reacquisition in adulthood	et al., 2002b
LA OFC 15%	M	P	Adult >PND 90	Ethanol re-instatement			Repeated deprivations increased both the magnitude and duration of the ADE	Rodd et al., 2003
24h 4BFC 10%, 20%, 30%		sP	Adult >PND 75	Ethanol re-exposure			Modest acute ADE during re-exposure	Serra et al., 2003
24h 3BFC 5%, 20%	M	P, HAD, AA, Wistar	Adult >PND 90	Ethanol re-exposure	Swim stress Foot shock induced relapse		Wistar, but not selected, rats increased relapse after swim stress; All lines increased relapse after foot shock	Vengeliene et al., 2003
24h 3BFC 5%, 20%	F	Wistar	Adolescent PND 31 Adult PND 71	Initiation Initiation Ethanol re-exposure	Swim stress-induced relapse		Relapse drinking similar in both groups; Repeated swim stress increased relapse modestly; Foot-shock increased relapse to a greater extent than swim stress, in the adolescents	Siegmund et al., 2005
24h 2BFC 15%	F	P	Adult >PND 90	Ethanol re-exposure	pVTA		Repeated deprivations increased reinforcing effects within pVTA	Rodd et al., 2005
LA OFC 15%	M	HAD1 & HAD2	Adult >PND 90	Ethanol re-instatement			Repeated deprivations increased both the magnitude and duration of the ADE.	Oster et al., 2006
LA OFC 10%	M	sP	Adult >PND 90	Ethanol re-instatement			Ethanol-associated (+) stimuli increased reinstatement responding	Maccioni et al., 2007b
24h 4BFC 10%, 20%, 30% 4 cycles of 4 days of deprivation X 4 days of re-exposure	M	P & HAD1 & HAD2	Adult >PND 75	Ethanol re-exposure			HAD rats expressed 24h ADE after short access and deprivation intervals; P rats displayed a modest 24h ADE under the same conditions	Bell et al., 2008a
LA OFC 10%, 20%, 30%	M	HAD-1 & HAD-2	Adult >PND 90	Ethanol re-instatement	Multiple deprivations		Multiple deprivations increased responding/ reinforcement; Shifted preference to higher concentrations; Prolonged the duration of the ADE up to 5 days	Rodd et al., 2009

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

24h 4BFC 5%, 10%, 20% 3BFC 6%, 16%	M	Wistar	Emerging Adulthood >PND 60	Ethanol re-exposure			Repeated deprivations produced compulsive-like drinking behavior during relapse	Vengeliene et al., 2014
Adrenergic and Mixed								
LA OFC 10% Appetitive vs Consummatory responding	M	P & HAD2	Adult >PND 90	Yohimbine Antagonist	Systemic	Alpha1Rs, Alpha2Rs	Yohimbine enhanced reinstatement responding	Bertholomey et al., 2013
LA 2BFC 10%	M	P	Adult >PND 70	Prazosin Antagonist Propranolol Antagonist	Systemic	Alpha1R BetaR	Prazosin + propranolol reduced relapse drinking	Rasmussen et al., 2014
24h 3BFC 15%, 30%		P	Adult >PND 70	Prazosin Antagonist	Systemic	Alpha1R	Prazosin prevented the expression of an ADE	Froehlich et al., 2015
LA 2BFC 10%	M	P	Adult >PND 70	Prazosin Antagonist Naltrexone Antagonist	Systemic	Alpha-1R MOR, DOR, KOR	Prazosin + naltrexone reduced relapse drinking	Rasmussen et al., 2015
Cannabinoid								
2BFC 10%	M	sP	Adult >PND75	SR147778 Antagonist	Systemic	CB1R	SR147778 reduced relapse drinking	Gessa et al., 2005
LA OFC 15%	F	P	Adult >PND 90	SR141716A Antagonist CP 55,940 Agonist	Systemic	CB1R CB1R	SR transiently reduced relapse responding ; CP increased relapse responding	Getachew et al., 2011
Cholinergic								
24h 2BFC 10%	M	P	Adult >PND 75	Sazetidine-A Partial agonist	Systemic	a4b2 containing nAChRs	Sazetidine-A and naltrexone reduced relapse drinking	Rezvani et al., 2010
LA OFC 15%	F	P	Adult >PND 90	Nicotine Agonist	Systemic	nAChRs	Nicotine time-dependently enhanced relapse drinking	Hauser et al., 2012a
Corticotropin								
24h 2BFC 10%	M	P	Adult >PND 90	CP154,526 Antagonist CRA1000 Antagonist	Systemic	CRF1 CRF1	Both CP and CRA reduced relapse drinking	Overstreet et al., 2007
Dopaminergic and Mixed								
24h 3BFC 5%, 20%	M	P & HAD	Adult >PND 90	BP 897 Partial agonist SB-277011-A Antagonist	Systemic	D3R	BP 897 and SB-277011-A reduced relapse drinking	Vengeliene et al., 2006
24h 2BFC 10%	M	P	Adult >PND 90	Haloperidol	Systemic	D2R, D3R,	Haloperidol and olanzapine	Overstreet et al.,

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

				Inverse agonist, Agonist, Antagonist Olanzapine Antagonist Inverse agonist		D4R Sigma2R, HTR1A HTR2, HTR7, alpha1, alpha2 HTR3, HTR6, HTR7, alpha1, alpha2, mAChR, D1R, D2R HTR2, H1	reduced relapse drinking	2007
LA OFC 15%	F	P	Adult >PND 90	Cocaine Modulator	Systemic	SERT, DAT, NET	Cocaine enhanced relapse responding if administered 30 min or 4h prior to test session	Hauser et al., 2014b
GABAergic								
24h 2BFC 10%	M	P	Adult >PND 90	Flumazenil Antagonist	Systemic	GABRA-BDZ complex	Flumazenil reduced relapse drinking	Overstreet et al., 2007
Glutamatergic and Mixed								
24h 4BFC 5%, 10%, 20%	M	Wistar	Adult >PND 90	MPEP antagonist	Systemic	GRM5	MPEP reduced relapse drinking following repeated alcohol deprivations	Backstrom et al., 2004
24h 4BFC 5%, 10%, 20%	M	Wistar	Emerging Adulthood >PND 60	CGP37849 Competitive antagonist L-701.324 Antagonist Ifenprodil Antagonist Neramexane Antagonist	Systemic	NMDAR Glycine binding site GRIN2B GRIN, nAChR	CGP37849, L-701.324, ifenprodil and neramexane reduced relapse drinking	Vengeliene et al., 2005
LA OFC 10%	M	P	Adult >PND 90	MPEP Antagonist LY-341495 Antagonist CPCCOEt Antagonist	Systemic	GRM5 GRM2/3 GRM1	MPEP reduced relapse responding	Schroeder et al., 2005a
LA OFC 15%	F	P	Adult >PND 90	LY404039 agonist	Systemic	GRM2/3	LY404039 reduced relapse responding	Rodd et al., 2006
LA OFC 10%	M	Wistar	Adult	GYKI 52466 Antagonist	Systemic	AMPAR	GYKI 52466 dose-dependently reduced relapse responding	Sanchis-Segura et al., 2006
LA OFC 10%	M	Wistar	Adult > PND 60	Lamotrigine Inhibitor	Systemic	Na+ Channel control glutamate activity	Lamotrigine reduced relapse responding	Vengeliene et al., 2007

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

LA OFC 10%	M	P	Adult >PND 90	MPEP Antagonist	Systemic	GRM5	MPEP reduced relapse responding	Schroeder et al., 2008
24h 3BFC 15%, 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GTL1 (EAAT2)	Ceftriaxone reduced relapse drinking; Associated with upregulation of GLT1 in AcbCo and PFC	Qrunfleh et al., 2013
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	Ethanol reduced pAKT in Acb; CEF increased GLT1a, GLT1b and xCT in Acb and PFC as well as pAKT in Acb; CEF reduced intake	Alhaddad et al., 2014a
24h 3BFC 15% & 30%	M	P	Adult >PND 90	Ceftriaxone Up-regulator	Systemic	GLT1 (EAAT2)	CEF interfered with relapse intake when given during abstinence	Rao & Sari, 2014a
LA OFC 10%	M	Wistar	Adult >PND 90	Ro61-8048 kynurenine-3-monooxy-genase (KMO) Inhibitor	Systemic	GRIN2B	Ro61-8048 reduced relapse responding	Vengeliene et al., 2016a
LA OFC 10%	M	Wistar	Emerging Adulthood >PND 60	Memantine Antagonist	Systemic	NMDAR	Memantine reduced relapse responding	Vengeliene et al., 2015b
LA OFC 10 %	M	Wistar	Adult >PND 90	sodium-N-acetylhomotaurinate Na-AOTA calcium-bis(N-acetylhomotaurinate) Ca-AOTA	Systemic		Ca-AOTA, but not Na-AOTA, reduced relapse drinking, suggesting a role for calcium salts in acamprosate formulations	Spanagel et al., 2014
2BFC 10%	M	Wistar	Adult >PND 90	Org25935 Transporter inhibitor Acamprosate	Systemic	GlyT1 GlyT2 GABA/Glu Ca+	Org25935 reduced compulsive relapse drinking without tolerance to this effect; Acamprosate reduced compulsive relapse drinking	Vengeliene et al., 2010
3BFC 5%, 20%	F	Wistar	Adolescent PND 31 Adult PND 71	Acamprosate	Systemic	GABA/Glu Ca+	No differences in baseline drinking between rats initiating in adolescence vs adulthood; Relapse-like drinking was only seen in the adult initiators; Acamprosate also reduced relapse drinking in this group	Füllgrabe et al., 2007
4BFC 5%, 10%, 20% (ADE)	?	Wistar	Adult Long-term	A-705253 Calpain-	Systemic	NMDAR	The calpain inhibitor reduced relapse	Vengeliene et al., 2016b

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

LA OFC 5-10%			access	associated Modulator				
Opioid and Mixed								
LA 2BFC LA 10%		P	Adult	Naloxone antagonist	Systemic	MOR, DOR, KOR	Naloxone dose-dependently reduced relapse drinking	Badia-Elder et al., 1999
24h 2BFC 10%	M	P	Adult	Naltrexone antagonist	Systemic	MOR, DOR, KOR	Naltrexone reduced relapse drinking	Rezvani et al., 2010
LA OFC 15%	F	P	Adult	JDTic Antagonist	Systemic	KOR	JDTic reduced relapse responding	Deehan et al., 2012
LA OFC 15%	F	P	Adult >PND 90	Naltrexone Antagonist LY255582 Antagonist	Systemic	MOR, DOR, KOR MOR	Both Naltrexone and LY reduced relapse responding	Dhaher et al., 2012b
24h 2BFC 10%	M	sP	Adult	NE-100 antagonist	Systemic	Sigma OR	NE-100 prevented increases in relapse drinking	Sabino et al., 2009b
LA OFC 10%	M	Wistar	Adult >PND 90	Naltrexone Acamprosate	Systemic	MOR, DOR, KOR GABA/Glu Ca+	Chronic administration of naltrexone and the combination of naltrexone + acamprosate reduced relapse responding	Heyser et al., 2003
Peptidergic								
LA OFC 10%	M	Wistar	Adult >PND 60	Melatonin Agomelatine Mixed Agonist/ Antagonist SB242084 Antagonist	Systemic	MT1R MT2R HTR2C	Melatonin, agomelatine, and SB24208 reduced relapse drinking.	Vengeliene et al., 2015a
24h 2BFC 8%	F	P	Adult	NPY Agonist	ICV	NPY YRs	NPY reduced relapse drinking; Reduced continuous access drinking to a lesser extent	Gilpin et al., 2003
24h 2BFC 15%	F	P	Adult	NPY Agonist	CeA	NPY YRs	NPY in CeA reduced relapse, but not uninterrupted, drinking	Gilpin et al., 2008
LA OFC 10%	F	P	Adult	NPY Agonist	ICV	NPY YRs	NPY ICV decreased relapse responding	Bertholomey et al., 2011
LA OFC 15%	F	P	Adult >PND 90	SB-334867 Antagonist	Systemic	OX1R	SD-334867 reduced relapse responding	Dhaher et al., 2010
Serotoninergic and Mixed								
24h 2BFC 15%	M	P	Adult >PND 90	MDL 72222-Antagonist ICS205-930-Antagonist	Systemic	HTR3	Reduced relapse drinking.	Rodd-Henricks et al., 2000a
24h 2BFC 10%	M	P	Adult >PND 90	Buspirone	Systemic	HTR1A, HTR2C	Buspirone and SB242084	Overstreet et al.,

Table 6. Rat Studies on Relapse Behavior (ADE) of Alcohol Intake and Its Pharmacological Disruption.

				Partial agonist SB242,084 Antagonist			reduced relapse drinking	2007
24h 2BFC 10%	M	P & Wistar	Adult >PND 90	Ondansetron Antagonist Topiramate Modulator	Systemic	HTR3 GABRAs, GRIA, GRIK, carbonic anhydrase	Both ondansetron alone and in combination with topiramate blocked relapse drinking; Topiramate reduced relapse drinking but to a lesser extent than the combination	Lynch et al., 2011
Other								
24h 2BFC 10%	M	Fawn-Hooded, Long-Evans, & iP	Adult >PND 90	CVT-10216 Inhibitor	Systemic	ALDH2	CVT-10216 reduced relapse drinking in Fawn-Hooded rats	Arolfo et al., 2009
LA 2BFC 15%	M	P & HAD1	Adult >PND 75	Ibudilast Inhibitor	Systemic	PDE4	Ibudilast reduced relapse drinking in both lines	Bell et al., 2015

GlyT = Glycine Transporter; MTR = Melatonin Receptor; OXR = Orexin Receptor. See Tables 1 through 5 for other abbreviations.

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

Ethanol Access Procedures	Sex	Line	Age	Drug	Region	Molecular Target	Findings	Citation
LA OFC 10% Appetitive vs Consummatory responding	M	P, HAD1, & HAD2	Adult >PND 90				P > HAD1 > HAD2 for responding and operant seeking behavior	Czachowski & Samson, 2002
24h 2BFC 15% LA OFC 15% PSR	F	P	Adolescent PND 30-60 Adult 30 days after	Pre-exposure Re-instatement			Adolescent pre-exposure interfered with extinction; Adolescent pre-exposure enhanced and prolonged operant seeking behavior	Rodd-Henricks et al., 2002a
24h 2BFC 15% LA OFC 15% PSR	F	P	Adult PND 75-105 Adult 30 days after	Pre-exposure Re-instatement			Adult pre-exposure did not affect extinction; Adult pre-exposure did not affect seeking behavior; A discriminative odor stimulus (+) enhanced operant seeking behavior; 2 ml 15% ethanol bottle enhanced seeking behavior	Rodd-Henricks et al., 2002b
LA OFC 10%	M	sP	Adult >PND 90				Orosensory properties of ethanol (+ stimulus) leads to operant seeking behavior	Maccioni et al., 2007a
LA OFC 10% Appetitive vs Consummatory responding	M	P, HAD2, & Long- Evans	Adult >PND 90				Only P rats displayed increased levels of operant delay discounting (a measure of seeking behavior)	Beckwith & Czachowski, 2014
Adrenergic								
LA OFC 10% Appetitive vs Consummatory responding	M	P & HAD2	Adult >PND 90	Yohimbine Antagonist	Systemic	Alpha1Rs, Alpha2Rs	Yohimbine enhanced operant seeking in both lines.	Bertholomey et al., 2013
Cannabinoid and Mixed								
LA OFC 10%	M	Wistar & msP	Adult >PND 90	SR141716A- Antagonist	Systemic	CB1R	SR141716A reduced seeking behavior	Cippitelli et al., 2005
LA OFC 10%		iP	Adult >PND 90	SR141716A Antagonist MTEP Antagonist SCH58261 Antagonist	Systemic	CB1R Grm5 adenosine 2A	SR141716A with MTEP reduced cue-conditioned seeking; SR141716A with SCH58261 did not alter cue-conditioned seeking	Adams et al., 2010
LA OFC 15% PSR	F	P	Adult >PND 90	SR141716A- antagonist CP 55, 940- agonist	Systemic	CB1R	The CB1R antagonist reduced seeking; The CB1R agonist increased seeking	Getachew et al., 2011
Cholinergic and Mixed								

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

2BFC 12% LA OFC 12%	M	Long- Evans	Adult PND?	Nicotine Agonist	Systemic	nAChRs	Nicotine increased seeking behavior	Le et al., 2003
LA OFC 15% PSR	F	P	Adult >PND 90	Ethanol + Nicotine			Readily displayed ethanol + nicotine seeking behavior	Hauser et al., 2012a
LA OFC 15% PSR	F	P	Adult >PND 90	Nicotine Agonist	Systemic	nAChRs	Nicotine enhanced seeking behavior	Hauser et al., 2012b
LA OFC 15% PSR	F	P	Adult >PND 90	Nicotine Agonist Mecamylamine Antagonist	pVTA	nAChRs	Nicotine enhanced ethanol-seeking behavior; Mecamylamine attenuated nicotine's effects	Hauser et al., 2014a
Corticotrophin								
2BFC 12% LA OFC 12%	M	Wistar	Adult >PND 90	CP-154,526 Antagonist d-phe-CRF Antagonist	ICV	CRF	d-Phe-CRF and CP-154,526, attenuated stress-induced seeking	Le et al., 2000
Dopaminergic and Mixed								
LA OFC 10% Appetitive vs Consummatory responding	M	Long-Evans	Adult >PND 90	Raclopride Antagonist	Systemic	D2R	Raclopride reduced seeking at the low and high dose, but not intermediate, dose; Raclopride also reduced drinking	Czachowski et al., 2001a
24h 3BFC 5%, 20%	M	P & HAD	Adult >PND 90	BP 897 Partial agonist SB-277011-A Antagonist	Systemic	D3R	BP 897 and SB-277011-A reduced seeking behavior	Vengeliene et al., 2006
LA OFC 15% PSR	F	P	Adult >PND 90	SCH23390 Antagonist A-77636 Agonist	AcbSh, AcbCo	D1R	SCH reduced seeking; A-77636 increased seeking in AcbSh, but not the AcbCo	Hauser et al., 2015
LA OFC 15% PSR	F	P	Adult >PND 90	Quinpirole Agonist Ethanol	pVTA	D2R	Quinpirole microinjected into the pVTA reduced seeking; Quinpirole blocked ethanol-induced enhancement of seeking	Hauser et al., 2011
LA OFC 15% PSR	F	P	Adult >PND 90	Cocaine Reverser	Systemic	SERT, NET, DAT	Cocaine dose-dependently increased seeking behavior	Hauser et al., 2014b
GABAergic and Mixed								
LA OFC 10%	M	P	Adult >PND 90	3-propoxy-beta-carboline	VP Acb	GABRA1-BDZ complex	3-PBC in the anterior and medial VP produced marked	Harvey et al., 2002

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

				hydrochloride (3-PBC) Mixed agonist-antagonist	CPU		reductions in alcohol-maintained responding in a genetically selected rodent model of alcohol drinking	
LA OFC 10%	M	sP	Adult >PND 90	Baclofen Agonist	Systemic	GABRB	Baclofen reduced seeking behavior	Maccioni et al., 2008a
LA OFC 10%	M	sP	Adult >PND 75	GS39783 PAM Baclofen Agonist	Systemic	GABRB	Baclofen non-specifically reduced operant breakpoint; GS39783 reduced operant breakpoint	Maccioni et al., 2008b
LA OFC 10% Appetitive vs Consummatory behavior	M	sP	Adult >PND 60	GS39783 PAM	Systemic	GABRB	GS39783 inhibited both seeking and intake behavior	Maccioni et al., 2010b
Glutamatergic and Mixed								
LA OFC 10% Appetitive vs Consummatory responding	M	Long Evans	Adult >PND 90	Acamprosate Modulator	Systemic	GABA/Glu Ca+ channel	Acamprosate decreased intake but not seeking behavior	Czachowski et al., 2001b
LA OFC 10%	M	Long-Evans	Adult >PND 90	MPEP Antagonist	Systemic	GRM5	MPEP reduced cue-induced operant seeking behavior	Backstrom et al., 2004
LA OFC 10%	M	Long-Evans	Adult >PND 90	MK-801 Antagonist CGP39551 Antagonist L-701,324 Antagonist CNQX Antagonist	Systemic	GRIN GRIN GRIA/GRIK	L-701,324 and CNQX reduced cue-induced operant seeking behavior	Backstrom & Hyytia, 2004
LA OFC 10%	M	Long-Evans	Adult >PND 90	LY379268 Agonist (S)-3,4-DCPG [(S)-3,4-dicar-boxyphenyl-glycine] Agonist	Systemic	GRM 2/3 GRM8	Both compounds reduced operant seeking behavior	Backstrom & Hyytia, 2005
LA OFC 10%	M	Wistar	Adult >PND 90	Acamprosate Modulator Neramexane Antagonist	Systemic	GABA/Glu NMDAR	Acamprosate dose-dependently reduced (+) cue-induced seeking; Acamprosate did not affect (-) cue-induced seeking; The high dose of neramexane	Bachteler et al., 2005

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

							reduced acamprosate-induced (+) and (-) cue-induced seeking	
LA OFC 10%	M	sP	Adult >PND 90	MTEP Antagonist	Systemic	GRM5	MTEP reduced operant seeking behavior	Cowen et al., 2005b
LA OFC 10%	M	Wistar	Adult >PND 60	GYKI 52466 Antagonist	Systemic	AMPAR	GYKI 52466 dose-dependently reduced cue-induced operant seeking	Sanchis-Segura et al., 2006
LA OFC 15% PSR	M	P	Adult >PND 90	LY404039 Agonist	Systemic	GRM 2/3	LY404039 reduced operant seeking behavior	Rodd et al., 2006
LA OFC 10%	M	Wistar	Adult >PND 60	Lamotrigine, Inhibitor of voltage-gated Na+ channel	Systemic	Na+ channel control	Lamotrigine reduced seeking and relapse intake	Vengeliene et al., 2007
LA OFC 10%	M	P	Adult >PND 90	MPEP Antagonist	Systemic	GRM5	MPEP reduced cue-induced operant seeking behavior and pERK1/2 in AcbSh and BLA	Schroeder et al., 2008
LA OFC 10%	M	Wistar	Adult >PND 60	Anisomycin - protein synthesis inhibitor MK-801 Antagonist Acamprosate Modulator	Systemic ICV	NMDAR GABA/Glu Ca+	Anisomycin and MK-801 reduced cue-induced seeking behavior; Suggesting that memory reconsolidation disruption by these compounds; Acamprosate had no effect	von der Goltz et al., 2009
LA OFC 15%	M	iP	Adult >PND 90	Aniracetam Agonist, 6,7-dinitro-quinoxaline-2,3-dione Antagonist	Systemic	GRIA	Aniracetam potentiated cue-induced operant seeking; Aniracetam's effects were reversed by the antagonist	Cannady et al., 2013
LA OFC 10%	M	Wistar	Adult >PND 90	sodium-N-acetylhomotauri-nate (Na-AOTA) calcium-bis(N-acetylhomotauri-nate) (Ca-AOTA)	Systemic		Ca-AOTA, but not Na-AOTA, reduced seeking behavior; Suggesting calcium salts of acamprosate modulate its effects	Spanagel et al., 2014
LA OFC 10%	M	Wistar	Adult >PND 60	Memantine Antagonist	Systemic	NMDAR	Memantine reduced operant seeking behavior	Vengeliene et al., 2015b

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

LA OFC 10%	M	Wistar	Adult >PND 90	Ro61-8048-Inhibitor kynurenine-3-monooxygen-ase (KMO)	Systemic	NMDAR	Ro61-8048 reduced operant seeking behavior	Vengeliene et al., 2016a
Neuropeptide Y, Nociceptin/Orphanin, Neurokinin								
LA OFC 10% Appetitive vs Consummatory responding	M	msP	Adult >PND 90	N/OFQ Agonist	ICV	Nociceptin/ orphanin FQ N/OFQ & NOPR	N/OFQ reduced cue-induced operant seeking behavior	Ciccocioppo et al., 2004
LA OFC 10% Appetitive vs Consummatory responding	F	P	Adult >PND 90	NPY Agonist	ICV	NPYRs	NPY decreased operant seeking responding	Bertholomey et al., 2011
LA OFC 10%	M	Wistar	Adult >PND 90	JNJ-31020028 Antagonist	Systemic	NPY Y2R	JNJ altered stress-induced operant seeking behavior	Cippitelli et al., 2011
LA OFC 10%	M	Wistar	Adult >PND 90	L822429 Antagonist	Systemic	NK1R	L822429 reduced yohimbine (stress)-induced seeking	Schank et al., 2014
Opioid								
LA OFC 10%	M	Wistar	Adult >PND 90	Priming dose of ethanol Naltrexone Antagonist Fluoxetine Antagonist	Systemic	 MOR, DOR, KOR SERT	Naltrexone blocked ethanol-, but not stress-, induced operant seeking behavior; Fluoxetine blocked stress-induced more specifically than ethanol-induced operant reinstatement	Le et al., 1999
LA OFC 10%	M	P	Adult >PND 90	Naltrexone Antagonist Naltrindole Antagonist Naloxonazine Antagonist	Systemic	MOR, DOR, KOR DOR MOR	Naltrexone, naltrindole, and naloxonazine inhibited operant seeking behavior; Naloxonazine had non-selective behavioral suppression	Ciccocioppo et al., 2002
LA OFC 10%	M	Long-Evans	Adult >PND 90	Naltrexone Antagonist	Systemic	MOR, DOR, KOR	Naltrexone reduced cue-induced operant seeking	Backstrom & Hyytia, 2004
LA OFC 15% PSR	F	P	Adult >PND 90	JDTic Antagonist	Systemic	KOR	JDTic dose-dependently reduced operant seeking	Deehan et al., 2012
LA OFC 15% PSR	F	P	Adult >PND 90	Naltrexone Antagonist LY255582 Antagonist	Systemic	MOR, DOR, KOR MOR, DOR, KOR	Both Naltrexone and LY reduced operant seeking behavior, with LY being more potent	Dhaher et al., 2012b

Table 7. Rat Studies on Alcohol-Seeking Behavior and Its Pharmacological Disruption.

LA OFC 10% Appetitive vs Consummatory responding	M	P & Long-Evans	Adult >PND 90	Naltrexone Antagonist Naltrindole Antagonist, U50,488H Agonist	Systemic	MOR, DOR, KOR DOR KOR	Naltrexone, naltrindole and U50,488H reduced intake, responding and seeking nonselectively; P rats were more sensitive to naltrindole's effects on intake and seeking	Henderson-Redmond & Czachowski, 2014
LA OFC 10% Appetitive vs Consummatory responding	M	P & NP & HAD	Adult >PND 90	Naltrexone Antagonist GSK152149 Antagonist	Systemic	MOR, DOR, KOR MOR	Naltrexone and GSK dose-dependently reduced cue-induced operant seeking, with GSK being more effective	Giuliano et al., 2015
Orexin								
LA OFC 15% PSR	F	P	Adult >PND 90	SB-334867 Antagonist	Systemic	Orexin1R	SB-334867 did not alter seeking behavior	Dhaher et al., 2010
LA OFC 10%	M	iP	Adult >PND 90	SB-334867 Antagonist	Systemic	OX1R	Cue-induced seeking occurred after immediate and protracted abstinence (5 months); SB-334867 reduced immediate and delayed cue-induced seeking as well as cue-induced c-fos expression; SB334867 disrupted progressive-ratio responding for ethanol but not sucrose	Jupp et al., 2011a, 2011b
Serotonin and Mixed								
LA OFC 15% PSR	F	P	Adult >PND 90	Nicotine Agonist Zacopride Antagonist CPBG Agonist	pVTA	HT3R nAChR	Nicotine-enhanced ethanol-seeking behavior is modulated by HTR3 in pVTA	Hauser et al., 2014a
Aldehyde dehydrogenase								
LA OFC 10%	M	iP & Long-Evans	Adult >PND 90	CVT-10216 Inhibitor		ALDH2	CVT-10216 reduced seeking behavior in iP and Long-Evans	Arolfo et al., 2009

PSR = Pavlovian Spontaneous Recovery of operant responding. See Tables 2 through 6 for other abbreviations.

Table 8. Rat Studies on Alcohol Withdrawal Behaviors and Its Pharmacological Amelioration.

Ethanol Access Procedures	Sex	Line	Age	Drug	Region	Molecular Target	Findings	Citation
Adrenergic								
24h 2BFC 10%	M	P	Adult >PND 90	Prazosin Antagonist Propranolol Antagonist	Systemic	Alpha1R Beta1R, Beta2R	Combination of prazosin and propranolol reduced intake after short withdrawal	Rasmussen et al., 2014
Dopaminergic Mixed								
24h 2BFC 10%	M	P	Adult >PND 90	Haloperidol, SB242,084 Inverse agonist, antagonist	Systemic	D2R, D3R, D4R, alpha1A, HTR2A, HTR2C GABRA-BDZ CRFR1	Haloperidol or SB242,084 failed to reduce anxiety-induced increases in ethanol intake and withdrawal-associated anxiety	Overstreet et al., 2007
GABAergic								
24h 2BFC 10%		P	Adult >PND 90	Bicuculline Competitive antagonist,	Systemic	GABRA K+ channels	Symptoms present after 6 week exposure as measured by bicuculline-induced seizures; Dependence resulted in increased intake and increased anxiety	Kampov-Polevy et al., 2000
24h 4.5% Ethanol Diet for 5 Day Cycles	M	Sprague-Dawley	Adolescent ~PND50	Flumazenil Antagonist DMCM Negative Allosteric Modulator	CeA	GABRA-BDZ complex	Flumazenil reduced withdrawal-induced anxiety; DMCM exacerbated withdrawal-induced anxiety, which was reversed by flumazenil	Knapp et al., 2007a
24h 4.5% Ethanol Diet for 5 Day Cycles	M	Sprague-Dawley	Adolescent ~PND50	Diazepam Ca2+ channel blocker Flumazenil Antagonist Baclofen Agonist	Systemic	GABRA-BDZ complex, diazepam binding site, GABRA-BDZ complex GABRB	Diazepam, flumazenil, and baclofen dose-dependently reduced withdrawal-induced anxiety and its sensitization	Knapp et al., 2007b
Opioid								
24h 2BFC 10%	M	P	Adult >PND 90	Naloxone Antagonist	Systemic	MOR, DOR, KOR	Naloxone did not alter withdrawal-induced anxiety	Overstreet et al., 2007
Serotonergic								
24h 2BFC 10%	M	P	Adult >PND 90	Buspirone Partial agonist	Systemic	HTR1A, HTR2, D3R, D4R,	Buspirone reduced withdrawal-induced anxiety;	Overstreet et al., 2007

Table 8. Rat Studies on Alcohol Withdrawal Behaviors and Its Pharmacological Amelioration.

				SB242,084 Antagonist Olanzapine Inverse agonist, antagonist		SigmaR HTR2, H1R, mAChR4/5, D2R	SB242084 did not alter withdrawal-induced anxiety; Olanzapine reduced withdrawal-induced ethanol intake and anxiety	
Peptidergic								
24h 2BFC 10%	M	P	Adult >PND 90	CP154,526 Antagonist CRA1000 Antagonist	Systemic	CRF1	CRA1000 and CP154, 526 reduced withdrawal-induced ethanol intake and anxiety	Overstreet et al., 2007
LA OFC 10%	M	Wistar	Adult >PND 90	JNJ-31020028 antagonist	Systemic	NPY Y2R	JNJ reduced withdrawal-induced anxiety	Cippitelli et al., 2011
Neuroimmune								
24h 4.5% Ethanol Diet for 5 Day Cycles	M	Sprague-Dawley	Adolescent ~PND50	LPS, IL-1-beta, MCP1, TNFalpha Agonist Flumazenil Antagonist	ICV	Cytokine-associated receptors GABRA-BDZ complex	Cytokines sensitized withdrawal-induced anxiety; Flumazenil blocked cytokine sensitization	Breese et al., 2008

See Tables 1 through 7 for abbreviations.

1) Several selectively bred rat lines serve as valid animal models of alcoholism
2) Selectively bred rat lines serve as animal models of adolescent binge drinking
3) Treatments for multiple stages of the addiction cycle have been tested in these rats
4) The role of pharmacogenetics can be evaluated in these selectively bred rat lines