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Ethanol Consumption: How Should We Measure It? Achieving Consilience between Human and Animal Phenotypes

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Abstract

There is only modest overlap in the most common alcohol consumption phenotypes measured in animal studies and those typically studied in humans. To address this issue, we identified a number of alcohol consumption phenotypes of importance to the field that have potential for consilience between human and animal models. These phenotypes can be broken down into three categories: 1) abstinence/the decision to drink or abstain; 2) the actual amount of alcohol consumed and 3) heavy drinking. A number of suggestions for human and animal researchers are made in order to address these phenotypes and enhance consilience. Laboratory studies of the decision to drink or abstain are needed in both human and animal research. In human laboratory studies, heavy or binge drinking that meets cut-offs used in epidemiological and clinical trials should be reported. Greater attention to patterns of drinking over time is needed in both animal and human studies. Individual differences pertaining to all consumption phenotypes should be addressed in animal research. Lastly, improved biomarkers need to be developed in future research for use with both humans and animals. Greater precision in estimating blood alcohol levels in the field together with consistent measurement of breath/blood alcohol levels in human laboratory and animal studies provides one means of achieving greater consilience of alcohol consumption phenotypes.

Keywords

alcohol; animal models; biomarkers; genetics; heavy drinking; human laboratory models

INTRODUCTION

Although a pattern of increasing alcohol consumption is generally acknowledged as a hallmark of alcoholism, pattern of intake is not incorporated directly into the DSM-IV criteria. Several of the DSM-IV criteria relate closely to quantity and frequency of consumption, though. Two of the criteria that are most relevant are increased tolerance and the “larger/longer” criterion in which alcohol is consumed in larger quantities and/or over a longer period of time than the

individual intends. Also highly relevant are the criteria that relate to consumption despite the experience of negative consequences (APA, 1994).

Despite the strong connection between quantity and frequency of alcohol consumption and high-risk drinking, there is only modest overlap in the most common drinking phenotypes measured in animal studies (e.g., intake and preference during 24-hr two-bottle choice tests) and those typically studied in humans (e.g., number of abstinent and heavy drinking days). Our primary goal will be to delineate the consumption phenotypes that are of greatest importance and accordingly, should be explored in both human and animal research and to identify strategies to encourage greater consilience in future research. We have organized the consumption phenotypes into three categories: 1) abstinence/the decision to drink or abstain; 2) the actual amount of alcohol consumed and 3) heavy drinking (i.e., drinking that exceeds a threshold associated with risk of harm). We begin with an overview of the relevant methods in epidemiological and clinical research, human laboratory studies and animal models, describe the consumption phenotypes typically measured in each approach, and finally provide suggestions about how to achieve greater consilience between human and animal consumption phenotypes.

I. METHODS FOR ASSESSING ALCOHOL CONSUMPTION

Clinical and epidemiological studies

Self-report questionnaires or interviews are the standard method to obtain drinking data in these studies. A number of valid and reliable methods for obtaining self-report data on alcohol consumption exist (see Del Boca and Darkes, 2003, for a review). The most straightforward are quantity/frequency measures in which participants are simply asked to report how often they typically consume alcohol, along with how many drinks they tend to consume. Findings have consistently shown that individuals tend to under-report their drinking when these methods are used (Sobell and Sobell, 1995a). An alternate “paper and pencil” measure is the Daily Drinking Questionnaire (DDQ; Collins et al., 1985), in which participants are asked to report their typical frequency and quantity of alcohol consumption on each of the seven days of the week for a given period of time. The authors reported evidence supporting the construct validity of the measure.

The “gold standard” is to obtain daily reports of alcohol drinking using either the Timeline Follow-back (TLFB; Sobell and Sobell, 2003) or Form 90 interviews (Miller and DelBoca, 1994). In the TLFB, retrospective reports of the number of standard drinks consumed on each day during a specified period are obtained with the use of a calendar including memory prompts (e.g., holidays). These data have been shown to be valid for retrospective reports as long as 12 months prior to data collection (Sobell and Sobell, 2003). The Form 90 is essentially a combination of “grid” measures like the DDQ and calendar measures like the TLFB. Data obtained from these instruments can be used to derive a number of summary drinking measures, including abstinence, percentage of drinking days, percentage of heavy drinking days (e.g., 5 or more for men; 4 or more for women), average amount consumed per drinking day and peak number of drinks consumed in a day. Patterns of drinking over time can also be described.

Given that assessment time is limited, a task force of the National Council on Alcohol Abuse and Alcoholism recommended that all studies include at least three questions in order to capture patterns of alcohol consumption over a 12 month period (NIAAA, 2003). These include questions about frequency of drinking, the number of drinks consumed on a typical drinking day and the frequency of binge drinking (5 or more standard drinks within a 2 hour period for men; 4 or more for women). When more time is available, investigators are encouraged to include additional questions regarding the maximum number of drinks consumed in a 24-hour period over the past 12 months and during the person’s lifetime and the frequency of consuming

the maximum in the past 12 months. The three question set advocated by NIAAA is similar to the three alcohol consumption questions from the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), referred to as the AUDIT-C (Bush et al., 1998), which has been validated in both Veterans Administration (Bush et al., 1998; Bradley et al., 2003) and in primary care samples (Bradley et al., 2007). The response options in the NIAAA items are different than in the AUDIT-C and the AUDIT-C defines a heavy drinking occasion as consuming six or more drinks, regardless of gender and without a time qualifier.

In contrast to these methods, daily ratings of alcohol consumption in which participants report on drinking occurring the day before, can be obtained either by completing a questionnaire on the internet (e.g., Neal and Fromme, 2007) or with the use of an automated telephone system in which participants respond to a series of questions about their drinking (e.g., Perrine et al., 1995). Using hand-held computers, it is also possible to obtain real-time self-reports of participants' drinking (Carney et al., 1998). Carney and colleagues compared data obtained with a TLFB with real-time drinking data obtained using hand-held computers and concluded that the data were roughly comparable for aggregate drinking; however, the hand-held computers were more effective for the observation of patterns of alcohol use over time.

Human laboratory models

Human alcohol administration laboratory studies typically take place over the course of several hours within a given day. There are two main alcohol administration approaches used with human participants. In one type, participants are administered a fixed dose of alcohol and their responses to this dose (e.g., subjective responses) are monitored. In the second type, participants are typically administered an initial, "priming" dose of alcohol, followed by a period when participants can decide whether or not they would like to consume additional drinks and if so, the number of drinks they would like to consume within pre-determined limits. The latter method, often referred to as an *ad libitum* paradigm, will be our focus here given the objective of this paper to characterize alcohol consumption phenotypes.

The basic objective of *ad libitum* paradigms is to assess experimental manipulations and/or other variables for their utility in predicting how much participants will consume in a laboratory setting. A common experimental manipulation is to treat participants with a medication or placebo and to observe the effects of this manipulation on *ad libitum* consumption (e.g., O'Malley et al., 2002; Anton et al., 2004). A popular non-pharmacologic experimental manipulation involves exposure to alcohol cues designed to elicit urges to drink (e.g., Monti et al., 1987; Colby et al., 2004). A variety of predictor variables have been evaluated for their utility in predicting alcohol consumption in laboratory paradigms, including subjective effects of alcohol (Corbin et al., 2008), alcohol-related expectancies (Bot et al., 2005) and family history of problem drinking (Krishnan-Sarin et al., 2007).

At present, there are three main variants of the *ad libitum* human alcohol paradigm. In one variant (e.g., Corbin et al., 2008), participants are given access to alcohol until a fixed period of time elapses or, given safety concerns, participants reach a predetermined maximum number of drinks or maximum blood alcohol concentration (BAC) (National Advisory Council on Alcohol Abuse and Alcoholism, 2005). Non-alcoholic drinks may also be available (e.g., Davidson et al., 1996; Bot et al., 2005). The access period may follow a beverage preload consisting of a sex- and weight-adjusted alcohol prime or a low-dose, taste-matched placebo, such as non-alcoholic beer (e.g., MacKillop, 2006) or a concoction meant to mimic a mixed drink (e.g., McKee et al., 2006).

The second variant is a behavioral economic approach in which alcohol consumed in the laboratory is associated with a "cost" to the research participant (e.g., O'Malley et al., 2002; Anton et al., 2004). A priming drink is often administered first. In the O'Malley et al. (2002)

and Anton et al. (2004) studies, the priming drink was gender- and weight-adjusted to achieve a target BAC of 0.03 g/dl. Following the priming drink, participants have the option of consuming additional drinks or retaining an amount of money approximately equal to the cost of a drink for each drink that they do not consume. A set number of drinks are available for a specified period of time, typically an hour. Additional *ad libitum* hours are often used.

The third variant of the human *ad libitum* consumption paradigm is the “taste test” (e.g., Marlatt et al., 1973; 1975; Colby et al., 2004). Participants are presented multiple options of a given alcoholic beverage (e.g., different brands of beer), which they are asked to rate on a series of qualities. Participants are instructed that they can consume as much of the beverages in a given period as they would like to make their ratings. Afterward, investigators measure how much alcohol remains in the containers to arrive at the amount of alcohol consumed.

Human *ad libitum* consumption paradigms offer a measure of external validity because participants in these studies typically consume drink units that are similar to those that they drink on their own. Potential threats to internal validity are the myriad causes underlying participants’ decisions related to drinking in the lab, which can be difficult to control or account for (e.g., motivation to drink at that moment) (Zimmerman et al., 2008). The pharmacokinetics of oral alcohol administration is also highly variable. For instance, the association between time of consumption and time when peak observed BAC was reached varied by a factor of three across participants in a recent study by Ramchandani et al. (2006). Intravenous (I.V.) alcohol administration addresses these issues by reducing the variability of alcohol pharmacokinetics and removing potential confounds such as taste preferences and rate of gastrointestinal absorption. With the use of a computer program, ethanol can now be delivered via I.V. in increments that are analogous to orally consumed drink units (see Zimmerman et al., 2008).

Another approach, which is useful for humans but not a candidate for consilience, is a procedure where participants are asked how much more they would like to consume, following initial beverage administration (Rose and Duka, 2006). Under this “imagery” procedure, participants are given varying doses of alcoholic or non-alcoholic drinks and asked at different time points to estimate how much more they would like to drink if given the opportunity.

Animal studies

Ethanol self-administration studies in animals typically take place over the course of several days. In the majority of these studies, dependent measures are obtained through direct assessment of the amount of ethanol consumed, although biomarkers (namely, BAC) are implemented as well. Heilig and Koob (2007) articulated the basic animal models of ethanol consumption and seeking: 1) voluntary or free-choice consumption; 2) operant self-administration and 3) reinstatement of ethanol seeking following extinction of operant self-administration (i.e., a relapse model). The behavior of animals in these models can vary from relatively low to excessive levels based on genetic influences and a variety of experimental parameters (e.g., duration of access, ethanol concentration, circadian timing of access). A history of dependence has been shown to enhance ethanol intake in operant self-administration (e.g., Chu et al., 2007; O’Dell et al., 2004; Roberts et al., 2000), reinstatement (e.g., Ciccocioppo et al., 2003; Liu and Weiss, 2002) and voluntary drinking models (e.g., Becker and Lopez, 2004; Finn et al., 2007; Rimondini et al., 2003).

Voluntary consumption models—Perhaps the best-known variant of the voluntary consumption model is the two-bottle choice paradigm. In this paradigm, animals are presented with access to two bottles; typically, one contains an ethanol solution and the other contains a non-ethanol beverage (usually water). The bottles can be presented in an open (i.e., available throughout) or limited access (i.e., available only during certain times of the day) basis. The

two-bottle choice paradigm is used as a means of assessing general avidity for alcohol (Tabakoff and Hoffman, 2000). Its disadvantages include its relative coarseness as a measure (Heilig and Koob, 2007) and the lack of any measure of the motivational component of behavior (Tabakoff and Hoffman, 2000).

Operant self-administration models—In operant models (e.g., Files et al., 1998), the animal must, in some way, “work” to obtain ethanol, most often by pressing a lever. This approach allows an investigator to observe how much effort an animal will put into obtaining ethanol and accordingly, the extent to which ethanol acts as a reinforcer for the animal. One of the main benefits of this approach is that it affords the researcher the opportunity to independently evaluate motivational as opposed to consummatory components of self-administration behavior (Tabakoff and Hoffman, 2000). A negative aspect is the amount of time required for training (Tabakoff and Hoffman, 2000).

Relapse models—In their review of relapse models in rats, Le and Shaham (2002) highlighted two models: reinstatement and alcohol deprivation. In a reinstatement model, the first step is to set up an operant contingency in which the animal works to obtain alcohol, which can be paired simultaneously with an additional cue (e.g., a light or tone). The reinforced behavior is then extinguished by the removal of ethanol. After a period of deprivation, ethanol is reintroduced in a non-contingent manner, the same paired cue is reintroduced, or a foot-shock stressor is introduced. After the prior cue or stressor is presented, reinstatement of lever pressing for ethanol is measured although no ethanol is provided in most models. To control for nonspecific activity or response generalization, an alternate, “inactive” lever is also provided in some models. Presses on the previously reinforced lever act as a dependent measure of motivation to seek ethanol (Le and Shaham, 2002).

In alcohol deprivation models, a period of ethanol access is followed by an ethanol deprivation period. When access to ethanol is re-introduced, a temporary increase in ethanol administration, compared to baseline, can typically be observed (Khisti et al., 2006). This transient spike in consumption is referred to as the alcohol deprivation effect (ADE) (Sinclair & Senter, 1967; Spanagel & Holter, 2000). As Le and Shaham (2002) point out, the ADE has been observed in studies making use of both voluntary consumption and operant methods. The ADE was recently demonstrated in rats selectively bred for high ethanol drinking (HAD-1, HAD-2). These rats, which normally consume about 7 g/kg/day under baseline conditions, increased their daily intakes to about 16–18 g/kg/day after four cycles of ethanol deprivation (Rodd et al., 2008).

II. CROSS-SPECIES COMPARISON OF CONSUMPTION PHENOTYPES

Consumption phenotypes can be organized into three categories: 1) abstinence or the decision to drink; 2) the actual amount of alcohol consumed and 3) heavy drinking. The relevant consumption phenotypes, by category, are listed in Table 1, along with a brief description of their current status in human clinical and epidemiologic/survey research, human laboratory models and animal models.

Abstinence/decision to drink or abstain

Clinical and epidemiologic/survey research—Perhaps the most basic consumption phenotype is abstinence from alcohol when it is available (i.e., lack of alcohol seeking). While moderate drinking is a reachable treatment goal for many heavy drinkers, for severely dependent individuals, controlled drinking may not be feasible and thus, strict abstinence may be a more appropriate objective (Sobell and Sobell, 1995b). Self-report remains the main method of determining abstinence in both clinical trials and epidemiologic studies. Although ethanol can be measured directly in breath, blood and urine, it is rapidly metabolized and can

only be used to confirm very recent abstinence (e.g., over several hours). Ethyl Glucuronide (EtG) is a metabolite of alcohol that can be used to evaluate recent drinking for somewhat longer periods (24 hours to several days). Other biomarkers, such as glycoprotein carbohydrate-deficient transferrin (CDT) and liver function tests (e.g., gamma glutamyl transpeptidase, GGT) have been used primarily in clinical trials. However, concerns about their sensitivity and specificity mean that they are usually employed as secondary outcomes or to confirm self-reports (for reviews of the use of biomarkers in alcohol research, see Allen et al., 2001; Montalto and Bean, 2003; Swift, 2003 or Peterson, 2004).

Human laboratory models—Given its clinical value, abstinence should be modeled in the laboratory, but at present, it does not receive adequate research attention. Abstinence-relevant phenotypes, however, can be derived from current paradigms and some studies report the number of participants who decide not to drink during experiments (e.g., Duka et al., 1998; Drobos et al., 2003; McKee et al., 2009). A relevant timing-related phenotype is latency to begin drinking, which is usually defined as the first sip of alcohol taken (Davidson et al., 1996; 1999; O'Malley et al., 2002; Anton et al., 2004). The length of time before the first sip is taken is essentially a period when the participant elects not to drink, thus these latency variables are relevant to the abstinence phenotype. Accordingly, experimental manipulations and/or predictor variables could be examined for their relation to the latency to first sip. Some cue exposure studies have also permitted participants the opportunity to consume or not consume alcohol following cue exposure (e.g., Kaplan et al., 1983; Cooney et al., 1997; Colby et al., 2004). The use of cue exposure paradigms to study abstinence is of value given that alcohol-related cues can elicit craving and lead to relapse among patients trying to achieve and maintain abstinence from alcohol.

Animal research—In animal ethanol administration paradigms, much attention has been given to studying variables that lead animals to seek ethanol or to consume ethanol excessively. Less attention has been paid to variables that underlie low levels of ethanol intake or to behavioral contingencies that reduce intake or produce abstinence in animals that once displayed ethanol preference. Informed use of existing animal genetic models such as inbred strains, rodent lines selectively bred for high or low ethanol intake and genetically engineered mice (Crabbe, 2002) might aid in efforts to improve our understanding of these variables and contingencies. For example, a better understanding of the genetic mechanisms underlying low ethanol drinking in non-preferring genotypes (e.g., NP and LAD rats, DBA/2 mice) could aid in the development of new pharmacotherapies to reduce ethanol intake. Similarly, the development of new behavioral procedures designed to reduce intake or produce abstinence could be studied in genotypes that normally consume high amounts of ethanol (e.g., P and HAD rats, C57BL/6 mice).

While the decision to abstain is not modeled well in animal research, certain animal paradigms (e.g., reinstatement models) might be relevant. Reinstatement constitutes a decision to drink although, as discussed earlier, no actual alcohol consumption takes place. It has been found that reinstatement can be attenuated with certain compounds. Naltrexone, for instance, has been found to attenuate ethanol-induced reinstatement of ethanol seeking in rats (Le et al., 1999). Failure to reinstate ethanol consumption in such a model could be conceptualized as representing abstinence. In addition, latency to first lick (when it can be obtained) is reported in some studies (e.g., Ford et al., 2007). This variable—similar to latency to first sip in human studies—represents the timing with which the decision to drink is made and the period of time before consumption is initiated can be viewed as a period of abstinence. A range of alternate mechanisms needs to be controlled for however, since consumption may be the result of motivation to obtain calories or taste rather than the pharmacologically reinforcing actions of alcohol.

The progressive ratio (PR) schedule, in which the instrumental response requirement to obtain an ethanol reinforcer is progressively increased until the animal ceases to respond (Brown et al., 1998), might be thought of as a model of deciding to stop drinking. The PR schedule, however, is frequently applied inappropriately, with the breakpoint (properly defined as the ratio at which responding ceases) being determined as the highest ratio achieved in a limited time period. Consider two animals responding for a reinforcer, one of which responds at a higher rate than the other animal. Now consider that the response requirement increases with every reinforcer earned. Clearly, in a 10-minute experiment, in which neither animal approaches the response requirement at which responding is disrupted, the faster responding animal will have emitted more responses, earned more reinforcers, and thus reached a higher ratio value than the more-slowly responding animal. It is difficult to interpret such data in terms of either motivation to obtain ethanol, or as a decision to stop drinking, as the ratio achieved is a simple function of response rate. While no researcher is likely to use such a short session, many researchers take their break-point estimate as response ratio reached by the end of a one- or two-hour session. The argument is the same. For that reason, it is important to define the breakpoint in terms of pauses in instrumental responding that clearly reflect insufficient motivation to perform the extended schedule. That is not a simple measure though, as animals performing under fixed ratio schedules are likely to pause in responding. One approach to determining a breakpoint may be to estimate the mean length of such pauses under an appropriate fixed ratio schedule, and to define breaking as a pause longer than a value two standard deviations higher than this mean. Even when the breakpoint is properly determined, it is not clear that the PR schedule offers more than a simple extinction schedule, with a clearly defined criterion for achieving extinction. In addition, consumption of the reinforcer itself influences performance of PR schedules, possibly explaining why breakpoints on PR schedules with ethanol as the reinforcer are invariably lower than when psychostimulants are the reinforcer, reflecting the response disruptive properties of ethanol and facilitating properties of psychostimulants (Brown and Stephens, 2002).

Amount of alcohol consumed

Clinical and epidemiologic/survey research—The second consumption phenotype concerns precisely how much alcohol one consumes. In clinical and epidemiologic/survey research, this is commonly expressed as the amount of alcohol an individual consumes per day, per drinking occasion or during another period of time, such as per week or per month. Typically, drinks are reported in standard drink units. Although there are differences both within and across countries (Devos-Comby and Lange, 2008), the NIAAA definition stipulates that a standard drink is 0.6 oz (17.74 ml) of pure alcohol. This amount is equivalent to 12 oz. (354.84 ml) of beer, 5 oz. (147.85 ml) of table wine or 1.5 oz (44.36 ml) of (80 proof, 40% alcohol by volume) hard liquor (NIAAA, 2005). Some investigators, however, have converted drink estimates obtained using self-report methods to more precise measures such as grams or ounces of ethanol consumed (e.g., Alte et al., 2003). An alternate phenotype that has gained popularity in the college drinking literature is estimated blood alcohol concentration (BAC), calculated using self-reported quantity of drinks consumed, the amount of time taken to consume them and the participant's sex and weight. In a meta-analysis of individual-level interventions to reduce college drinking, Carey et al. (2007) reported decreases in estimated peak BAC post-intervention. The Form 90 (Miller and DelBoca, 1994) also requests the information needed to calculate estimated BACs for the two heaviest drinking days during the monitoring period although recent clinical trials (e.g., The COMBINE Study Research Group, 2003) have not reported this as an outcome of treatment. Quantity of alcohol consumed has been included in a quantitative measure of alcohol consumption developed for use in gene-mapping studies (Agrawal et al., 2009). The specific variable included is log transformed and captures the typical consumption participants report during the 12-month period in their lives

when they drank the most. Like the other variables in this measure, this variable was found to be heritable according to psychometric twin modeling.

Human laboratory models—Like clinical and epidemiologic/survey research, reporting of consumption in drink units is typical in human laboratory studies (e.g., Davidson et al., 1996; 1999; O'Malley et al., 2002; Drobles et al., 2003; Anton et al., 2004; Krishnan-Sarin et al., 2007). In contrast with clinical trials and epidemiological studies, in which the amount of alcohol is held constant across drink units, in laboratory self-administration studies, the amount of alcohol in each drink is typically individualized in order to achieve a “standard” blood alcohol level based on factors including weight, sex and age using the Widmark equation (Widmark, 1981). Reporting of the precise amount of alcohol consumed in units such as grams, ounces or milliliters, is also more common in human laboratory studies than in clinical or epidemiologic studies (e.g., Sharkansky and Finn, 1998), particularly in laboratory studies utilizing the “taste test” approach (e.g., Marlatt et al., 1973; Colby et al., 2004; Marcziński et al., 2005). Blood or breath alcohol concentrations are also reported often as a dependent measure in laboratory studies (e.g., Davidson et al., 1996; 1999; Drobles et al., 2003; O'Malley et al., 2002; Krishnan-Sarin et al., 2007). Although obtaining BACs frequently during an experiment can interrupt drinking, BACs provide the most direct measure of alcohol exposure that summarizes the effects of the amount consumed, patterns of drinking, metabolism, sex and other individual differences.

Animal models—A number of consumption phenotypes pertaining to the amount of ethanol consumed can be assessed in animal research. Measures more precise than those usually reported in human studies (most typically grams per kilogram, e.g., Bell et al., 2006a) are the norm. The assessment of amount of ethanol consumed in animal models poses some key challenges. The distinction between low or moderate versus excessive levels of consumption is an important one, given that some compounds have been found to be differentially efficacious in animal models dependent upon level of consumption (Egli, 2005; Heilig and Koob, 2007). For instance, the FDA approved alcoholism medication acamprosate selectively suppresses excessive but not lighter consumption in rats (Rimondini et al., 2002).

Laboratory rodents will consume relatively small, but measurable amounts of ethanol without having been genetically selected for high ethanol preference and in the absence of a history of dependence. These relatively low levels of consumption (i.e., up to approximately 2–2.5g/kg/24h in a rat, or 5–6 g/kg/24h in a mouse) are not necessarily related to pharmacologically reinforcing properties of ethanol and are thus not likely relevant for models pertaining to alcohol use disorders (Heilig and Koob, 2007). At these lower levels which are unlikely to produce pharmacologically relevant BACs, ethanol is probably consumed for its caloric content and/or its taste.

Certain inbred mouse strains normally consume alcohol at much greater levels, which might be mediated in part by alcohol's pharmacological effects. An example is C57BL/6 mice, which have been found to drink greater than 10 g/kg/day under standard two-bottle choice tests (Yoneyama et al., 2008). High levels of consumption (5–10g/kg/24h in a rat, or 12–20g/kg/24h in a mouse) can also be induced using animal lines genetically selected for ethanol preference (see Bell et al., 2006a; Ciccocioppo et al., 2006; Sommer et al., 2006) following induction of dependence through chronic exposure to ethanol—often using vapor (Heilig and Koob 2007) or other manipulations (e.g., Rhodes et al., 2007; Rodd et al., 2008).

Use of BAC may allow for even more precise definitions of high drinking levels than are possible using g/kg of consumption. The assessment of BAC in animal research, however, poses a considerable methodological challenge. Under continuous access conditions, laboratory rodents drink in bouts that occur primarily during the dark (active) phase of the

circadian cycle. They also metabolize ethanol quickly. If 24h consumption is measured and blood is sampled for BAC, the probability of capturing adequate BACs is therefore low and individual differences in timing of consumption peaks will lead to difficulties in interpreting the values obtained across a group. One remedy for this problem is offered by limited access paradigms (Egli, 2005). If access is offered during only a discrete period (e.g., 60 min), consumption and BAC curves are forced into a higher degree of synchrony (e.g., Roberts et al., 2000; Rodd-Henricks et al., 2001; Rhodes et al., 2005). This strategy, however, occurs at the expense of limiting total brain ethanol exposure in a way that may affect the relevance of this phenotype in relation to human consumption. An alternative strategy, using a continuous access procedure in which the temporal pattern of intake is monitored, would be to collect blood samples shortly after bouts that meet some minimum level of intake per unit time. New noninvasive technologies to measure breath alcohol levels in rodents could be used (Javors et al., 2005; Ginsburg et al., 2008). Following up on initial work by Dole, Ho and Gentry (1985), computer programs could also be developed to estimate blood alcohol levels using data from systems that permit simultaneous microstructural analysis of the animals' alcohol and fluid intake (Boyle et al., 1997; Reidelberger et al., 1996).

Heavy drinking

Consumption phenotypes related to heavy drinking can be broken down into two categories: 1) consumption of “too much too fast” and 2) “too much too often” (Li et al., 2007)

Clinical and epidemiologic/survey research – “too much too fast”—The phenotype of heavy drinking days is commonly assessed in clinical trials and in epidemiologic and survey research. For instance, Pettinati et al. (2006) reported that, in the naltrexone literature, relapse tends to be equated with one or more occasions of heavy episodic drinking. The centrality of heavy episodic drinking was affirmed by an expert panel convened by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001, who declared percent heavy drinking days to be the “sentinel” outcome measure in clinical research (Allen, 2003). The definition of heavy drinking day that was adopted was five or more drinks in a day for males and four or more drinks in a day for females (i.e., the “5/4 definition”).

Maximum alcohol consumption in a 24-hour period is an alternate heavy drinking phenotype. This variable can be assessed as a measure of treatment efficacy in which the highest number of drinks participants report consuming in a 24-hour period during treatment is compared to their heaviest baseline day (e.g., Carey et al., 2007). There is strong evidence, based on epidemiologic findings, that the maximum alcohol consumption phenotype has a strong genetic loading. In the Minnesota Twin Family Study, father's lifetime maximum 24-hour alcohol consumption predicted negative outcomes in their adolescent offspring, including conduct and substance use disorders (Malone et al., 2002). This endophenotype has also been associated with a diagnosis of alcohol dependence and has shown genetic linkage in a genome-wide scan (Saccone et al., 2000; Dawson et al., 2005).

Along with a variable capturing typical quantity of consumption, variables assessing frequency of heavy drinking days during the 12-month period of heaviest use and lifetime maximum 24-hour consumption were also included in a quantitative measure developed for use in gene-mapping studies (Agrawal et al., 2009). These variables were found to be heritable according to psychometric twin modeling.

A recent change to the conceptualization of heavy drinking advocated by the NIAAA reflects added emphasis on the “too fast” aspect of heavy drinking. In 2004, a time window was added to the definition of heavy episodic drinking, now referred to as “binge drinking” (NIAAA, 2004). Binge drinking is considered to be a drinking episode that is likely to raise blood alcohol concentration to 0.08 g% or higher. Given that most adults would reach this level by consuming

5 or more drinks (4 for females) *in a period of about two hours*, in 2004, the definition of a binge was amended to include this two-hour time qualifier.

Human laboratory models – “too much too fast”—Despite the centrality of heavy drinking in clinical and epidemiological research, reports of human laboratory studies rarely present outcomes according to whether or not drinking exceeded heavy drinking cut-offs. Perhaps the closest thing to a heavy drinking phenotype reported currently in human laboratory models is the percentage of participants who reach a pre-determined limit in their consumption. This limit may be a particular number of drinks or a maximum BAC, as in Corbin et al. (2008).

Nonetheless, several timing-related phenotypes that reflect speed of consumption are frequently reported in human laboratory models. These include the length of the intervals between sips (O'Malley et al., 2002) and the latency to finish individual drinks or to terminate an entire drinking session (Davidson et al., 1996; 1999; Anton et al., 2004). When participants in human laboratory studies provide readings indicative of high breath or blood alcohol concentration, this is indicative of consumption of “too much too fast,” as well. Although not current practice, binge drinking that meets the new NIAAA guidelines or drinking that results in a BAC of 0.08 g% or higher could be reported in laboratory studies.

One could argue that the assessment of “too much too fast” in human laboratory studies is artificial, given that drinking in these studies is typically time limited both to a single session and to a particular period of time within that single session. Thus, participants may tailor their drinking to the time limitations inherent in the study and accordingly, consume a high number of drinks in a relatively short amount of time. While this caveat should be kept in mind, a decision to drink alcohol in this manner is, of course, under the control of the participants and thus, this type of drinking pattern stands as an example of excessive, “too much too fast” drinking, albeit a pattern that is in some sense influenced by aspects of the study's methods.

Animal models– “too much too fast”—The distinction between animal models of excessive and light/moderate drinking provides researchers with elegant means of comparing heavier with lighter levels of consumption. Samson (2000) points out that control over the oral consumption of all substances, including ethanol, relates to two factors: amount consumed during individual periods or bouts and amount of time between bouts (i.e., inter-bout intervals). Thus, excessive drinking could be the result of consumption of large amounts of ethanol within bouts and or rapid drinking characterized by relatively brief periods between bouts, particularly relevant to the “too much too fast” concept.

Extensive research has been conducted with the ethanol preferring P rat, one type of excessive drinking animal (see Bell et al., 2006a, for a review). Given the tendency of P rats to consume ethanol during discrete bouts during the dark cycle, Bell and colleagues developed a model of binge drinking in which P rats are exposed to multiple 1-hour periods of access to multiple ethanol concentrations and water in the dark cycle. In this paradigm, P rats will typically self-administer approximately 2 g/kg in each 1-hour access period and will consume to this level repeatedly within a given session. Drinking in the dark (DID) procedures have also been used with mice, involving single-bottle limited access as well as two-bottle choice paradigms. A procedure where animals are given an opportunity to drink in a two-bottle choice paradigm for 2 hours beginning 2–3 hours after lights out leads to considerable alcohol consumption. Ford et al. (2008) reported average baseline (i.e., a session immediately preceding treatment with an experimental drug) consumption rates of 3.29 g/kg per 2-hour session by C57BL/6J mice drinking a 10% ethanol solution. Crabbe et al. (2009) have taken the subsequent step of breeding a line of mice that has been found to drink to high blood ethanol concentrations in a single-bottle limited access DID paradigm.

Analogous to human laboratory models, timing-related phenotypes can be assessed in animal models, including the duration of drinking bouts in continuous access paradigms (e.g., Weisinger et al., 1999; Brunell and Spear, 2005). Pattern of licking can also be assessed (Bell et al., 2006b) and is facilitated by the use of lickometer chambers, which permit researchers to obtain fine-grained data about the microstructure of drinking sessions (e.g., Griffin et al., 2009). For instance, Ford et al. (2008) found that manipulation of levels of the neurosteroid allopregnanolone (ALLO) did not affect the overall amount of 10% ethanol solution consumed by female mice, however by using lickometer chambers it was possible to determine that lick frequency decreased with mid-to-high doses of ALLO and that bout size decreased with high ALLO doses.

BACs could also be used to assess the extent to which animals consume ethanol in a manner analogous to the binge pattern stipulated by NIAAA in their revised definition (2004). For example, Bell et al. (2006a) state that in their dark cycle/binge drinking paradigm involving limited access to multiple concentrations of ethanol and water, P rats routinely achieve BACs over 120 mg%, exceeding the 80 mg% level in the updated NIAAA definition of binge drinking. Similarly, Crabbe et al. (2009) reported that in a 4 hour single-bottle limited access paradigm involving a 20% ethanol solution, 56% of mice bred for heavy DID consumption drank to blood ethanol concentrations of 100 mg% or greater, suggesting that DID-bred mice may provide a good animal model of binge drinking.

The importance of the quantity, frequency and speed of ethanol drinking in the development of a heavy drinking phenotype was nicely illustrated in a recent long-term (12-month) study of continuous-access (22 h/day) ethanol self-administration by cynomolgus monkeys (Grant et al., 2008). These investigators used principal components analysis to identify intake pattern variables measured during the induction of self-administration that were predictive of a heavy drinking phenotype (≥ 3 g/kg/d during the subsequent 12 months of self-administration). One of the strongest and most interesting predictors of heavy drinking to emerge was the percentage of the daily dose limit (1.5 g/kg/d) during the induction phase that monkeys consumed in their largest bout. Monkeys that displayed a pattern of ethanol “gulping” during the initial training phase, in which daily ethanol intake was limited by the experimenter, were more likely to meet the criteria for heavy drinking defined in the study (i.e., > 3 g/kg/day) during subsequent ethanol self-administration when there was no daily limit on intake.

The relevance of phenotypes related to the “too much too fast” concept for genetic studies is illustrated by recent work in both non-human primates and inbred mice. Under social drinking conditions, rhesus macaques rarely drink to intoxication. However, a gain-of-function mutation at the locus encoding the mu-opioid receptor gene, *rhOPRM1* 77C->G, not only renders male carriers more responsive to psychomotor stimulating effects of ethanol, but also makes them drink to intoxication almost every time access to alcohol is offered (Barr et al., 2007). Studies comparing the pattern of intragastric ethanol self-infusion in alcohol-dependent inbred mice have also shown that DBA/2 mice (which normally avoid ethanol in oral consumption studies) will administer a greater portion of their daily intakes in larger magnitude bouts than alcohol-preferring C57BL/6 mice, suggesting that dependent DBA/2 mice display a “gulping” phenotype whereas C57BL/6 mice display a “sipping” phenotype (Fidler et al., 2006).

Clinical and Epidemiological Studies - “too much too often”—To this point, we have focused on heavy drinking in the sense of consuming too much alcohol in a given day, however heavy drinking can also be construed as drinking a higher quantity of alcohol than is recommended over a longer period of time than a day (i.e., “too much too often”). The NIAAA physician’s guidelines (2005) regarding weekly drinking (i.e., no more than 14 drinks in a week for males, no more than 7 for females) is an example of a measure of heavy drinking over time that has been implemented in epidemiologic research. Based on analyses of the National

Longitudinal Alcohol Epidemiology Survey (NLAES), Dawson (2000) concluded that by considering both the NIAAA daily (i.e., no more than 4 drinks in a day for males, 3 for females) and weekly drinking guidelines, one strikes a good balance between sensitivity and specificity in the prediction of a number of alcohol-related outcomes, including alcohol dependence and impaired driving.

Human and animal laboratory models- “too much too often”—We located no recent human studies in which self-administered drinking occurring over multiple days was modeled although an early study examined drinking patterns of alcoholics under conditions where unrestricted access to ethanol was compared to circumstances in which access was dependent on performance of a simple operant task (Mello and Mendelson, 1972).

In animal research, drinking over multiple days is frequently modeled (e.g., Rodd-Henricks et al., 2001; Overstreet et al., 2002; Rodd et al., 2008). For instance, in a study of the alcohol deprivation effect, following a six-week free choice training period, ethanol was withheld from alcohol-preferring P rats for initial periods of 2 or 8 weeks, followed by three successive deprivation periods of 2 weeks each. A two-week period of free choice access to ethanol followed each deprivation period (Rodd-Hendricks et al., 2001). This study also serves as an example of excessive consumption in animals occurring over several days, which could be thought to represent a “too much, too often” pattern. Following the fourth and final deprivation period, average daily ethanol consumption in deprived P rats in this study ranged from 11–18 g/kg during the first week of alcohol reinstatement, in comparison with an average of approximately 6 g/kg/day in non-deprived, control rats.

A model of withdrawal-induced consumption has been developed with mice (Becker and Lopez, 2004; Lopez and Becker, 2005). After initial training to consume ethanol in a limited-access (2 hours per day), two-bottle choice paradigm, dependence is brought about through intermittent periods in which ethanol is administered via vapor exposure for 16 hours and withdrawn for the subsequent 8 hours. After successive days of exposure followed by non-exposure, animals enter into a period of forced abstinence (e.g., 32 hours in Becker and Lopez, 2004; 72 hours in Griffin et al., 2009). Following the abstinence period, over a period of days, they are engaged in successive 2 hour-long two-bottle choice tests, which are the same as those on which they were initially trained (Becker and Lopez, 2004; Lopez and Becker, 2005). In comparison with control mice exposed to air rather than ethanol vapor, whose consumption patterns tended to be consistent, the dependent mice showed a monotonic pattern where they consumed increasing amounts of ethanol across the successive 2-hour limited access sessions, peaking at an average of 4.1 g/kg during the final session (Griffin et al., 2009). Finn et al. (2007) had obtained parallel results using a similar procedure and also found that the increase in consumption observed in dependent mice was attenuated with a CRF receptor antagonist. Although the animals in this paradigm may very well be in withdrawal following the forced abstinence period, the spike in consumption observed in dependent animals compared with controls extends beyond the period of acute withdrawal (Lopez and Becker, 2005), calling into question whether this increase in consumption is driven strictly by compensation for withdrawal.

There is no analogous model in humans where *ad libitum* consumption is tested following withdrawal. While participants in *ad libitum* consumption studies are typically required to abstain from alcohol the day of and sometimes the evening prior to the drinking session, these sessions typically begin with a priming drink (O’Malley et al., 2002; Anton et al., 2004). This precludes researchers from having the opportunity to observe the extent to which *ad libitum* consumption may be driven by withdrawal specifically. These procedures could, however, be modified to omit the priming drink and to study a somewhat longer period of abstinence.

III. DIRECTIONS FOR FURTHER DEVELOPMENT OF CONSUMPTION PHENOTYPES

Researchers face a conceptual challenge in attempting to achieve consilience between human and animal drinking phenotypes. Discussion of human drinking phenotypes has an assumed endpoint, namely drinking related to a clinical alcohol use disorder. The clinical construct of alcoholism (as opposed to simple physical dependence, addressed in a companion paper), is based on criteria that attempt to capture a maladaptive pattern of alcohol use. Thresholds for heavy drinking that constitute such a pattern in humans - "too much too fast" or "too much too often" - will often lead to adverse social or medical consequences. There is clearly no equivalent to adverse social or medical consequences in experimental animals, thus it may seem difficult to establish what constitutes "excessive" or "heavy" drinking in animal models.

A potentially useful tool to achieve consilience, or translation, despite these limitations, is offered by pharmacology. Translational research involving the opiate antagonist naltrexone has already informed this issue to some extent (see O'Malley & Froehlich, 2003). Naltrexone, a drug that reduces acute positive reinforcement by alcohol (McCaul et al., 2000), would be predicted to primarily limit drinking phenotypes related to the "too much too fast" construct, irrespective of whether the subject is alcohol dependent (King et al., 1997). Emergence of additional pharmacological probes with well defined pharmacodynamic modes of action, such as kappa-opioid (e.g., nor-binaltorphimine, Walker and Koob, 2008) or CRH1 receptor antagonists (Seymour et al., 2003), will facilitate translation between human and animal models. It should be noted though that the use of animal models to test pharmacological probes is not without limitations. According to Egli (2005, p. 309), "it is not clear at present whether any single paradigm or combination of paradigms differentiates clinically effective from clinically limited compounds." In his review, Egli cites examples of "false positives"—medications that have been found to alter drinking behavior in animal models, but have not demonstrated clinical efficacy.

In addition to conducting more translational research involving pharmacological probes, a second overarching suggestion for enhancing consilience concerns the role of individual differences. In animal models, greater effort to evaluate the effects of individual differences that are important to drinking (or abstinence) in humans (e.g., sex, nicotine dependence) would help to enhance consilience in the study of all of the consumption phenotypes discussed here.

Several specific steps could also be taken by researchers in order to improve consilience between common human and animal alcohol consumption phenotypes. In Table 2, we present a short list of consumption phenotypes for which consilience could be enhanced and some ideas for future research that may help to accomplish this goal.

Abstinence phenotypes

Several steps could be taken to adapt human *ad libitum* consumption paradigms in order to obtain information relevant to abstinence from alcohol, an important phenotype frequently measured in clinical and epidemiological studies. At a minimum, investigators could report the number of subjects who opt not to drink after a priming drink or cue exposure. A further developmental step would be to provide participants with different incentives to not drink and then to observe the effects of these measures on the decision to drink or abstain. For example, a reward (e.g., earning money) or punishment (e.g., loss of payment) could be provided to those who abstain or drink during the session. With these modifications, researchers could then test the effects of various manipulations and individual differences on the decision to drink or abstain.

In animals, a potentially useful measure of the decision to stop drinking is provided by instrumental schedules in which both ethanol and an alternative reinforcer are available. Gisburg and Lamb (2008) proposed a model in which sucrose and ethanol are both available. In one condition, signaled by an environmental cue, a particular response gives access to ethanol on a relatively dense schedule, while an alternative response gives access to sucrose on a lean schedule. In the alternative condition, signaled by a different cue, sucrose is available on a denser schedule. With adequate training, rats learn to switch responding between ethanol-appropriate responses and sucrose-appropriate responses, according to the schedule currently signaled. Thus, the environmental cue that signals increased sucrose availability could be considered as triggering a decision to “abstain” from ethanol. This schedule seems to offer an approach that could be adapted for use in both animal and human research.

The conventional, two-bottle choice paradigm could also be modified, such that if an animal chooses ethanol, the alternate reinforcer (e.g., sucrose-treated water) would become unavailable for a certain period of time. This modification would enable researchers to determine the animals’ willingness to trade another resource for ethanol. This would enhance consilience with human behavioral economic *ad libitum* paradigms in which participants consume alcohol in exchange for reductions in their pay for participating in the study. The repeated choice of alcohol over alternate reinforcers (e.g., spending time with family or at hobbies) is an important aspect of alcohol use disorders (APA, 1994) and therefore, this is an important area of further research.

Another issue that is both relevant to the decision to drink or abstain and a key component of alcohol use disorders is consumption in the face of negative consequences (APA, 1994). While this phenomenon is a clear focus of clinical and epidemiologic/survey research in humans, it has not been modeled well in the lab on either the human or the animal side. The closest thing to a negative consequence in human laboratory studies is the loss of a small portion of one’s monetary payment due to the decision to drink in behavioral economic models (e.g., O’Malley et al., 2002). To our knowledge, negative consequences have not been modeled effectively in the animal ethanol literature, although there are examples from the cocaine literature (see Deroche-Gamonet et al., 2004 and Vanderschuren and Everitt, 2004). In designing such models, investigators should keep in mind the uncertain nature of negative consequences, namely that negative consequences do not occur on every drinking occasion.

Heavy or binge drinking

Consilience among survey, clinical and human laboratory studies would be improved if researchers make two modifications to their research practices. One, in surveys and clinical trials, estimated BACs should be calculated to parallel the direct measurement of BAC in the laboratory. Two, in human laboratory studies, the number of participants who consumed enough alcohol to exceed heavy drinking cut-offs should be reported to parallel measures in survey and clinical research. In animal studies, researchers should report blood/breath alcohol concentrations (estimated or actual) and develop for all species cut-offs for excessive consumption based on measures of impairment similar to those used with human subjects, as Grant et al. (2008) did for cynomolgus monkeys.

Alcohol use within 24-hour periods, several days and over the long-term

While the modeling of ethanol consumption over several days is a strength of animal research, researchers do not typically provide information regarding patterns of alcohol consumption within 24-hour periods, leading to potential problems in the interpretation of results. For example, an animal may be able to achieve what appears to be a relatively high daily g/kg ethanol intake by drinking a large number of small volume bouts, most of which fail to produce a meaningful pharmacological effect. This pattern is not as relevant to human alcohol use

disorders as high levels of consumption over shorter periods of time. One solution is to observe patterns of licking using tools such as lickometers, operant chambers or other methods that allow a fine-grained temporal analysis of ethanol intake (e.g., number of drinking bouts per day, inter-bout interval, etc.; see Files et al., 1998 and Grant et al., 2008 for examples of these techniques in research with rats and primates, respectively). Similar measures of patterns of consumption are common in human laboratory research, thus increased use of these techniques in animal research would enhance consilience.

Human laboratory models in which drinking occurs over several days are rarely used. Instead, researchers usually study alcohol consumption over a period lasting no longer than several hours. Adding additional sessions would permit examination of whether drinking increases in subsequent days in a given model, along with what experimental manipulations and/or individual differences predict drinking over several days.

In addition, the inclusion of prospective follow-up studies to examine how drinking topography predicts drinking in the long-term and the development of dependence provides another opportunity for achieving consilience between human laboratory research and animal models. Schuckit's study documenting that a low subjective response to a fixed dose of alcohol administered in the laboratory predicts alcoholism 10 years later (Schuckit, 2004) highlights the potential of this approach in human subjects. Grant and colleagues' (2008) study is an excellent example of this approach using nonhuman primates.

BAC and other biomarker phenotypes

Further research on biomarkers is needed in both human and animal research. Noninvasive methods for monitoring BAC in animals and sensors that unobtrusively monitor BACs continuously in the field for clinical and survey research would represent important advances. Metabolites of alcohol, such as Ethyl Glucuronide (EtG), are promising, relatively new biomarkers (Peterson, 2004), however further research is needed (Peterson, 2004; SAMHSA, 2006).

CONCLUSION

While perfect consilience between human and animal consumption phenotypes is not possible, several steps could be taken to enhance consilience. Efforts could be made in animal studies to ascertain how individual differences influence ethanol consumption. Existing human and animal laboratory models could be further developed to better model abstinence, an important phenotype in epidemiological and clinical studies. In human laboratory studies, reporting instances of heavy or binge drinking more consistently would increase parallels with outcomes reported in clinical trials and epidemiological studies. Alcohol use occurring over several days could be modeled in human laboratory studies and in animal studies, greater attention could be paid to temporal patterns of ethanol intake observable within 24-hour periods. Improved biomarkers need to be developed for use with both humans and animals.

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Table 1

Alcohol consumption phenotypes of importance in human and animal research

Variable(s)/ topic	Human clinical and epidemiologic research	Human laboratory models	Animal models
Abstinence/ decision to drink or abstain	<ul style="list-style-type: none"> • Very common and based on self-report • Use of biomarkers (e.g., %CDT, Blood or breath alcohol concentration [BAC]) for this purpose is limited 	<ul style="list-style-type: none"> • Participants given choice whether or not to drink • Percent who decide to drink reported in some studies • Relevant timing-related phenotype: latency to first sip 	<ul style="list-style-type: none"> • Not well-modeled overall, but some animal paradigms are relevant (e.g., reinstatement) • Focused instead on setting up contingencies in which animals will drink • Relevant timing-related phenotype: latency to first lick
Amount of alcohol consumed	<ul style="list-style-type: none"> • Standard drink units typically • Measures more precise than drink units (e.g., g ethanol) reported rarely • Estimated BAC's in college literature 	<ul style="list-style-type: none"> • Standard drink units common • More precise measures (e.g., oz of alcohol) reported sometimes • BAC's commonly reported 	<ul style="list-style-type: none"> • Precise measures reported exclusively, often g/kg of ethanol consumed. BAC's sometimes reported
Heavy drinking too much too fast too much too often	<ul style="list-style-type: none"> • Heavy drinking days (5/4 definition) reported often • Binge drinking: definition of 5/4 drinks within two hours or less recently endorsed by NIAAA • Maximum consumption in a day (lifetime or within a time frame) • NIAAA weekly guidelines > 14/7 drinks/week occasionally reported 	<ul style="list-style-type: none"> • Drinking typically monitored for a period lasting up to several hours • Whether a pre-determined consumption limit is reached sometimes reported • Heavy/binge drinking rates could be derived • Patterns of drinking (e.g., length of intervals between sips) commonly reported • High BAC's indicative of "too much" consumption, "too fast" • Heavy drinking over multiple days rarely modeled 	<ul style="list-style-type: none"> • Drinking within 24 hour periods often not reported • Amount of ethanol consumed by rats (and recently mice) bred or trained for excessive as opposed to light/moderate drinking • Licking patterns reported in some studies (e.g., rate of licking, such as licks per minute) • High BAC's indicative of "too much too fast" • Drinking over multiple days frequently modeled

Consumption phenotypes in bold

Table 2

Suggestions for the further development of consumption phenotypes in a manner that enhances consilience

Consumption phenotype development goal	Suggestions for future research
Further development of abstinence/decision to drink or abstain phenotypes	Models of abstinence should be enhanced in both animal and in human research. At minimum, the percentage of participants deciding not to drink in human alcohol self-administration studies should be reported. Models of the decision to drink despite adverse consequences should be created for both humans and animals.
Modeling/reporting of heavy or binge drinking , in contrast with light or moderate drinking	Animal researchers should continue to establish levels of drinking in various species to parallel important levels established for human subjects. At minimum, the percentage of participants who exceed heavy drinking cut-offs in laboratory studies should be reported to increase correspondence with clinical/epidemiological phenotypes.
Model alcohol use within 24-hour periods, over several days and over the long-term	Alcohol use occurring over several days is modeled in animal research, however greater attention should be paid to patterns of consumption occurring within drinking periods of 24 hours or less. Human laboratory models with drinking opportunities provided over consecutive days should be developed. Prospective follow-up of participants in human studies (and animal research) could be incorporated to examine the predictive utility of early patterns of drinking.
Enhancement of BAC and other biomarker phenotypes	Further research is needed in humans and animals. Nonintrusive sensors that would deliver accurate BAC readings in clinical and epidemiological studies and noninvasive measures for animal studies would be particularly useful.

Consumption phenotypes in bold