Published in final edited form as:
Curr Drug Abuse Rev. 2010 June ; 3(2): 92–102.

Hangover and Risk for Alcohol Use Disorders: Existing Evidence and Potential Mechanisms

Thomas M. Piasecki[*,1], **Brandon M. Robertson**[1], and **Amee J. Epler**[2]

[1]Midwest Alcoholism Research Center and Department of Psychological Sciences, University of Missouri, Columbia, Missouri, USA

[2] G.V. (Sonny) Montgomery VA Medical Center, Jackson, Mississippi, USA

Abstract

Hangover may be related to propensity to develop alcohol use disorders (AUDs). However, the etiological role, if any, played by hangover in AUD is unclear. From a motivational perspective, hangover can be construed as either a deterrent to future alcohol consumption or a setting event for negative reinforcement that could promote deviant drinking practices (e.g., "hair-of-the-dog" drinking). Hangover could be related to AUD risk even if it does not play a direct role in promoting or inhibiting near-term drinking. For example, measures of hangover might serve as symptoms of AUD or as markers of individual differences that more directly account for AUD risk. Empirical evidence (though usually indirect) exists to support contentions that hangover is related to both risk for and protection from AUD. In this article, we briefly address variation in assessment strategies in existing hangover research because measures of hangover frequency and hangover susceptibility may prove to have different correlates. Next, we review the existing, limited evidence on relations between hangover and AUD risk. Finally, we sketch a variety of theoretically-informed hypotheses that might help delineate productive lines of inquiry for this emerging field.

Keywords

hangover; alcohol; alcohol use disorder; risk; individual differences

Because hangover consists of an aversive constellation of symptoms and is contingent upon heavy drinking, it is natural to assume that it deters or punishes alcohol consumption. By extension, one might infer that persons especially prone to hangover would be, on average, more abstemious and perhaps protected from developing alcoholism. As we review below, population subgroups with differing risks for alcohol use disorders (AUDs) indeed appear to differ with respect to measures of hangover. Curiously, though, excess hangover has been reported in groups at *both* increased and decreased risk for AUD. The purpose of this article is to review the existing evidence bearing on the potential linkage between hangover and AUD. This literature is in its infancy. Consequently, most of the available evidence consists of cross-sectional associations, and data have been gathered via a variety of research

[*]Correspondence to: Thomas M. Piasecki, Ph.D., Department of Psychological Sciences, 210 McAlester Hall, University of Missouri, Columbia, MO, 65211, USA, Phone: 573-882-8877, Fax: 573-882-7710, piaseckit@missouri.edu.

designs. We begin by briefly reviewing variation in hangover assessment and discuss how the assessment strategy may influence the nature and interpretation of associations between hangover and AUD risk. Next, we review associations between hangover measures and AUD risk factors, bearing in mind these assessment issues. Although existing research findings provide mostly indirect evidence, they permit the advancement of a variety of hypotheses concerning mechanisms that could account for links between hangover and increased or decreased risk of clinically significant drinking problems. We conclude by laying out some of the possibilities, in the hope this may point to productive avenues for future research.

Strategies for Assessing Hangover

Investigators have used a variety of assessments and research designs to investigate associations between hangover and AUD risk. We do not provide a detailed, comprehensive review of hangover assessments here, as this is beyond the scope of the current article. However, we begin with a brief consideration of some of the major approaches to hangover assessment because this identifies important variations in methodology that are pertinent for critically evaluating the existing empirical evidence.

Perhaps the most important distinction can be drawn between measures of *susceptibility* to hangover and the *occurrence* or *frequency* of hangover. These two approaches are roughly aligned with laboratory and survey methods, respectively. Laboratory studies most often aim to assess individual differences in hangover susceptibility by administering a fixed dose of alcohol to participants and then assessing variation in the presence or severity of the hangover syndrome or individual hangover symptoms [e.g. 1, 2]. In contrast, survey investigations most commonly assess individual differences in the frequency of hangover during some period of time, such as the past year [e.g., 3, 4]. These two measurement strategies may assess the same construct, but there is no guarantee that they will do so.

The issue arises from the fact that hangover is a drinking-contingent, dose-dependent experience - whereas the investigator can control the dose of alcohol in the laboratory to isolate susceptibility effects, the respondent makes the decisions concerning the timing and amount of alcohol consumption that are reflected in the survey answers. Logically, then, survey-elicited reports of frequent hangover in the past year may reflect multiple causes, including (but not necessarily limited to) individual differences in: (a) susceptibility to hangover effects, (b) drinking practices, and (c) the modification of drinking behavior by hangover effects. That is, one could achieve a high tally of hangovers in a year by being very liable to experience one after any drinking, drinking heavily and frequently, or by being undeterred from drinking despite hangovers. These influences on hangover frequency could have discrepant relations with AUD risk. If laboratory- and survey-based assessments tap different kinds of information, it is possible that findings arising from these designs will sometimes point to different conclusions.

Diary or ecological momentary assessment designs involve asking drinkers to record details of drinking episodes and any associated hangover experiences in real time, often for an extended period [5-9]. These kinds of designs combine some of the features of laboratory

and survey research. As in laboratory studies, diary designs allow the investigator to examine the symptoms and time course of individual hangover events. In the typical diary design, drinking behaviors are merely observed, not prescribed by the investigator. The disadvantage of this is that the investigator does not control dosing and must settle for collecting measures of the amount consumed. However, surrendering control of the drinking decisions to the participant has some offsetting advantages. One is that the investigator can simultaneously investigate the correlates of drinking behavior and hangover responses. Similarly, diary data permit scrutiny of the (potentially distinct) correlates of hangover occurrence or frequency vs. susceptibility (e.g., relation between hangover endorsement and amount of alcohol consumed).

A variety of other assessment issues complicate interpretation of existing data. In many diary studies and surveys, drinkers are asked to report the number of “drinks” consumed in a selected or typical drinking episode. Participants are sometimes coached or prompted concerning the definition of a “standard drink” [e.g. 7], but drinkers often do not have an accurate sense of what constitutes a “drink,” particularly for beverages that are freely-poured [10-12]. Therefore, self-reports of the number of drinks consumed in an event have limited precision. Similarly, some diary designs and survey instruments rely on the subject to determine whether or not a “hangover” occurred. The term “hangover” is subjective and could mean different things to different drinkers. Some of the evidence reviewed below is open to alternative interpretations invoking these kinds of assessment limitations. For example, some apparent risk group differences in hangover might be explained by group differences in the accuracy of drinking reports or “hangover” thresholds. To the extent that such factors contribute to measurement error, they could also make it harder for small studies to powerfully test group differences. This could account for some null findings.

Hangover and AUD Risk Factors: Cross-Sectional Evidence

Family History of Alcoholism

Alcohol use disorders run in families [e.g., 13, 14]. Four studies have used survey designs to test associations between family history of problem drinking and hangover frequency. Newlin & Pretorious [3] administered a measure tapping a variety of past-year hangover symptoms to a sample of male college students, including 13 sons of alcoholics and 25 sons of non alcoholics. There were modest risk group differences in quantity and frequency of past-year drinking. Even after taking these different drinking practices into account, the sons of alcoholics reported more frequent past-year hangover than the sons of nonalcoholics. Slutske et al. [4] administered a different retrospective assessment of past-year hangover symptoms to a sample of 1,230 college drinkers, 23% of whom reported a history of alcohol problems in a biological parent. The offspring of parents with alcohol problems reported more past-year hangover symptoms, even when risk group differences in drinking practices were covaried. Earleywine [15] did not detect significant differences between familial risk groups on a measure of past-year hangover frequency in a sample of 111 college drinkers. Piasecki, et al. [16] examined reports of past-year “headache (hangover)” the morning after drinking, collected on 6 occasions over an 11 year period from students recruited into a longitudinal, familial high-risk study. At all waves, offspring of alcoholics reported higher

hangover frequency. However, these risk group differences were only significant at the first two waves, when members of the sample were approximately 18 and 19 years old, respectively. It is noteworthy that hangover frequency declined over time in both risk groups in this research. Thus, the group differences in hangover frequency were observed when hangovers were most prevalent. This raises the possibility that the sensitivity of hangover frequency as a risk indicator may depend upon the developmental period in which it is assessed.

A small body of evidence has used laboratory designs to test associations between familial risk and hangover susceptibility, with mixed results. McCaul, et al. [17] examined the time courses of a variety of responses to a 1.0 g/kg alcohol challenge in 16 sons of alcoholics and 16 controls. Compared to the controls, sons of alcoholics reported elevated scores on a 10-item withdrawal/hangover scale that persisted for 6-7 hours after alcohol administration. Span & Earleywine [18] conducted a study in which 20 sons of alcoholics and 20 controls participated in two sessions of alcohol administration (.5 g/kg). Offspring of alcoholics reported more severe hangover symptoms the morning after these challenge sessions. Finally, Howland et al. [1] reported pooled analyses from 3 cross-over studies in which participants received placebo on one occasion and alcohol (1.2 g/kg for men and 1.1 g/kg for women) on the other. Self-reported hangover was absent after 97% of the placebo sessions, but approximately 75% of the participants reported at least mild hangover after the alcohol session. In a multivariate logistic regression model that also included sex, age, beverage type and drinking practices, family history of alcoholism was unrelated to the odds of hangover endorsement after the alcohol condition.

One study using daily diary methodology examined the relation between familial risk and hangover. Piasecki, et al. [7] asked 127 college students to carry electronic diaries over a 14 day period. Each morning, the students rated whether they had consumed alcohol the night before. If they had, they reported whether or not they experienced a “hangover (even just a little)” as a result. This assessment strategy, intended to be sensitive to post-intoxication symptoms that might not otherwise rise above students' personal threshold for hangover endorsement, was referred to by the authors as an index of “hangoverlike experiences” (HLEs). Thirty-four students (27%) reported that at least one biological parent had a history of alcohol problems. Students with parental problems were found to be more likely to endorse HLE in the diary over the course of the study. HLE was endorsed after 65% of drinking days among students with parental alcohol problems, compared to a base rate of 41% among students denying parental problems. Students with parents who had drinking problems reported consuming more drinks per occasion, but they were still found to be more likely to endorse HLE compared to students who denied parental problems even when the number of drinks in the episode was covaried. This potentially suggests that parental alcohol problems are associated with an increased HLE/hangover susceptibility.

In sum, although research into the question of whether familial risk for AUD is linked to hangover spans decades, the body of evidence remains small. Null findings have been reported, but when significant effects are found, they consistently point toward more frequent hangover or increased susceptibility to hangover among drinkers at high familial risk.

Sex Differences

There are clear sex differences in the prevalence of AUD, with men being more likely than women to earn both past-year and lifetime diagnoses [19]. Thus, in the broad or ultimate sense, men are at higher risk for AUD than women. On the other hand, a small literature examining the course of AUDs suggests women who are diagnosed reach clinically significant milestones more quickly than do men [e.g., 20, 21]. It could be argued that this "telescoping" of the time from drinking initiation to problem expression indicates an increased susceptibility to AUD among women assuming sufficient alcohol exposure.

Retrospective survey investigations have often found that men report more frequent past-year hangovers than women [4, 16, 22, 23]. Men also tend to drink more heavily than do women [e.g., 4, 16, 23, 25]. Thus, men have more opportunities to develop hangover. Some survey studies have found that women are predicted to have more frequent hangover once sex differences in the heaviness and frequency of drinking is accounted for. For instance, Slutske et al. [4] tested sex differences in individual past-year hangover symptoms and found two effects: men reported more frequently experiencing vomiting and sweating more than usual after drinking compared to women. However, men also reported drinking more frequently, consuming more drinks per occasion, and getting drunk more often than women. When these drinking practices were taken into account, women were found to be more likely to report 9 of 13 measured hangover symptoms. In the longitudinal high-risk study reported by Piasecki et al. [16], multilevel models reflected the expected association between heavy drinking frequency and hangover frequency. However, this relation was moderated by sex, such that heavy drinking frequency was more strongly related to hangover among women than men. These kinds of findings have been tentatively interpreted as evidence that women are more susceptible to hangover than are men [4, 16].

The vast majority of laboratory studies involving hangover induction have limited recruitment to a single sex, typically men. Most studies involving both men and women and explicitly testing sex differences in next-day symptoms have not found significant effects [1, 26-30]. Verster and colleagues recently reported a laboratory investigation in which women were found to report more severe symptoms the day after alcohol administration [31]. However, no sex differences were found for objective measures of cognitive performance in this study. Slight differences in dosing protocols across studies might help to explain the discrepant effects. Verster et al. [31] administered alcohol on the basis of body weight (1.4 g/kg). In contrast, other recent challenge studies failing to find sex differences in hangover symptoms attempted to equate subjects on a target breath alcohol concentration (BrAC) [e.g., 1, 29, 30, 32]. For example, Rohsenow, et al. [29] administered 1.2 g/kg ethanol to men and 1.0 g/kg to women so that all subjects would reach a target BrAC of 0.10 g%. Such procedures may permit more stringent tests of sex differences.

Diary studies have produced mixed evidence of sex differences in hangover susceptibility. Jackson [5] asked a sample of undergraduates to make once-daily web-based reports on drinking behaviors. Analyses examined the predictive validity of various cut scores that might be used to index "binge" or heavy episodic drinking. One criterion measure was the severity of hangover symptoms rated each day after drinking occurred. Fifteen or more drinks appeared to be the optimal threshold for predicting hangover symptoms for men,

whereas 10 or more drinks appeared to be a more appropriate hangover threshold for women. In our diary investigation of college students [7], we found men and women did not differ with respect to the likelihood of reporting an HLE during the 14-day study period. However, women were found to be more likely to report HLE given the occurrence of drinking. In an additional model, we found an interaction between the number of self-reported drinks consumed and sex in predicting HLE endorsement, such that the relation between number of drinks and HLE endorsement was stronger among women. Women reported consuming an average of 8.2 drinks the night prior to mornings on which they experienced HLE. In contrast, men reported an average of 15.1 drinks prior to HLE. These findings suggested possible increased susceptibility to HLE among women compared to men. Two studies of young Danish tourists on holiday, however, failed to find sex differences in the severity of acute hangover symptoms the day after drinking when the number of drinks consumed was covaried [8,9].

When sex differences in hangover have been found, analyses have typically examined the *number* of drinks consumed. It is notable that laboratory research, in which *dose* of alcohol is more carefully controlled, has generally failed to find sex differences in hangover. In laboratory studies in which all participants are equated on a target breath alcohol concentration, men must consume more drinks than women [e.g., 32]. Sex differences in the pharmacokinetics of alcohol therefore appear to provide a reasonable account for the pattern of existing evidence. At the same number of drinks, women are more prone to hangover than men, but this is likely explained by the tendency for women to attain higher blood alcohol concentrations (BACs). At equivalent BACs, men and women appear to be indistinguishable with respect to most hangover effects.

Smoking

Cigarette smoking and tobacco dependence are strongly related to heavy drinking and AUD [33-36]. Tobacco and alcohol are frequently used simultaneously [e.g., 37] providing an opportunity for pharmacologic modulation of alcohol responses by smoking. Additionally, smokers likely differ from nonsmokers with respect to alcohol sensitivity owing to common genetic vulnerabilities for drinking and smoking as well as acquired processes such as cross-tolerance [38, 39]. Smoking has been explored as a correlate of hangover in only a handful of studies. In one epidemiologic survey of Finnish men, measures of lifetime smoking exposure were higher among frequent hangover sufferers (though statistical tests were not reported) [40]. A small number of laboratory studies have included smokers and reported tests for differences in hangover symptomatology; none found significant moderation of hangover by smoking status [26, 27, 41]. In our diary investigation of college students [7], we found that smokers were more likely than nonsmokers to report HLE during the observation period. However, this effect appeared attributable to differences in the frequency of drinking because it was eliminated when analyses were restricted to post-drinking days. Smokers and nonsmokers reported comparable numbers of drinks, on average, prior to HLE (10.0 and 10.1, respectively). Hesse and Tutenges [8] found that, among young tourists, neither being a regular smoker nor smoking the night before the assessment was associated with current hangover severity. In sum, limited evidence hints that hangover may be more frequent among smokers. If so, this is likely to be explained by

more frequent drinking among smokers because smoking status does not appear to be associated with differential hangover susceptibility.

Alcohol Metabolizing Genes

Acetaldehyde, a metabolic byproduct of ethanol, is toxic and produces physical signs and symptoms (e.g., facial flushing, tachycardia, headache, nausea) if it accumulates [42]. Because these “flushing” responses overlap with the hangover syndrome, there is a plausible rationale for expecting that genetic variants associated with either more active forms of alcohol dehydrogenase (ADH, the enzyme needed to break down alcohol to acetaldehyde) or less active forms of aldehyde dehydrogenase (ALDH , the enzyme needed for elimination of acetaldehyde) would be related to measures of hangover. Alleles associated with increased acetaldehyde and flushing phenotypes are robustly associated with protection from AUD [42-44].

Two survey investigations have demonstrated associations between *ALDH2* alleles and hangover in East Asian populations [23, 24]. Wall and colleagues [24] did not find an association between the flushing-related *ALDH2*2* genotype and past-year hangover frequency in a sample of college students of Chinese, Japanese, or Korean descent. However, carriers of *ALDH2 *2* alleles scored significantly higher on a measure asking participants to estimate the severity of the hangover they would experience after consuming 6 drinks (if male) or 4 drinks (if female) over the course of a few hours. Yokoyama, et al. [23] found that the relation between the amount of daily alcohol consumption and hangover frequency was stronger among male Japanese workers with an *ALDH2*1/2*2* genotype compared to *ALDH2*1* homozygotes. When asked to indicate the number of drinks typically preceding hangover, carriers of *ALDH2*2* reported lower consumption compared to drinkers homozygous for *ALDH2* 1*. A third study [45] investigated the association between *ADH1B* and expected severity of hangover after 6 or 4 drinks (depending upon sex) in a sample of college students of European descent. Carriers of the flushing-related *ADH1B*2* allele reported anticipating more severe hangover at this level of drinking. Thus, existing data are fairly consistent in indicating that drinkers with genotypes known to lead to acetaldehyde accumulation and confer protection from AUD are also more susceptible to hangover effects, at least as gauged by retrospective survey or self-reports of the expected aftereffects of drinking.

Other Individual Differences

Personality Risk—A handful of investigations have explored relations between hangover and the MacAndrew scale [46], an empirically derived MMPI scale thought to index personality risk for alcoholism. Earleywine [15] found that frequency of hangover symptoms in the past year increased with higher scores on the MacAndrew scale in a sample of college student drinkers. This association was significant in a model controlling typical drinking practices and other factors. In another investigation of college students, Earleywine [47] computed residual past-year hangover frequency scores from a regression analysis in which average quantity of alcohol per occasion was entered as a predictor. Conceptually, these residuals tap something like hangover susceptibility, i.e., individual differences in hangover frequency not accounted for by drinking practices. Residual hangover scores were

cross-sectionally associated with scores on both the MacAndrew scale and the Short Michigan Alcoholism Screening Test (SMAST) [48], a measure tapping symptoms of problem drinking. Personality risk interacted with residual hangover scores in predicting alcohol problems, such that the MacAndrew scale was only associated with SMAST scores among individuals who reported frequent hangover. Among women, residual hangover scores statistically mediated the association between personality risk and problem drinking. These findings might suggest that personality risk is only translated into disordered drinking among those drinkers with a permissive biological substrate (indexed by hangover susceptibility) [47]. Span and Earleywine [18] administered the MacAndrew scale to participants in their familial high-risk alcohol challenge study. Results revealed no relation between MacAndrew scores and the severity of next-day symptoms after alcohol challenge. Thus, the evidence linking personality risk and hangover susceptibility is mixed.

Heavy Drinking—Frequency of hangover was cross-sectionally related to self-reports of heavy drinking frequency in a number of the survey studies described above [4, 16, 47]. Other studies have documented similar associations. Maney, et al. [49] classified adolescent current drinkers in the National Longitudinal Study of Adolescent Health as either high or low risk, based on whether or not they reported a lifetime “binge” involving consumption of 5 or more drinks in a sitting. They then compared high- and low-risk drinkers with respect to a variety of alcohol-related problems. Across all these comparisons, the largest effect size was found for lifetime hangover experience, with the high-risk group being significantly more likely to report hangover. In a survey of middle-aged Finnish men, Kauhanen, et al [40] found that monthly or more frequent hangover was concentrated in the highest quartile of drinking heaviness (43.8% vs. 6.6% in the pooled lowest 3 quartiles). Of course, such findings may simply reflect the fact that hangover is a dose-dependent phenomenon, and so only heavier drinkers have the opportunity to develop hangovers. However, as we detail in later sections, it is possible to construe these relations as consistent with a variety of explanations.

Sensitivity to Alcohol—Some evidence hints that hangover propensity might be associated with individual differences in alcohol response. Ylikahri, et al. [2] found those who reported severe hangover the day after a standard challenge dose rated themselves as more intoxicated immediately post-drink compared to individuals who did not complain of severe hangovers the next day. Those suffering severe hangover attained BACs equivalent to those of other participants, suggesting the elevated intoxication reports reflected differences in alcohol sensitivity per se. Thus, hangover-reactive individuals may be more sensitive to *both* the immediate and post-intoxication effects of alcohol.

Prospective Associations between Hangover and Subsequent AUD

To our knowledge, the results from the longitudinal high-risk study reported by Piasecki, et al. [16] represent the only direct test of whether hangover measures predict later AUD outcomes. In this study, 489 college freshmen at high or low familial risk for alcoholism were assessed on six occasions spanning 11 years (up to when participants were approximately age 30). Hangover frequency during the freshman year predicted diagnoses of any AUD *(DSM-III* alcohol abuse or alcohol dependence) [50] 7 and 11 years later, even

when freshman year diagnostic status, frequency of heavy drinking, sex, and familial risk were covaried. Other acute consequences of heavy drinking during the freshman year (blackout, tolerance, perceived dependence, morning drinking, and withdrawal) were univariately associated with later AUD diagnoses, but only withdrawal (i.e., "Have you ever had 'the shakes' after stopping or cutting down on drinking?") was significant when covariates were included. Freshman year hangover frequency incrementally improved the model that included freshman year withdrawal and other covariates. Thus, frequent hangover forecasted the onset of AUDs. This prediction of AUD at later waves was unique to hangover and withdrawal-like adverse reactions to drinking during the freshman year, not a general pattern associated with any negative consequence of drinking.

Hypotheses Concerning Links between Hangover Measures and AUD

The available evidence, though quite limited, suggests the links between hangover measures and AUD could be complex or multifaceted. In this section, we sketch some hypotheses that could be generative in future research. It is unlikely that we have identified all the possible mechanisms, and it is also likely that many of these ideas will ultimately prove to be incorrect. Our chief goal at this stage is to illustrate that there are numerous ways to conceptualize (and hence, to investigate) relations between hangover measures and AUD risk. Broadly speaking, the hypotheses can be grouped according to whether they posit that hangover discourages drinking, encourages drinking, or is independent of local drinking behavior.

Hangover as a Punisher

It is intuitively appealing to conjecture that hangover should be a punisher that deters future drinking. Certainly, depictions of hangover in popular culture often highlight feelings of regret and resolutions to avoid alcohol. The widespread interest in hangover cures [51] suggests many drinkers find hangover aversive. (On the other hand, this same search for cures suggests drinkers may view hangovers as an inconvenient impediment to drinking, viz., a problem to be solved rather than a deterrent).

Of the evidence reviewed above, the literature concerning links between alcohol metabolizing genes and hangover provide the clearest support for the notion that hangover discourages drinking. Genotypes associated with aversive flushing responses to alcohol are both indicators of protection from AUD and, apparently, markers of increased susceptibility to hangover. It is also noteworthy that the flushing response to alcohol is similar to the response to alcohol with disulfiram, a pharmacotherapy used to deter drinking [42, 52]. One potential caveat is that it is not entirely clear from existing evidence that persons susceptible to the flushing syndrome are actually referring to the same phenomenon as other drinkers when they use the term "hangover." Conceivably, self reports of "hangover" among those prone to flushing might be influenced, at least partly, by reflections on their more immediate aversive reactions to alcohol consumption. Although acetaldehyde has been posited to be a major cause of hangover symptoms [53, 54], other mechanisms have been hypothesized as well (e.g., beverage congeners [30, 55-57]; immune and inflammatory processes [28, 57, 58]; sleep disturbance [25, 30]). Thus, it is possible that drinkers susceptible to the flushing

syndrome experience next-day hangovers that are qualitatively different from those of other drinkers because they arise from a different profile of contributory causes.

Hangover is a delayed effect of drinking, not typically arising until the blood alcohol concentration starts to fall and peaking when BAC is near zero [2, 41]. Reinforcers and punishers tend to have maximum behavioral influence when they are delivered immediately after the target behavior [59]. Because the influence of a punisher weakens with delay, hangover could be quite aversive without necessarily having a strong effect on drinking behavior. In this regard, it is interesting that the clearest evidence linking hangover susceptibility to protection from AUD comes from persons prone to the flushing syndrome. For these individuals, hangover susceptibility might not be a core mechanism accounting for AUD protection. Instead, hangover complaints may serve as a marker of their (potentially more behaviorally potent) immediate aversive reactions to alcohol.

Conditioned Taste Aversion—The prominence of nausea in hangover suggests conditioned taste aversion (CTA) learning is one possible mechanism through which hangover could deter drinking. CTA represents a powerful, primitive defensive system specifically prepared to punish ingestion of toxic substances. Relative to other forms of Pavlovian conditioning, CTA is unique in that associations can be formed between conditioned stimuli (CSs; flavors) and an unconditioned stimulus (USs; malaise) even when a long delay occurs between their presentations [60]. Thus, CTA learning could occur even though hangover tends to arise many hours after drinking initiation. Notably, there is a substantial literature using inbred rodent strains to examine genetic relations among CTA acquisition and other alcohol-related phenotypes, such as acute and chronic withdrawal and home cage ethanol drinking [e.g., 61-63]. This literature may serve as a fertile source of hypotheses useful for future investigations of possible associations among hangover, drinking avoidance, and individual differences.

There are some reasons to question the generality or significance of any role for CTA in accounting for the avoidance of alcohol after hangover. CTA learning involves associating a novel flavor with malaise. Drinkers will often have had extensive prior exposure to the flavor(s) of the beverage(s) causing a particular hangover, and this could inhibit the acquisition of CTA learning. Of course, alcoholic beverages come in many flavors. Thus, hangover might promote avoidance of a specific beverage (or novel foods consumed during drinking episodes) rather than avoidance of alcohol consumption per se.

In sum, although it seems plausible that hangover should punish drinking, there is need to explicitly document this. Research is also needed to identify any individual differences in deterrence of drinking and to delineate the processes through which it may operate.

Hangover as a Motivator of Drinking

Theories of addiction often point to the use of a drug to alleviate aversive abstinence effects as a key process in the escalation of use and development of dependence [64]. Because alcohol relieves its own after-effects, hangover symptoms may set the occasion for negative reinforcement from drinking [3, 18].

Such “hair-of-the-dog” drinking could lead to problems for the drinker via several routes. Morning drinking tends to run afoul of social norms, and thus may initiate a transition to more generally deviant patterns of alcohol involvement. To the extent that it interferes with role obligations, morning drinking could result in “telescoping” by hastening the emergence of clinically significant impairment necessary to earn AUD diagnoses. Morning drinking could also promote the development of physical dependence by both increasing the total amount of alcohol consumed and by leaving fewer periods of abstinence in a typical day.

It is important to note that hair-of-the-dog drinking need not be synonymous with morning drinking. If hangover effects are long-lasting, an individual might still experience symptomatic relief upon drinking at later, more socially acceptable times of day. At least in theory, hair-of-the-dog drinking could promote a pathological pattern of consumption, even if it occurs only occasionally. For example, Baker et al. [64] proposed a reformulated negative reinforcement model of addiction positing that manifestations of physical dependence occur early in the drug use career and that instances of drug-contingent relief of withdrawal are formative influences on the pathway to drug dependence. Such experiences theoretically cause the user to learn to use the drug as a prepotent response to negative affect. Thus, hangover might not need to serve as a frequent trigger of drinking. Instead, a few instances of hangover relief might spur problematic drinking by stamping in a maladaptive learned association between distress or discomfort (from any source) and alcohol use. In this light, it is notable that among the various reasons people give for consuming alcohol, coping motives are most strongly related to problematic alcohol use [65].

Hangover as a Marker

A host of possible explanations conceptualize hangover measures as markers of other important traits of the drinker. None of these accounts *require* any acute modulation of drinking behavior by the hangover state to explain an association between hangover measures and AUD risk. However, these accounts are frequently compatible with the possibility that hangover has local and direct effects on drinking behavior.

Rising Limb Effects—Individual differences in the experienced *initial* effects of drinking may have a bigger influence on future drinking behavior than do delayed punishing effects. It is intriguing to speculate that hangover could represent a “rebound” or “mirror image” of hedonically positive initial intoxication effects [3]. Some theorists have suggested that hangover might be conceptualized as an opponent process [66] “b-state” that is recruited to counter the affective disturbance provoked by an alcohol US [3, 9, 67]. From this perspective, one might predict that the hangover should be related to the size of the “a-state” to be opposed. Thus, persons who either drink very heavily (i.e., behaviorally inducing large a-states) or are constitutionally sensitive to alcohol reward (i.e., sensitive to large a-states) should be more likely to report hangovers. In either case, the signal function of the hangover report may be to indirectly identify individuals who are deriving especially large affective or hedonic benefits soon after consuming alcohol in their daily lives.

As noted earlier, some evidence suggests drinkers who are susceptible to hangover also report stronger subjective intoxication from a fixed dose of alcohol [2]. Interestingly, offspring of alcoholics [68-70] and persons with flushing-related genotypes [71] may be more sensitive to some effects of alcohol on the rising limb of the blood alcohol curve. Because both groups may be more sensitive to hangover as well, it seems plausible that increased initial sensitivity to alcohol might covary with hangover susceptibility more generally. However, this hypothesis remains to be explicitly tested.

Withdrawal and Tolerance—The symptoms of hangover resemble those of alcohol withdrawal [72]. Theorists have frequently entertained the notion that hangover is a form of acute alcohol withdrawal [3, 9, 15, 54, 67, 73]. From this perspective, it has been hypothesized that measures of hangover susceptibility could be early markers of individual differences in the liability to developing physical dependence.

In humans, the existence of the acute withdrawal phenomenon has been demonstrated most vividly in the opiate literature. In these studies, participants are administered a single dose of opiate, then administered an opiate antagonist a few hours later. At low doses of opiate, administration of the antagonist simply reverses opiate effects. However, when the antagonist is administered after a high dose of opiate, many of the classic signs of chronic opiate withdrawal (e.g., yawning, watering eyes, dysphoria) are observed [e.g., 74]. Such data suggest a single dose of drug may be sufficient to rapidly provoke tolerance-like adaptations and withdrawal symptoms. That is, the roots of physical dependence may be evident after a single dose of drug. The data also suggest that an acute withdrawal response is most likely to occur with large doses of drug. Notably, hangover is also a dose-dependent phenomenon.

Although animal models of acute alcohol withdrawal have been developed [e.g., 75], acute withdrawal has not received extensive study in humans. However, a great deal of evidence documents acute tolerance to alcohol. For example, subjective responses to alcohol are diminished on the descending limb of the blood alcohol concentration curve compared to comparable BACs on the rising limb [e.g., 76, 77]. Similarly, subjective responses to alcohol diminish over time when the blood alcohol concentration is clamped at a constant level [78]. In the current context, it is interesting that offspring of alcoholics show more pronounced acute tolerance to alcohol compared to offspring of nonalcoholics [78]. Taken together with the evidence reviewed earlier suggesting familial risk for alcoholism may be related to hangover susceptibility, these findings hint at the possibility that hangover could represent an acute withdrawal syndrome arising from intra-administration adaptations to the drinking episode (i.e. acute tolerance). Such speculation is also compatible with a model proposed by Begleiter & Porjesz [79], which posits that offspring of alcoholics possess a neural constitution that makes them susceptible to increased tolerance, enhanced reinforcement from alcohol, and increased liability to physical dependence and withdrawal-like effects.

It is possible to unify these speculations about acute tolerance and withdrawal with the opponent process account mentioned earlier. The opponent process model posits that the b-state is recruited to counteract the a-state. Thus, if hangover is construed as a b-state, it is conceivable that it is a marker or outgrowth of the very compensatory processes responsible

for tolerance. If so, it may mark the operation of a core component of addiction. For example, Koob & LeMoal's allostatic model [80], a reformulated opponent-process account of addiction, highlights the recruitment of brain anti-reward processes to counteract drug-attributable reward dysregulation as a key milestone in the development of drug dependence.

Risky Patterns of Intake—Hangover could serve primarily as a marker of distinctive, problematic patterns of alcohol intake. As noted earlier, there is a sense in which this observation is self-evident and not especially interesting - drinking heavily is a necessary precondition for hangover. What we suggest here is that reports of hangover may be especially sensitive markers of very high-dose binge exposures that might contribute unique information about AUD risk. Alcohol use is often measured in survey research using quantity-frequency measures or indexes of “binge” drinking that use somewhat low thresholds (i.e., 5 drinks in a sitting for men, 4 drinks for women) [5, 81]. At least among young drinkers, hangover events are preceded by drink totals that significantly exceed these levels [5, 7]. Thus, hangover measures may reflect the occurrence of very large binges. It is interesting to apply this explanation to some of the suggestive evidence reviewed earlier. For instance, if offspring of alcoholics are more likely to engage in very large binges, the residual association between familial risk and hangover after covarying conventional measures of typical drinking practices may simply reflect this specific group difference in drinking pattern. Similarly, the prospective association between hangover frequency and later AUD [16] might simply reflect the fact that adding information concerning the occurrence of very large binges to the prediction model more fully represents individual differences in drinking pattern and intensity. Alternatively, large binges might have unique consequences (e.g., neurotoxic effects on cognitive abilities; [82]) that could affect subsequent drinking behaviors.

Hangover occurrence could conceivably be a marker of unique intra-episode patterns of use. For instance, hangover might be related to consuming shots or “gulping” drinks in a way that produces an especially steep rising slope of the blood alcohol concentration curve [3]. Blackout, another “morning after” phenomenon, has been related to the speed of consumption [83, 84]. Additionally, differences in alcohol response between offspring of alcoholics and nonalcoholics may be accentuated under conditions of speeded alcohol administration [68]. BAC slope may or may not turn out to be the important parameter. The main point is that hangover could mark some *manner of drinking* that adds incremental variance above *amount of drinking* in predicting AUD risk.

The opponent process model predicts susceptibility to hangover could be *acquired* because the b-state is thought to become stronger and more efficiently recruited with practice [66]. Consistent with this assertion, a recent study of hangover among young tourists found that the drinkers who had been on holiday (and presumably drinking) for longer reported more severe acute hangover symptoms [8]. A second, prospective study using a similar sample demonstrated that hangovers became more severe over the course of the holiday and that the relation between the number of drinks consumed and hangover severity become stronger on later days [9].

The conditioned compensatory response model of tolerance [87] might also suggest hangover experiences could change with experience. This model places greater emphasis on the role of associative learning in eliciting drug-opposite responses. One interesting type of associative learning, termed the homoreflex, occurs when the early portion of an interoceptive experience comes to serve as a conditioned stimulus signaling later components of the experience [e.g., 64, 85, 86]. In the case of drug self-administration, the initial sensations produced by drug ingestion should be natural predictors of later, larger drug effects. These intra- administration associations may contribute to tolerance and withdrawal by eliciting conditioned compensatory responses that counter the homeostatic disturbance caused by drug [87]. Indeed, prior training with large doses of drug has been shown to be associated with acute withdrawal-like responses when a low dose of drug designed to mimic drug onset cues is administered [88].

This raises the possibility that frequent binge drinkers could eventually become more susceptible to hangover after *low-to-moderate* doses of alcohol because the effects of their initial drink(s) come to evoke homoreflexive responses that anticipate the occurrence of a large binge. When drinking is moderate, disproportionate compensatory responses might manifest as hangover. In other words, binge drinkers may inadvertently train themselves to be vulnerable to “alcohol-elicited alcohol withdrawal” [cf. 88]. If such a process occurs, it could have the ironic consequence of discouraging drinking restraint.

As mentioned earlier, Span and Earleywine [18] found that sons of alcoholics reported elevated hangover symptoms after alcohol challenge compared to sons of nonalcoholics. Interestingly, the sons of alcoholics also reported higher symptoms the morning after a *placebo* session. The risk groups did not differ with respect to expectancies for hangover effects prior to beverage administration, suggesting this was not the source of group differences following the placebo administration. Conceivably, the placebo beverage might have mimicked alcohol cues sufficiently to provoke a hangover-like compensatory response or opponent process among the sons of alcoholics. Of course other explanations, including measurement error, could explain the same finding.

Traits and Abilities—Hangover might associate with risk or protection from AUD by marking individual differences in traits or abilities that are more directly involved in AUD risk.

Hangover may be an effective deterrent for drinking for most alcohol users. These individuals may not report frequent hangover because one or two isolated hangovers is sufficient to spur them to use self-regulation strategies to keep alcohol consumption within a safer range. If this is the case, then *frequent* hangover is potentially a marker of the tendency to *persist* in drinking despite hangover. This could be explained by a deficit in the ability to learn from punishment contingencies. A recent study of college student drinkers found that students tended to overestimate how many drinks would be required to experience a future hangover (compared to reports of past hangovers) [89]. Interestingly, the extent to which students overestimated their drinking capacity was associated with typical drinking heaviness. Thus, a failure to learn from past drinking experiences appeared linearly related to drinking behavior. In addition, low IQ has been found to correlate with frequent hangover

[90] and could play a role in this kind of process. Research has also shown that impaired punishment learning, like hangover, is associated with a familial history of alcoholism [91].

Individual differences in impulsivity are related to AUD risk [92]. Avoiding hangover requires forgoing the short-term reward promised by the next drink to avert a delayed consequence. Highly impulsive individuals may find it especially difficult to balance these competing signals and effectively regulate their drinking, particularly under the influence of alcohol, which impairs inhibitory control [93]. Finn and colleagues [94] recently demonstrated that impulsivity moderated the association between negative alcohol expectancies and heavy drinking practices. They showed that negative expectations about how one would feel the day after heavy drinking (including hangover effects) were associated with lower drinking. However, this relation was much weaker among persons high in impulsivity.

Another possibility is that frequent hangover could reflect neuropharmacologic vulnerabilities to impaired control over drinking within an episode. For instance, Krystal and colleagues have demonstrated that alcoholics and their relatives show blunted responses to *N*-methyl *D*-aspartate glutamate receptor antagonists [95, 96]. Because ethanol is a glutamate antagonist, they suggested that these individuals may be insensitive to critical "stop signals" that normally serve as warnings to cease drinking. Thus, offspring of alcoholics may report more frequent hangover because they have difficulty detecting their limits [97]. More generally, it is conceivable that frequent hangover is a marker of a diminished capacity to sense the consequences of drinking and use this information to regulate behavior.

Diagnostic Considerations—Hangover frequency or propensity might influence the likelihood that an individual earns an AUD diagnosis. A key concept in AUD diagnosis is that drinking causes impairment or distress for a drinker. A susceptibility to hangover might increase the chances that a given drinker develops problems secondary to his or her drinking. Imagine two individuals who drink the same amount, but one is more susceptible to hangover effects than the other. The hangover-susceptible drinker is more likely to suffer the next day, experience role impairment (e.g, skip work or school) and perhaps drink to alleviate the hangover, potentially compounding role impairment. These extra burdens from drinking may allow drinking-related problems to "ripen" enough to be diagnosable.

Hangover could be construed as a supplemental diagnostic criterion. The plausibility of this suggestion is supported by several recent investigations using item response theory. These studies show that a wide array of drinking-related experiences complement existing diagnostic criteria in defining a unitary continuum of drinking problems [e.g., 98, 99]. Additionally, several diagnostic criteria for DSM-IV alcohol dependence [100] can be understood as directly or indirectly related to hangover. We have already described potential overlap between hangover, tolerance, and withdrawal. Use of alcohol in larger amounts or for longer than intended and spending time recovering from the effects of alcohol are additional alcohol dependence symptoms with clear conceptual relations to hangover.

Alternatively, it is possible that hangovers contribute to misclassification. For instance, if hangover is truly distinct from withdrawal [54], then symptomatic overlap between hangover and alcohol withdrawal symptoms might lead to overdiagnosis of alcohol dependence.

Conclusions

Relations between hangover and AUD risk and protection processes have received only sporadic attention in alcohol research. This may be partly attributable to the intuitive plausibility of the hypothesis that hangover deters drinking – this seems so obvious that it may not appear to require testing. As we have shown, some available evidence supports this idea, but a fair amount of data can be adduced to support the opposite conclusion. We have tried to illustrate that there are numerous ways to think about the meaning of hangover assessments and their relation to drinking behaviors. Research is needed that specifically probes (a) whether, when, how, and for whom hangover affects near-term drinking behaviors, and (b) the correlates of hangover frequency and susceptibility. Research is also needed to understand how increased hangover susceptibility could be (possibly) associated with both AUD risk (e.g. familial risk) and protection (e.g., flushing syndrome). Conceivably, hangover susceptibility might be traceable to a heterogeneous set of causes (e.g., alcohol metabolism, associative learning, neuropharmacologic risk factors) and these different pathways may account for some of the seemingly-discrepant findings in the existing literature. Increasing basic research into the pathogenesis of hangover will undoubtedly eliminate some hypotheses and suggest still more ways of conceptualizing hangover-AUD relations.

Acknowledgement

Preparation of this article was facilitated by support from NIH grants 5P60AA011998 and 5T32AA013526.

References

1. Howland L, Rohsenow DJ, Allesnworth-Davies D, et al. The incidence and severity of hangover the morning after moderate alcohol intoxication. Addiction. 2008; 103:758–65. [PubMed: 18412754]
2. Ylikarhri RH, Huttunen MO, Eriksson CJP, Nikkila EA. Metabolic studies on the pathogenesis of hangover. Eur J Clin Invest. 1974; 4:93–100. [PubMed: 4832720]
3. Newlin DB, Pretorious MB. Sons of alcoholics report greater hangover symptoms than sons of nonalcoholics: A pilot study. Alcohol Clin Exp Res. 1990; 14:713–6. [PubMed: 2264599]
4. Slutske WS, Piasecki TM, Hunt-Carter EE. Development and initial validation of the Hangover Symptoms Scale: Prevalence and correlates of hangover in college students. Alcohol Clin Exp Res. 2003; 27:1442–50. [PubMed: 14506405]
5. Jackson KM. Heavy episodic drinking: Determining the predictive utility of five or more drinks. Psychol Addict Behav. 2008; 22:68–77. [PubMed: 18298232]
6. Muraven M, Collins RL, Morsheimer ET, Shiffman S, Paty JA. The morning after: Limit violations and the self-regulation of alcohol consumption. Psychol Addict Behav. 2005; 19:253–62. [PubMed: 16187803]
7. Piasecki TM, Slutske WS, Wood PK, Hunt-Carter EE. Frequency and correlates of diary-measured hangoverlike experiences in a college sample. Psychol Addict Behav. 2010; 24:163–9. [PubMed: 20307125]

8. Hesse M, Tutenges S. Evening experiences versus drinking indicators as predictors of hangover on a summer holiday. Am J Addict. 2009; 18:130–4. [PubMed: 19283564]
9. Hesse M, Tutenges S. Predictors of hangover during a week of heavy drinking on holiday. Addiction. 2010; 105:476–83. [PubMed: 20402991]
10. Wansink B, van Ittersum K. Shape of glass and amount of alcohol poured: Comparative study of the effect of practice and concentration. BMJ. 2005; 331:1512–4. [PubMed: 16373735]
11. White AM, Kraus CL, McCracken LA Swartzwelder HS. Do college students drink more than they think? Use of a free-pour paradigm to determine how college students define standard drinks. Alcohol Clin Exp Res. 2003; 27:1750–6. (2003). [PubMed: 14634490]
12. Lemmens PH. The alcohol content of self-report and “standard” drinks. Addiction. 1994; 89:593–601. [PubMed: 8044126]
13. Dawson DA, Harford TC, Grant BF. Family history as a predictor of alcohol dependence. Alcohol Clin Exp Res. 1992; 16:572–5. [PubMed: 1626658]
14. Hussong A, Bauer D, Chassin L. Telescoped trajectories from alcohol initiation to disorder in children of alcoholic parents. J Abnorm Psychol. 2008; 117:63–78. [PubMed: 18266486]
15. Earleywine M. Personality risk for alcoholism covaries with hangover symptoms. Addict Behav. 1993; 18:415–20. [PubMed: 8213295]
16. Piasecki TM, Sher KJ, Slutske WS, Jackson KM. Hangover frequency and risk for alcohol use disorders: Evidence from a longitudinal high-risk study. J Abnorm Psychol. 2005; 114:223–34. [PubMed: 15869353]
17. McCaul ME, Turkkan JS, Svikis DS, Bigelow GE. Alcohol and secobarbital effects as a function of familial alcoholism: Extended intoxication and increased withdrawal effects. Alcohol Clin Exp Res. 1991; 15:94–101. [PubMed: 2024739]
18. Span SA, Earleywine M. Familial risk for alcoholism and hangover symptoms. Addict Behav. 1999; 24:121–5. [PubMed: 10189979]
19. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. Drug Alcohol Depend. 2004; 74:223–34. [PubMed: 15194200]
20. Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, Mattson ME. Telescoping of landmark events associated with drinking: A gender comparison. J Stud Alcohol. 1999; 60:252–60. [PubMed: 10091964]
21. Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, Diehl A. Neuroimaging of gender differences in alcohol dependence: Are women more vulnerable? Alcohol Clin Exp Res. 2005; 29:896–901. [PubMed: 15897736]
22. Smith CM, Barnes GM. Signs and symptoms of hangover: Prevelance and relationship to alcohol use in a general adult population. Drug Alcohol Depend. 1983; 11:249–69. [PubMed: 6617465]
23. Yokoyama M, Yokoyama A, Yokoyama T, et al. Hangover susceptibility in relation to aldehyde dehydrogenase-2 genotype, alcohol flushing, and mean corpuscular volume in Japanese workers. Alcohol Clin Exp Res. 2005; 29:1165–71. [PubMed: 16046871]
24. Wall TL, Horn SM, Johnson ML, Smith TL, Carr LG. Hangover symptoms in Asian Americans with variants in the aldehyde dehydrogenase (ALDH2) gene. J Stud Alcohol. 2000; 61:13–7. [PubMed: 10627091]
25. McKinney A, Coyle K. Alcohol hangover effects on measures of affect the morning after a normal night's drinking. Alcohol Alcohol. 2006; 41:54–60. [PubMed: 16260448]
26. Collins WE, Chiles WD. Laboratory performance during acute alcohol intoxication and hangover. Hum Factors. 1980; 22:445–62. [PubMed: 7429513]
27. Collins WE. Performance effects of alcohol intoxication and hangover at ground level and at simulated altitude. Aviat Space Environ Med. 1980; 51:327–35. [PubMed: 7369966]
28. Wiese JG, McPherson S, Odden MC, Shlipak MG. Effect of Opuntia ficus indica on symptoms of the alcohol hangover. Arch Intern Med. 2004; 164:1334–40. [PubMed: 15226168]
29. Rohsenow DJ, Howland J, Minsky SJ, Greece J, Almeida A, Roehrs TA. The Acute Hangover Scale: A new measure of immediate hangover symptoms. Addict Behav. 2007; 32:1314–20. [PubMed: 17097819]

30. Rohsenow DJ, Howland J, Arendt JT, Almeida, et al. Intoxication with bourbon versus vodka: Effects on hangover, sleep, and next-day neurocognitive performance in young adults. Alcohol Clin Exp Res. 2010; 34:509–18. [PubMed: 20028364]
31. Verster JC, van Duin D, Volkerts ER, Schreuder AH, Verbaten MN. Alcohol hangover effects on memory functioning and vigilance performance after an evening of binge drinking. Neuropsychopharmacology. 2003; 28:740–6. [PubMed: 12655320]
32. Howland J, Rohsenow DJ Greece JA, et al. The effects of binge drinking on college students' next-day academic test-taking performance and mood state. Addiction. 2010; 105:655–65. [PubMed: 20403018]
33. Morgen CS, Bové KB, Larsen KS, Kjær SK, Grønbæk M. Association between smoking and the risk of heavy drinking among young women: A prospective study. Alcohol Alcohol. 2008; 43:371–5. [PubMed: 18223292]
34. Jensen MK, Sorenson TIA, Andersen AT, et al. A prospective study of the association between smoking and later alcohol drinking in the general population. Addiction. 2003; 98:355–63. [PubMed: 12603235]
35. Madden PAF, Bucholz KK, Martin NG, Heath AC. Smoking and the genetic contribution to alcohol dependence risk. Alcohol Res Health. 2000; 24:209–14. [PubMed: 15986715]
36. Jackson KM, Sher KJ, Wood PK, Bucholz KK. Alcohol and tobacco use disorders in a general population: Short-term and long-term associations from the St. Louis Epidemiological Catchment Area Study. Drug Alcohol Depend. 2003; 71:239–53. [PubMed: 12957342]
37. Piasecki TM, McCarthy DE, Fiore MC, Baker TB. Alcohol consumption, smoking urge, and the reinforcing effects of cigarettes: An ecological study. Psychol Addict Behav. 2008; 22:230–9. [PubMed: 18540720]
38. True WR, Xian H, Scherrer JF, et al. Common genetic vulnerability for nicotine and alcohol dependence in men. Arch Gen Psychiatry. 1999; 56:655–61. [PubMed: 10401514]
39. Drobes DJ. Concurrent alcohol and tobacco dependence: Mechanisms and treatment. Alcohol Res Health. 2002; 26:136–42.
40. Kauhanen J, Kaplan GA, Goldberg DD, Cohen RD, Lakka T, Salonen JT. Frequent hangovers and cardiovascular mortality in middle-aged men. Epidemiology. 1997; 8:310–4. (1997). [PubMed: 9115028]
41. Ylikarhri RH, Leino T, Huttunen MO, Poso AR, Eriksson CJP, Nikkila EA. Effects of fructose and glucose on ethanol-induced metabolic changes and on the intensity of alcohol intoxication and hangover. Eur J Clin Invest. 1976; 6:93–102. [PubMed: 1253812]
42. Edenberg HJ. The genetics of alcohol metabolism: Role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007; 30:5–13. [PubMed: 17718394]
43. Luczak SE, Glatt SJ, Wall TL. Meta-analyses of ALDH2 and ADH1B with alcohol dependence in Asians. Psychol Bull. 2006; 132:607–21. [PubMed: 16822169]
44. Macgregor S, Lind PA, Bucholz KK, et al. Associations of ADH and ALDH2 gene variation with self report alcohol reactions, consumption, and dependence: An integrated analysis. Hum Mol Genet. 2009; 18:580–93. [PubMed: 18996923]
45. Wall TL, Shea SH, Luczak SE, Cook TAR, Carr LG. Genetic associations of alcohol dehydrogenase with alcohol use disorders and endophenotypes in white college students. J Abnorm Psychol. 2005; 114:456–65. [PubMed: 16117582]
46. MacAndrew C. The differentiation of male alcoholic outpatients from nonalcoholic psychiatric patients by means of the MMPI. Q J Stud Alcohol. 1965; 26:238–46. [PubMed: 14320345]
47. Earleywine M. Hangover moderates the association between personality and drinking problems. Addict Behav. 1993; 18:291–7. [PubMed: 8342441]
48. Selzer ML, Vinokur A, van Rooijen L. A self-administered Short Michigan Alcoholism Screening Test (SMAST). J Stud Alcohol. 1976; 36:117–26. [PubMed: 238068]
49. Maney DW, Higham-Gardill DA, Mahoney BS. The alcohol-related psychosocial and behavioral risks of a nationally representative sample of adolescents. J Sch Health. 2002; 72:157–63. [PubMed: 12029813]
50. American Psychiatric Association Diagnostic and statistical manual of mental disorders. 3rd ed.. Author; Washington, DC: 1980.

51. Pittler MH, Verster JC, Ernst E. Interventions for preventing or treating alcohol hangover: Systematic review of randomised controlled trials. BMJ. 2007; 331:1515–18. [PubMed: 16373736]
52. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: A half of a century later. J Clin Psychopharmacol. 2006; 26:290–302. [PubMed: 16702894]
53. Jung TW, Lee JY, Shim WS, et al. Rosiglitazone relieves acute ethanol-induced hangover in Sprague-Dawley rats. Alcohol Alcohol. 2006; 41:231–5. [PubMed: 16554376]
54. Prat G, Adan A, Sánchez-Turet M. Alcohol hangover: A critical review of explanatory factors. Hum Psychopharmacol Clin Exp. 2009; 24:259–267.
55. Verster JC. The alcohol hangover – a puzzling phenomenon. Alcohol Alcohol. 2008; 43:124–6. [PubMed: 18182417]
56. Bendtsen P, Jones AW, Helander A. Urinary excretion of methanol and 5-hydroxytryptophol as biochemical markers of recent drinking in the hangover state. Alcohol Alcohol. 1998; 33:431–8. [PubMed: 9719404]
57. Chapman L. Experimental induction of hangover. Q J Stud Alcohol. 1970; (Suppl 5):67–85. [PubMed: 5450666]
58. Kim D, Kim W, Yoon S, et al. Effects of alcohol hangover on cytokine production in healthy subjects. Alcohol. 2003; 31:167–70. [PubMed: 14693266]
59. Rachlin, H. Judgment, decision, and choice: A cognitive-behavioral synthesis. W.H. Freeman and Company; New York: 1989.
60. Freeman, KB.; Riley, AL. The origins of conditioned taste aversion learning: A historical analysis.. In: Reilly, S.; Schachtman, TR., editors. Conditioned taste aversion: Behavioral and neural processes. Oxford; New York: 2009. p. 9-33.
61. Green AS, Grahame NJ. Ethanol drinking in rodents: Is free-choice drinking related to the reinforcing effects of ethanol? Alcohol. 2008; 42:1–11. [PubMed: 18164576]
62. Metten P, Crabbe JC. Alcohol withdrawal severity in inbred mouse (Mus musculus) strains. Behav Neurosci. 2005; 119:911–25. [PubMed: 16187819]
63. Phillips TJ, Broadbent J, Burkhart-Kasch S, et al. Genetic correlational analyses of ethanol reward and aversion phenotypes in short-term selected mouse lines bred for ethanol drinking or ethanol-induced conditioned taste aversion. Behav Neurosci. 2005; 119:892–910. [PubMed: 16187818]
64. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: An affective processing model of negative reinforcement. Psychol Rev. 2004; 111:33–51. [PubMed: 14756584]
65. Cooper ML, Frone MR, Russell M, Mudar P. Drinking to regulate positive and negative emotions: A motivational model of alcohol use. J Pers Soc Psychol. 1995; 69:990–1005. [PubMed: 7473043]
66. Solomon RL. The opponent-process theory of acquired motivation. Am Psychol. 1980; 35:691–712. [PubMed: 7416563]
67. Gauvin, DV.; Cheng, EY.; Holloway, FA. Biobehavioral correlates.. In: Galanter, M., editor. Recent Developments in Alcoholism, Volume 11: Ten Years of Progress. Plenum Press; New York: 1993. p. 281-304.
68. Conrod PJ, Peterson JB, Pihl RO, Mankowski S. Biphasic effects of alcohol on heart rate are influenced by alcoholic family history and rate of alcohol ingestion. Alcohol Clin Exp Res. 1997; 21:140–9. [PubMed: 9046387]
69. Newlin DB, Renton RM. High risk groups often have higher levels of alcohol response than low risk: The other side of the coin. Alcohol Clin Exp Res. 2010; 34:199–202. [PubMed: 19951303]
70. Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: A critical review and analysis. Psychol Bull. 1990; 108:383–402. [PubMed: 2270234]
71. Wall TL, Thomasson HR, Scuckit MA, Ehlers CL. Subjective feelings of alcohol intoxication in Asians with genetic variations in ALDH2 alleles. Alcohol Clin Exp Res. 1992; 16:991–5. [PubMed: 1443441]
72. Swift R, Davidson D. Alcohol hangover: Mechanisms and mediators. Alcohol Health Res World. 1998; 22:54–60. [PubMed: 15706734]

73. Crabbe JC, Phillips TJ. Pharmacogenetic studies of alcohol self-administration and withdrawal. Psychopharmacology (Berl). 2004; 174:539–60. [PubMed: 14551670]
74. Bickel WK, Stitzer ML, Liebson IA, Bigelow GE. Acute physical dependence in man: effects of naloxone after brief morphine exposure. J Pharmacol Exp Ther. 1988; 244:126–32. [PubMed: 3335995]
75. Chester JA, Risinger FO, Cunningham CL. Ethanol reward and aversion in mice bred for sensitivity to ethanol withdrawal. Alcohol Clin Exp Res. 1998; 22:468–73. (1998). [PubMed: 9581655]
76. Schweizer TA, Vogel-Sprott M. Alcohol-impaired speed and accuracy of cognitive functions: A review of acute tolerance and recovery of cognitive performance. Exp Clin Psychopharmacol. 2008; 16:240–50. [PubMed: 18540784]
77. Martin CS, Balaban CD, McBurney DH. Tonic and phasic processes in the acute effects of alcohol. Exp Clin Psychopharmacol. 2006; 14:209–18. [PubMed: 16756425]
78. Morzorati SL, Ramchandi VA, Flury L, Li TK, O'Connor S. Self-reported subjective perception of intoxication reflects family history of alcoholism when breath alcohol levels are constant. Alcohol Clin Exp Res. 2002; 26:1299–306. [PubMed: 12198408]
79. Begleiter H, Porjesz B. What is inherited in the predisposition toward alcoholism? A proposed model. Alcohol Clin Exp Res. 1999; 23:1125–35. [PubMed: 10443977]
80. Koob GF, Le Moal M. Addiction and the brain antireward system. Annu Rev Psychol. 2008; 59:29–53. [PubMed: 18154498]
81. Wechsler H, Nelson TF. Binge drinking and the American college student: What's five drinks? Psychol Addict Behav. 2001; 15:287–91. [PubMed: 11767258]
82. Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav. 2009; 23:715–22. [PubMed: 20025379]
83. Goodwin DW, Crane JB, Guze SB. Alcoholic “blackouts”: A review and clinical study of 100 alcoholics. Am J Psychiatry. 1969; 126:191–8. [PubMed: 5804804]
84. White AM, Signer ML, Kraus CL, Swartzwelder HS. Experiental aspects of alcohol-induced blackouts among college students. Am J Drug Alcohol Abuse. 2004; 30:205–24. [PubMed: 15083562]
85. Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. Psychol Rev. 2001; 108:4–32. [PubMed: 11212632]
86. Dworkin, BR. Learning and physiological regulation. University of Chicago Press; Chicago: 1993.
87. Siegel S, Baptista MAS, Kim JA, McDonald RV, Weise-Kelly L. Pavlovian psychopharmacology: The associative basis of tolerance. Exp Clin Psychopharmacol. 2000; 8:276–93. [PubMed: 10975617]
88. McDonald RV, Siegel S. Intra-administration associations and withdrawal symptoms: Morphine-elicited morphine withdrawal. Exp Clin Psychopharmacol. 2004; 12:3–11. [PubMed: 14769091]
89. Mallett KA, Lee CM, Neighbors C, Larimer ME, Turrisi R. Do we learn from our mistakes? An examination of the impact of negative alcohol-related consequences on college students’ drinking patterns and perceptions. J Stud Alcohol. 2006; 67:269–76. [PubMed: 16562409]
90. Batty GD, Deary IJ, Macintyre S. Childhood IQ and life course socioeconomic position in relation to alcohol induced hangovers in adulthood: The Aberdeen children of the 1950s study. J Epidemiol Community Health. 2006; 60:872–4. [PubMed: 16973534]
91. Finn PR, Kessler DN, Hussong AM. Risk for alcoholism and classical conditioning to signals for punishment: Evidence for a weak behavioral inhibition system? J Abnorm Psychol. 1994; 103:292–301.
92. Dick DM, Smith G, Olausson P, et al. Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol. 2010; 15:217–26. [PubMed: 20148781]
93. Fillmore MT, Ostling EW, Martin CA, Kelly TH. Acute effects of alcohol on inhibitory control and information processing in high and low sensation-seekers. Drug Alcohol Depend. 2009; 100:91–9. [PubMed: 19004578]

94. Finn PR, Bobova L, Wehner E, Fargo S, Rickert ME. Alcohol expectancies, conduct disorder and early-onset alcoholism: Negative alcohol expectancies are associated with less drinking in non-impulsive versus impulsive subjects. Addiction. 2005; 100:953–62. [PubMed: 15955011]

95. Krystal JH, Petrakis IL, Limoncelli D, et al. Altered NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients. Neuropsychopharmacology. 2003; 28:2020–8. [PubMed: 12888778]

96. Petrakis IL, Limoncelli D, Gueogueva R, et al. Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. Am J Psychiatry. 2004; 161:1776–82. [PubMed: 15465973]

97. Krystal JH, Petrakis IL, Krupitsky E, Schutz C, Trevisan L, D'Souza DC. NMDA receptor antagonism and the ethanol intoxication signal: From alcohol risk to pharmacotherapy. Ann N Y Acad Sci. 2003; 1003:176–84. [PubMed: 14684445]

98. Krueger RF, Nichol PE, Hicks BM, et al. Using latent trait modeling to conceptualize an alcohol problems continuum. Psychol Assess. 2004; 16:107–19. [PubMed: 15222807]

99. Saha TD, Chou SP, Grant BF. Toward an alcohol use disorder continuum using item response theory: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2006; 36:931–41. [PubMed: 16563205]

100. American Psychiatric Association Diagnostic and statistical manual of mental disorders. 4th ed.. Author; Washington, DC: 1994.

Key Learning Objectives

- Review cross-sectional and prospective evidence concerning the linkage between hangover measures and risk for alcohol use disorders.
- Highlight the possibility that measurement strategy (particularly hangover frequency vs. susceptibility) could affect the interpretation of any relations between hangover and alcohol use disorder risk factors.
- Illustrate numerous hypotheses that could explain linkages between hangover and alcohol use disorder risk. Although it is natural to assume hangover indexes drinking punishment, it is possible that this oversimplifies a complex phenomenon. Hangover measures might reflect a number of diverse, risk-relevant processes.

Questions for Future Research

- Does hangover acutely affect near-term drinking? Does hangover punish drinking, encourage drinking, or does the effect differ across individuals or situations? What kinds of motivational mechanisms account for any effects?
- Do measures of hangover susceptibility and frequency differ in the manner in which they are prospectively related to onset of alcohol use disorders?
- Is hangover related to important pharmacologic processes, such as acute tolerance, withdrawal, or rising limb effects?
- What personal traits, abilities, and behaviors are associated with both alcohol use disorder risk and hangover measures? Does hangover play a role in the risk process linking the trait(s) to alcohol use disorder, or does hangover merely serve as a marker of the trait(s)?