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The Alcohol Hangover Research Group Consensus Statement on Best Practice in Alcohol Hangover Research

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Abstract

Alcohol-induced hangover, defined by a series of symptoms, is the most commonly reported consequence of excessive alcohol consumption. Alcohol hangovers contribute to workplace absenteeism, impaired job performance, reduced productivity, poor academic achievement, and may compromise potentially dangerous daily activities such as driving a car or operating heavy

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machinery. These socioeconomic consequences and health risks of alcohol hangover are much higher when compared to various common diseases and other health risk factors. Nevertheless, unlike alcohol intoxication the hangover has received very little scientific attention and studies have often yielded inconclusive results. Systematic research is important to increase our knowledge on alcohol hangover and its consequences. This consensus paper of the Alcohol Hangover Research Group discusses methodological issues that should be taken into account when performing future alcohol hangover research. Future research should aim to (1) further determine the pathology of alcohol hangover, (2) examine the role of genetics, (3) determine the economic costs of alcohol hangover, (4) examine sex and age differences, (5) develop common research tools and methodologies to study hangover effects, (6) focus on factor that aggravate hangover severity (e.g., congeners), and (7) develop effective hangover remedies.

Keywords

Alcohol hangover; methodology; guidelines; research

INTRODUCTION

The alcohol hangover develops when blood alcohol concentration (BAC) falls considerably and peaks when it returns to almost zero [1]. The alcohol hangover may last up to 24 hours [1], and besides a feeling of general misery, several symptoms characterize the alcohol hangover including headache, tiredness, concentration problems, thirst, dizziness, nausea, cognitive impairment, and mood changes. At present, no theoretical model accounts for the pathology of alcohol hangover, nor have most studies systematically investigated the deleterious effects on daytime functioning without methodological confounds [2–4].

Among young adults, alcohol hangovers are reported as the most frequently occurring adverse effect of excessive alcohol consumption. Table 1 gives an overview of the top-10 most frequently experienced alcohol-related consequences among 800 Dutch students, scored using the brief Young Adult Alcohol Consequences Questionnaire [5]. As is evident, half of the top-10 items are related to alcohol hangover.

The impact of alcohol hangover on daily activities can be profound. A survey among Dutch university students [6] showed that more than half of them reported being unable to study when experiencing an alcohol hangover often or always (see Fig. 1). With an average hangover frequency of 2.7 days/month, 1 month a year is “lost” [6]. While one experimental study found no effects on academic performance [7], several experimental studies confirm that memory functioning is impaired during alcohol hangover [8, 9]. This is disturbing; especially since the core business of students is learning and remembering.

Alcohol hangovers are not limited to students and young adults. Hangovers are also common in the workplace. Frone [10] found that 9.23% (11.6 million workers) of the US workforce reported to work with a hangover in the past year, making it the most common form of alcohol-related workplace impairment in the survey. There is a significant relationship between alcohol consumption and next-day workplace absenteeism. A survey among 280 employees revealed a two-fold increased likelihood of absenteeism the day after alcohol consumption [11]. From the 173 days of absenteeism (of 5493 days at ‘risk’), 74 days (43%) occurred the day after alcohol consumption. Interviews by Ames and colleagues [12] revealed that about half of interviewed workers reported being at work while having a hangover. During hangover, workers felt significantly sicker, had conflicts or fights with co-workers and their supervisor, problems in completing the job, and fell asleep at work. Reduced productivity is common when having a hangover at work. A recent Norwegian

study [13] concluded that alcohol hangover is the largest substance abuse problem at the workplace. Employees reported that during the past year hangovers had resulted at least once in inefficient work (24.3%) and absence (6.2%).

Surprisingly, scientific evidence on the economic costs of alcohol hangover is scarce. A decade ago, Harwood [14] estimated the annual costs of alcohol hangover in U.S.A. at $185 billion, and although this amount was criticized for inaccuracy [15, 16] it gives an impression of the economic impact of hangovers on society.

To convince policymakers of the profound impact of alcohol hangover on daytime functioning this information is however essential. Therefore, future studies should aim to determine the costs of alcohol hangover in terms of reduced productivity and absenteeism. If reduced productivity, increased accident risk and absenteeism rates are translated into costs for society, this will likely increase the scientific and politic attention for alcohol hangover research.

Alcohol hangover has gained increased research attention the past decade, and in 2009 researchers from around the world united and founded the Alcohol Hangover Research Group (AHRG). At a satellite meeting of the Research Society on Alcoholism conference in San Antonio Texas, June 26th 2010, the AHRG conducted a symposium and consensus meeting to discuss potential guidelines for future alcohol hangover research. This article reflects the outcome of the discussion.

METHODOLOGICAL GUIDELINES AND POTENTIAL PITFALLS

Research on alcohol hangover has suffered from methodological shortcomings and a lack of a systematic approach. As a result, there is limited understanding of various basic issues, such as what biological processes cause alcohol hangover, and whether genetics play an important role. Also, it is unclear why, despite excessive alcohol consumption, there are great individual differences in the presence and severity of alcohol hangovers. Various research methodologies have been applied to examine alcohol hangover. The next sections will discuss the different methodologies, their strengths and weaknesses, and potential confounders and bias that may reduce the credibility of alcohol hangover studies.

PRECLINICAL STUDIES

Animal Research

Currently, there is a lack of an animal model that establishes a physiological correlate of one or more of the hangover symptoms.

Nonetheless, several preclinical studies conducted in rats have studied behavioral changes following administration of ethanol doses that are considered intoxicating in humans. For example, York and Regan [17] documented reduced operant activity and motor performance up to 16 hours after an acute ethanol administration. Morse and colleagues documented the induction of post-intoxication conditioned place aversion 10 hours after similar alcohol challenge [18]. Jung *et al.* [19] have reported reduced social interaction and overall social activity 18 hours after ethanol challenge. Whether these behavioral changes can be considered as correlates of hangover in humans remains to be established.

Additional animal studies using acute administration of intoxicating amounts of ethanol to rats and mice have tested the efficacy of potential hangover “cures” on the metabolism of ethanol, its first metabolite acetaldehyde and the enzymes that play a role in promoting this process [20–22]. These “cures” have been reported to promote a reduction of blood alcohol and acetaldehyde concentrations after an acute or chronic alcohol challenge. Since alcohol

hangovers may be accompanied by an increased acetaldehyde concentration, the authors suggest that these cures may therefore be effective in preventing alcohol hangover.

Studies with chronic alcohol administration should be interpreted with caution, because it is likely that alcohol withdrawal effects are measured rather than hangover effects. Animal models for alcohol withdrawal are not useful for studying hangover effects, because in withdrawal develops after receiving alcohol for days or weeks, while hangover occurs after a single episode and different CNS systems are involved [4]. The development of an animal model that enables testing alcohol hangover effects after a single alcohol challenge is essential to enhance our knowledge on the pathology of alcohol hangover.

Genetics and Individual Differences in Hangover Susceptibility

Some studies have focused on alleles associated with aldehyde dehydrogenase (ALDH) and flushing phenotypes in Asians [23–26]. It must be concluded that genetic research on alcohol hangover is still in its infancy. It is likely that genetics play an important role, especially if one takes into account the great individual differences in hangover severity and the fact that about 25% of heavy drinkers claim that they have never had a hangover [27]. Collection of DNA in ongoing and new studies is to be encouraged. Individual differences in susceptibility have occasionally been estimated by examining the residual variance in a hangover frequency measure after covarying measures of drinking quantity and frequency [28–30]. The assumption is that residual variance in hangover not accounted for by individual differences in drinking behavior may more clearly reveal individual differences in propensity to develop a hangover. Although this approach is defensible, it is recommended that more direct assessments of individual differences in hangover susceptibility be administered when this is a central focus of the research. For example, a questionnaire might assess the typical number of drinks required to produce a hangover [26] or the likelihood of experiencing a hangover at a given number of drinks [24–25]. Further experimental research involving repeated alcohol administration to the same individuals is needed to estimate the proportions of the population which are: (1) consistently resistant to hangover; (2) consistently susceptible to hangover; and (3) variably susceptible to hangover.

SURVEY STUDIES

Survey methods are essential for certain tasks, such as establishing the prevalence of hangovers in epidemiologic samples. Survey methods are also valuable for identifying the correlates of naturally occurring hangovers, including antecedent patterns of alcohol consumption and other potential contributory causes, individual differences, and consequences. Such information can be used to probe theoretical questions and also to identify phenomena worthy of closer scrutiny in laboratory-based experimental studies.

The current lack of well-validated, comprehensive instruments for assessing hangover-related information has probably contributed to the slow growth of hangover research [30]. Researchers have frequently devised their own assessments for survey studies, and so the literature contains a remarkable diversity of measurement strategies. Existing approaches include the use of face-valid, single-item assessments concerning the occurrence or frequency of hangover [31–36], multi-item assessments of occurrence or frequency of experiencing specific hangover symptoms [26, 29–30, 37], questions about the severity or duration of symptoms during a typical hangover, a recent hangover, or following a recent drinking episode [26, 35, 38–40], and questions asking respondents to estimate their likelihood of experiencing a hangover after consuming a specified amount of alcohol [24–25]. A number of the measures include items that were not found to be valid in hangover induction studies or that measure withdrawal or intoxication effects [41]. The development

and evaluation of survey instruments should be regarded as a valued activity in hangover research.

CLINICAL STUDIES

Naturalistic *vs* Laboratory Studies

Most experimental data on alcohol hangover comes from studies in humans. Two different approaches are used to study alcohol hangover: the naturalistic and experimental design in laboratories. In experimental studies, a standard amount of alcohol is administered and consumed in a fixed (and often short) period of time. Factors affecting hangover severity such as food intake, time of going to bed, activities during the evening and sleep can be standardized and controlled. On the other hand, “moral” hangover symptoms experienced in real life such as guilt and shame are examples of response domains potentially undercut by hangovers induced in a controlled laboratory setting [42]. Using an electronic diary design, Muraven and colleagues [43] found that when drinkers felt they had violated a self-imposed drinking limit, they were more likely to report feeling bad and guilty about their drinking the next morning. Guilt reactions predicted the amount of alcohol consumed later in the day and two days later. Hangover was not a focus of this research, but hangover symptoms were measured. Hangover was related to the amount of alcohol consumed the night before and the amount of guilt experienced the next morning (suggesting guilt might be regarded as part of the syndrome). Controlling for physical hangover symptoms weakened but did not eliminate the limit violation effects. Guilt reactions - symptoms unlikely to be observed in laboratory research - may play a vital role in linking “morning after” processes to subsequent drinking.

In the naturalistic design the amount and type of alcoholic beverages are not under experimental control [44, 45]. The participant’s activities are not under control and ingestion of alcohol is usually done over a longer period of time. Both study designs have their advantages and disadvantages. Important points to consider about the naturalistic approach are the fact that drinking time is under personal control, the place of consumption (i.e. the pub) is familiar to participants, and the rate of consumption and type of beverage can change during the evening. While this naturalistic approach has the advantage of being ecologically valid and mimicking a normal pattern of alcohol consumption, researchers may however prefer to control some of these factors that are left to the participant’s discretion for some studies. In studies where these can affect the outcomes being studied, choosing a controlled experimental design can be more appropriate. Future studies should make a direct comparison between both types of designs to determine to what extent they are complementary or distinct.

Treatment Dosage and Blinding

Alcohol hangovers are generally not experienced after consuming low dosages of alcohol. Evidence from experimental studies demonstrates that, to develop an alcohol hangover, an alcohol dosage that produces a peak BAC of at least 0.11% to 0.12% is necessary [46]. The peak BAC attained depends on various factors including sex, body weight, amount of time allowed for drinking, dilution of the beverage, and time since last meal [47]. The dose of alcohol expected to result in a particular BAC by body weight and adjusted for sex can be calculated using Watson’s formula [48] with gender adjustments per Friel *et al.* [49]. Since considerable individual differences are commonly observed, this provides only an estimate of the average BAC that will be obtained from breath analyses. While lower dose studies can allow only 15–30 min for drinking the alcohol, at the high levels required to produce hangover, it usually is necessary to allow an hour to minimize vomiting [7]. Several breath analyses should be conducted to follow the rise of BAC on the ascending limb to establish peak (maximum) BAC. Peak BAC is usually established after a 30 min absorption period

following end of beverage consumption, with relatively little difference in BAC between 15 min before and after this time [50, 51], allowing testing of any acute effects to be conducted in that window. BAC reaches zero around 8 to 11 hours after consuming the amount of alcohol required to induce hangover [1, 46, 52], with variability in time depending on the administered dose and individual differences. Alcohol hangover severity then rises rapidly as BAC falls, peaking when BAC approaches zero, and may last up to 20 hours after the start of alcohol consumption [1]. Figs. (2, 3) show the time course of hangover; Fig. (2) derived from data of Ylikahri *et al.* [1] and Fig. (3) derived from Penning *et al.* [53].

Some safety considerations when conducting alcohol administration studies need to be applied. First, participants should only include drinkers who at least occasionally in recent months drank as much as you will give them; giving a high dose of alcohol to a lighter drinker may be physically unsafe. Second, participants should be monitored continuously until their BACs descend to a safe level (such as .04 g% or lower) for three reasons: First, they could pass out, vomit while asleep, and aspirate their vomit with fatal results. Second, it is unsafe for them to drive or ride a bicycle, and walking may be unstable (e.g., they could fall off a curb), so they should be kept in a safe environment and monitored to prevent falls. Third, nausea and dizziness often results during acute administration, so medical or nursing care needs to be on-site. Consideration should also be given as to the ethics of administering alcohol to people with past or current alcohol use disorders, even if currently drinking. Also, pregnancy and breast feeding status must also be screened for female research participants.

Blinding is enhanced by using beverages of similar color in both conditions, using beer *vs* non-alcoholic beer, using a liquor with the least flavor (vodka), adding a strong flavor (e.g., mint), floating a small amount of alcohol on the placebo beverage and/or rubbing the rim of the glass with alcohol, and/or using a nose-clip while consuming the drinks. Performing several breath alcohol tests (as if the person on placebo had a rising BAC), or adding a second placebo dosage that participants are told is needed in order to achieve the required BAC may also help masking treatments [47]. However, at alcohol concentrations higher than 0.08%, blinding is not very effective because participants are aware of alcohol intoxication [47]. The research assistant who knows the true beverage condition must not be the same assistant who administers the experimental tasks, so that his/her knowledge does not bias the results.

When applying a naturalistic design blinding may be impossible, because participants consume alcohol at home or in the pub. The naturalistic study design is set-up in such a manner that participants know when they consume alcohol and when they do not. In experimental studies, the use of a placebo condition and active control is regarded as essential to determine the effects of the treatment that is under investigation. In experimental hangover research, most studies therefore consist of an alcohol condition and a placebo condition. Treatments are administered during the evening or night, and hangover (or placebo) effects are examined the following day.

In naturalistic designs, a method to prevent or reduce expectancy effects may be not mentioning the true purpose of the study and testing subjects once at weekdays (when they are unlikely to drink heavily) and once in the weekend (when they are likely to have been drinking heavily). These results can then be compared. The disadvantage of this approach is that the peak BAC may be too low even on a weekend day to produce a hangover.

Time of Testing

The question *when* to perform tests during alcohol hangover depends on the rationale of a specific study. The general advice is to start testing only when blood alcohol concentration is zero. Although this will introduce variability between subjects regarding the time between

drinking and testing, it assures that the effects that are measured are not confounded by those caused by acute intoxication effects of residual alcohol in the blood. A BAC as low as 0.02% has been shown to impair complex tasks such as divided attention and driving a car [54, 55]. When BAC is not zero, it cannot be determined whether impairment is caused by residual alcohol or due to hangover.

However, some studies are set up in such a manner that the BAC issue is of less importance. For example, if one wishes to determine the effects of alcohol consumption the night before on driving a car to and from work and mimic real life, the tests should be performed at the usual times participants are engaged in this activity. Another example is a study that aims to examine on-the-job performance. In these designs, BAC levels should be determined, but conducting of the tests should not be delayed. Other examples are studies using ambulatory assessments, such as electronic diaries. In such naturalistic designs in which the events of interest are assessed outside of the laboratory in the course of drinkers' daily experiences, it may not be feasible to collect data on BAC. In these cases, the "natural history" of hangover from the time of awakening until the resolution of symptoms or the resumption of drinking is a reasonable focus of the investigation. Measures such as self-reports of residual intoxication might be used as proxies or surrogates for BAC data.

MEASUREMENT OF THE PRESENCE AND SEVERITY OF ALCOHOL HANGOVER

Scientific communication and integration of survey data would be facilitated by increased precision in writing about the dimensions of hangover actually assessed in a given study. We recommend that, to the extent feasible, survey investigators use descriptive terminology (e.g., "hangover frequency", "hangover susceptibility" "hangover symptom count", "hangover severity") rather than simply referring to "hangover" when reporting their findings. It is recommended that the term *hangover severity* is reserved to describe measures of symptom intensity or magnitude and the term *hangover symptom count* is used to refer to tallies of the number of discrete symptoms endorsed. This distinction will promote clarity in scientific communication while allowing investigators to amass data using both approaches and conduct empirical tests of their overlap. Such tests might be profitably conduced using data from both retrospective surveys and ratings of acute hangover collected during experimental studies [41].

Measurement of Hangover Frequency

For many research applications, it is desirable to gather information about the frequency of hangover over some period of time, such as the past month or past year. (Items that assess hangover frequency can, of course, be readily re-scored to indicate simple presence *vs* absence of any hangover during the same period.) It is possible to achieve a given number of hangovers *via* multiple routes, such as by drinking frequently but being relatively invulnerable to hangover or by drinking rarely but being very sensitive to hangover effects. To be maximally informative, assessments of hangover frequency should be constructed so as to be able to distinguish (a) the overall number (or range) of hangover events during the time period and (b) the percentage of drinking occasions followed by hangover. An assessment of drinking practices during the same time frame, such as the frequency of excessive drinking, is a valuable adjunct for descriptive purposes or selecting subgroups for focused analysis (e.g., respondents matched on drinking frequency or intensity but differing in percentage of occasions followed by hangover).

Some retrospective hangover assessments have asked participants to rate the frequency with which individual symptoms are experienced after drinking [29–30, 37]. A disadvantage of

this approach is that it does not permit a determination of the clustering of symptoms. That is, it is unclear whether all the reported symptoms were experienced together or whether they were dispersed across different hangover episodes. An alternative approach is to ask respondents to identify the symptoms experienced in a single hangover event [35, 38–40]. The selected event may be a hypothetical aggregate (e.g., a "typical hangover") or an actual event (e.g., the most recent hangover or the worst hangover in some period). For research questions where retrospective information concerning the clustering of symptoms is crucial, this kind of strategy should be employed. Investigators should be mindful that selection of the reference event has consequences for interpretation. For instance, asking participants to reflect on a "typical hangover" requires them to generate integrative estimates that could be biased by selective recall or hangover expectancies. Asking a specific event, such as the most recent hangover, may prove problematic if individual respondents are retrospecting over very different time scales.

Measurement of Hangover Severity

Severity of hangover can be construed in two ways. One approach defines severity in terms of the magnitude or intensity of hangover or individual hangover symptoms during a typical hangover or a designated hangover event [38, 40]. This use of the term closely accords with the way "severity" is indexed in a typical laboratory investigation. The second approach uses a count of the number of distinct symptoms endorsed as an index of the diversity of hangover experiences [30]. This approach is similar to the strategy of using a count of the total number of diagnostic criteria met by an individual as an index of disorder severity in psychiatric epidemiology.

Hangover may include a wide array of symptoms, and it is often impractical or undesirable to attempt to assess all possible hangover symptoms. For many investigations, it will be sufficient to assess the core set of symptoms that are most reliably associated with hangovers in the laboratory. However, when feasible, it would be valuable to include items tapping additional, less common symptoms. Rarely reported symptoms could be important if they mark cases that are especially severe or that arise from unique causal pathways. Alternatively, infrequently reported symptoms may contribute error to an assessment. Rare symptoms may be too infrequently observed to study productively in laboratory settings, but may be more easily investigated in survey investigations with larger samples.

It is possible to rate overall hangover severity directly using one simple question that can be rated numerically from 'no hangover' to 'extreme or severe' hangover and to use this as the primary measure in some cases. The outcome of this question can then be used as the primary measure to relate to cognitive and psychomotor effects of alcohol hangover or biological correlates. Individual items (e.g., headache, fatigue, nausea) further allow insight in the nature of alcohol hangover experienced by a subject. These secondary outcomes may also permit calibration of the overall hangover severity score across samples or cultures if it turns out to be variable. On the other hand, many assessment researchers argue that a reliable multi-item measure is more valid than any single item, as discussed extensively elsewhere [56]. Thus, use of reliable and valid scales as the index of hangover seems more appropriate. In the past, researchers made their own lists of symptoms to compose hangover scales and calculate overall hangover severity. Yhilikari [1] constructed some of the first hangover scales for use in laboratory studies, with one comprising physical signs rated by observers and the other composed of self-reported symptoms. His research group used this method in several publications, but most other researchers did not adopt these because the scales had no psychometric development work. The observer-rated physical signs had a very low score, no data were presented on the value of individual signs, and Seppala *et al.* [57] reported that the physical signs were not valid. Chapman [46] also validated a number of individual hangover symptoms in his experimental studies but no scale development work

was done. Until recently, no psychometrically established hangover severity scale was available. Current research typically makes use of two hangover scales: Slutske *et al.* [30] developed the 13-item Hangover Severity Scale (HSS) for use in survey studies, and Rohsenow *et al.* [41] developed the 8-item Acute Hangover Scale (AHS) for use acutely in experimental administration studies. One notable difference between these scales, at least as originally published, is that the HSS assesses past year frequency of 13 symptoms whereas the AHS assesses the severity of currently experienced symptoms. Each list of items, though, could clearly be re-worded to cover a variety of time frames. Surprisingly, both scales include somewhat different hangover symptoms. Nevertheless they seem to predict overall hangover severity in a similar manner. While other hangover symptoms exist that are *not* included in these scales, this does not limit the reliability of these scales. Reliable and valid scales do not require that *all* possible items be included, just the ones that most reliably represent the construct [58]. Rohsenow [41] argued that it is important to include only items that were validated in controlled experimental administration studies and to exclude withdrawal symptoms.

There is debate about some items included in these scales. For example, Slutske's scale includes an item concerning "trouble sleeping" (i.e., something that is experienced *before* having a hangover), whereas Rohsenow's scale includes an item rating "overall hangover severity" (i.e., similar to the overall construct measured by the scale). The Acute Hangover Scale can be scored without including the "overall hangover severity item", without significantly lowering its reliability or validity [41]. Slutske *et al.* [30] argued that a rating of hangover includes people's attributions about the cause of their discomfort and therefore may be biased, so some researchers may prefer to use this measure without that one item. On the other hand, a person may report that they have hangover when their discomfort is due to other causes (e.g., lack of sleep *per se*) or not report hangover when in fact they have all the symptoms, due to their belief that alcohol is not the cause. The Hangover Symptoms Scale [30] deliberately omitted a question concerning "hangover" *per se*. This approach is similar to common practices in psycho-diagnosis: patients are diagnosed on the basis of reported symptoms, not asked to rate whether or not they have the target disorder. The disadvantage of this approach is that, at least at present, there are not established thresholds for determining the presence of hangover on the basis of symptom scores. This makes it difficult to count hangover events. It is thus recommended that investigators assess about "hangover" per se in addition to individual symptoms. Depending on investigator preference, scoring of survey responses may exclude the "hangover" item. Gathering information about "hangover" will provide a simple index that permits direct comparisons across samples and instruments and will foster empirical tests of the relations between ratings of individual symptoms and the "hangover" response. It is notable that, when participants are asked to rate the severity of currently experienced "hangover" in the laboratory, this item correlates strongly with ratings of other common hangover symptoms [41]. Although current scales may have their limitations, both are useful in determining which hangover symptoms are present, and the overall hangover severity.

In conclusion, severity of hangover can thus be measured using a single item scale or a by rating several symptoms. At present, too little is known about the symptomatic presentation of hangover to evaluate whether these two approaches measure the same latent construct. If there are wide individual differences in symptomatic profile, the two approaches might not be interchangeable. For example, some individuals might experience only one or two symptoms, but experience them very intensely, whereas other individuals might develop a diffuse set of low-grade hangover symptoms. Each presentation might be counted as "severe" in one scoring scheme but not the other. Both approaches may contribute to the generation of important descriptive information.

Although consensus was not reached on this issue at the 2010 Alcohol Hangover Research Group meeting, more research and validation of a uniformly accepted measure for the presence and severity of hangover is required [59].

Measurement of Hangover Duration

The duration of hangover symptoms is rarely assessed, not since Ylikarhi *et al*. [1]. Where possible, this information should be gathered because it could provide important descriptive information, such as an indication of the burden imposed by hangovers in daily life or the period of risk for "hair-of-the-dog" drinking. Assessments of duration might take multiple forms, ranging from a simple question about the typical number of hours with discernible symptoms [26] to a structured reconstruction of a target event [60] to administering alcohol and assessing hangover every 2 hours from onset until it stops [1].

Choice of Tests

When studying residual effects of heavy alcohol use, it is crucial that tests are chosen that measure a clear psychological or behavioral construct and have proven psychometric properties. In past research this has not always been the case. For example, dated driving simulators had little predictive validity towards actual driving [54]. The tests, often comprising a steering wheel and road-like scenery on a computer screen, had low ecological validity. Participants experienced these tests more like a divided attention or adaptive tracking tests, and important factors that could increase the ecological validity of the test (e.g., the presence of other traffic) and the potential to tap into higher order issues of decision making and risk taking were lacking.

Parameters used in the test preferably should have a clear relevance to daily activities. For some popular tests it is unclear what is studied, because several skills and abilities are needed simultaneously to conduct the test. For example, in the Digit Symbol Substitution Test (DSST), subjects have to copy symbols corresponding to a number between 0 and 9, completing as many as possible within a certain period of time. In this test one measures a combination of working memory, reaction speed, eye-hand coordination, and drawing skills. Investigators should be aware of the constructs that tests measure when deciding which tests to employ in research. Taking the example of the driving test, one would expect parameters with relevance to vehicle control (e.g., lane weaving of the car or standard deviation of speed) or traffic safety (e.g., inappropriate out of lane crossings or failure to comply with rules of the road) to be measured. This has also been problematic in past research, for example in driving simulator studies in which participants were instructed to drive as fast as possible from point A to B [61]. Choosing parameters such as the latter reduce the relevance of the study to real life.

When considering neurocognitive physical, physiological, or biomechanical tests, these should also be chosen based on the hypothesized mechanisms of effect of hangover, rather than choosing tests based on having been affected by acute alcohol consumption or other drug administration. Moreover, the duration of the tasks selected is also important, as motivation or other factors can overcome the small changes in performance that could be observed in short duration testing during hangover.

Experimental Setup: Crossover *vs* Between Subject Designs

In a crossover design, subjects are tested several times in different conditions (e.g., during hangover and after placebo). The advantage of this design is that within-subject variability doe not play an important role. For example, it can be assumed that if a subject is poor in remembering words this will affect his or her performance equally on each test day. In contrast, when applying a between subjects design (e.g., comparing a hangover group with a

placebo group) one risks comparing good performers with poor performers. Random allocation to different treatment groups minimizes this risk, but variability remains higher when compared to within subject designs. Given the individual nature of experiencing hangover symptoms and severity, one may prefer to use a within subject design. For example, when more than one hangover condition is included in the study design (e.g., comparing a bourbon challenge with a vodka challenge) a repeated measures design would be preferred.

On the other hand, ineffective blinding may be a disadvantage of a repeated measures design. Participants are very good at detecting when they are given alcohol. Therefore, in a repeated measures design they can deduce which was placebo, such that blinding is ineffective in both conditions [62]. Also, given the difficulty of getting participants to come back more than twice, in some studies only a between-subjects or mixed between- and within-subjects design is feasible [52].

Taken together, investigators must be aware of the problems of both kinds of design (between and within subjects) and choose which to use with care. Researchers should work to minimize the use of weaker designs for alcohol hangover research whenever possible.

Sample Size

A major problem of past studies has been the low sample size. While the study by Chapman [46] included 91 drinkers, many studies performed before 1990 often had sample sizes below N=10. The low power makes it hard to interpret results from these studies and explains why results from studies are often inconclusive. Sample size calculation is essential to ensure sufficient power when setting up hangover research. The sample size and power should be based on a clear rationale about expected effects for the primary outcome measure of the study. As hangover studies are likely to experience drop-outs, the number recruited should be higher, so that the number of participants with complete data matches the power analysis. An additional consideration might be that ethical constraints limit the doses of alcohol that would generally be administered in an experimental study. If you can not elicit the hangover at “full strength” you may need to increase the number recruited to compensate for the blunted effect size. Also, Howland *et al.* [27] revealed that about 25% of people do not experience alcohol hangovers. If having experience with alcohol hangovers is not an inclusion criteria, the number recruited should be increased to cover these hangover-free subjects. The practice of ensuring that there are sufficient participants would improve the validity and reproducibility of study results.

Sex

In the past most hangover research has been performed on men. More recent studies included both men and women, but small sample sizes generally do not allow a direct comparison between the sexes. Very few studies have focused on women only [63]. During acute intoxication, sex differences are common on some measures, even when using sex-adjusted dosing [9], because women are more sensitive to the effects of alcohol. Results from a recent survey [53] show that hangover is significantly more severe and lasts longer among women when compared to men (see Fig. 3), consistent with data from Smith and Barnes [39]. It is likely that any sex differences in hangover would have an impact on cognitive and psychomotor functioning. However, the results of these studies could be an artifact of women attaining a higher BAC at the same number of drinks compared to men; such studies should equate sexes based on differences in the number of drinks required to attain the same BAC. For adult women, adjusting for both the average weight differences and differences in response to alcohol, the number of drinks should be adjusted by 70% compared to men [64]. When sex-adjusted dosing was used in experimental studies, no

differences in hangover severity or incidence were significant in most studies [27, 46, 52], but significant in one by Verster *et al.* [9]. Future studies should continue to investigate potential sex differences in hangover severity, the nature of symptoms that are experienced, and residual effects of intoxication on cognitive and psychomotor performance.

Age

Most hangover research is performed on young adults. There is however no reason to assume that hangovers are not experienced by adults of all ages. Research does show that drinking patterns change across ages, and heavy drinking episodes that may result in hangover are much less often experienced as age increases (See Fig. 4) [65].

Fig. (4), showing data from over 200,000 US adults, illustrates that the highest percentage of heavy drinkers is found among young adults. Thereafter, the percentage of heavy drinkers decreases rapidly [65], but is not absent. In this study, heavy drinking was defined as consuming at least 4 (women) or 5 (men) alcoholic drinks on a single occasion. Surveys among employees reported that rates of absenteeism due to alcohol consumption and hangovers significantly reduced when growing older, and are most prevalent among males younger than 35 years old [13, 66].

It is unknown whether hangover symptoms and severity change with age and this should be an important aim of future research. Incidence of hangover did not differ significantly by age when combining data from 172 participants (age 12–50 years old) in three experimental studies [67] but 80% of these drinkers were under 30 years old. Although research in underage drinkers has serious ethical limitations, research in adolescents is of importance too since excessive drinking and alcohol hangovers may have a significant impact on brain development and cognitive functioning. More hangover research on populations ranging in age from young adult to elderly is needed to ascertain any age-related effects.

Congeners

Congeners are compounds naturally occurring in alcoholic beverages that result from sources such as the grains, wine skins, and/or casks used in the making of beverages, or that are added during production. These include substances such as amines, amides, adetones, acetaldehydes, polyphenols, methanol, histamines, fusel oil, esters, furfural, and tannins [4, 68, 69]. Although ethanol alone or with almost no congeners is sufficient to produce a hangover [9], congeners may worsen alcohol hangover severity [52]. The difficulty with research into the impact of specific congeners is that there are many different types and the effect of each specific compound on alcohol hangover is unknown. To complicate matters, there are great differences between different types of alcoholic beverages. For example, different types of whisky (bourbon, brandy, Scotch, American, Canadian) varied significantly in all congeners studied, with bourbon having more than 3 times as much total congeners by weight as Canadian whiskey [69]. Hence, not all whisky-types are alike and this may have an impact on the way they may contribute to hangover severity.

Before investigating effects of specific congeners, research has focused on determining whether congeners affect hangover by comparing drinks with very low congener content (e.g., vodka) with beverages with very high congener content (e.g., bourbon). These studies [46, 52] confirmed that beverages with higher congener content produce more severe hangover symptoms, but no effects of congeners on cognitive and psychomotor functioning were found [52]. Future research into congener effects could start by further investigating these extremes (i.e. vodka *vs* bourbon), but eventually it would be helpful to develop some kind of congener-index that allows a direct comparison of different alcoholic beverages and their effects.

Tolerance and Long Term Effects

There is mixed evidence about the relationship of drinking patterns among those who drink heavily enough to experience hangover to the propensity or severity of hangovers experienced. Surveys that include people who never drink enough for hangover to result have an obvious confound since people who rarely drink heavily do not have an opportunity to experience hangover. Among heavy drinkers in experimental hangover studies, no relationship was found between quantity/frequency of drinking and whether or not they reported a hangover in the studies [67]. A recent study of young Danish students showed that with repeated heavy drinking (i.e. at least 12 units a day) alcohol hangovers became more severe during a week spent on holiday [70]. However, this could just mean that people who drink more heavily also drink more heavily on holiday rather than reflecting chronic effects *per se*. It is unclear whether tolerance or resistance develops for hangovers when drinking more often. It would be useful to investigate in a controlled way whether people with greater tolerance to alcohol's acute effects also show more tolerance to hangover effects after the same g/kg dose of alcohol.

Little is known about the long term health consequences of having hangovers frequently. Unfortunately, most studies concerned with long term health outcome of alcohol consumption do not question participants about the presence and severity of alcohol hangovers. This area of research warrants further investigation with validated and universally accepted tools.

Associated Behaviors

Assessments of ancillary constructs, such as beverage preferences, smoking, illicit drug use, or sleep, may shed light on the causes of hangover. For example, individual differences in circadian rhythmicity (i.e. circadian typology) is a factor that may be taken into account, because it could influence performance of participants [71] and may interact with hangover effects. Other behaviors, such as hair-of-the-dog drinking or use of analgesics, could be important for interpreting items concerning hangover severity or duration. Consequences of hangovers, such as morning drinking, failure to fulfill work or school obligations, or resolutions to quit or cut down drinking also have descriptive and theoretical value.

DISCUSSION

This consensus paper highlights several gaps and inconsistencies in the hangover research literature which strongly suggests that many topics related to alcohol hangover need to be studied systematically or in more detail. Moreover, various issues of importance such as sex and age differences have not been studied sufficiently to draw appropriate conclusions. Surprisingly the pathology of alcohol hangover still has not been properly characterized and, as a consequence, no validated effective hangover remedies are available. This is despite the fact that many people experience the profound socioeconomic and health consequences of the alcohol hangover. A possible explanation for the lack of scientific interest may be that an effective cure is often regarded as undesirable by people who view alcohol hangover as an adequate punishment for unwanted behavior (i.e. excessive drinking). Moreover, effective hangover cures may even stimulate binge drinking (i.e., drinking continuously for days in a row).

Until the last decade, hangover research was characterized by small sample sizes, inadequate methodologies, and arbitrarily chosen tests. As a result, outcome measures were difficult to compare between studies. There was little rationale regarding the pathology of alcohol hangover and the absence of an adequate animal model limited the progress in alcohol hangover research. Also, inadequate validated and universally accepted tools to determine

hangover symptoms and overall hangover severity contributed to the often mediocre quality of alcohol hangover research.

The main conclusion from this consensus paper is that researchers should learn from methodological shortcomings and pitfalls experienced in the past. By adopting sound methodologies, a clear rationale, and sufficient sample size future research in this field should be capable of systematically studying the causes, consequences and possible cures for the alcohol hangover.

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Learning Objectives

- Alcohol hangovers are a common consequence of excessive alcohol consumption
- Alcohol hangovers have serious socioeconomic consequences, are an important health risk factor, and contribute to accidents and injury
- Past hangover research has often suffered from methodological shortcomings such as small sample sizes

Future Research

- Determine the pathology of alcohol hangover
- Examine the role of genetics
- Determine the economic costs of alcohol hangover
- Examine sex and age differences
- Development and adoption of common research tools and methodologies to study hangover effects
- Focus on factor that aggravate hangover severity (e.g., congeners)
- Develop effective hangover remedies

Fig. 1.
The majority of surveyed Dutch students report always or often being unable to study when experiencing an alcohol hangover [6].

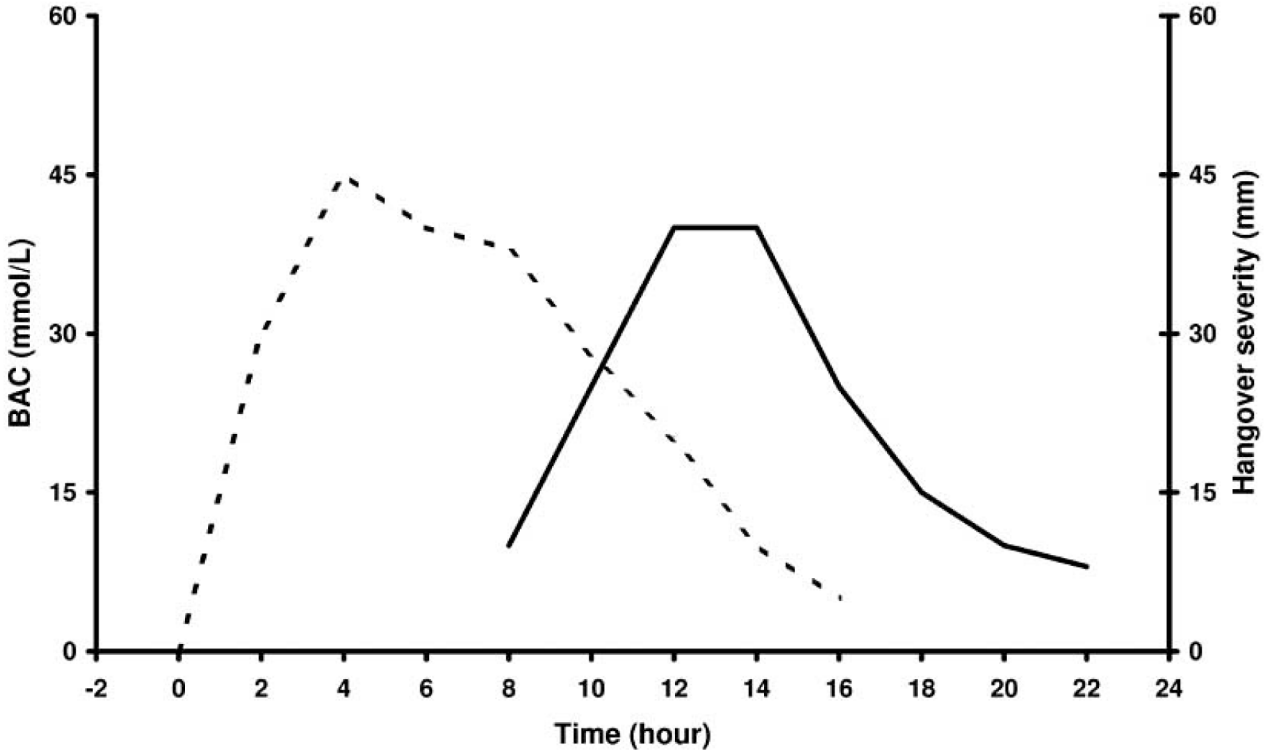

Fig. 2.

Commonly observed changes over time in blood alcohol concentration (BAC, dashed line) and alcohol hangover severity. Hangover severity is most pronounced when blood alcohol concentration reaches zero (in this example at 12 to 14 hours after the start of alcohol consumption). Derived from data of [1].

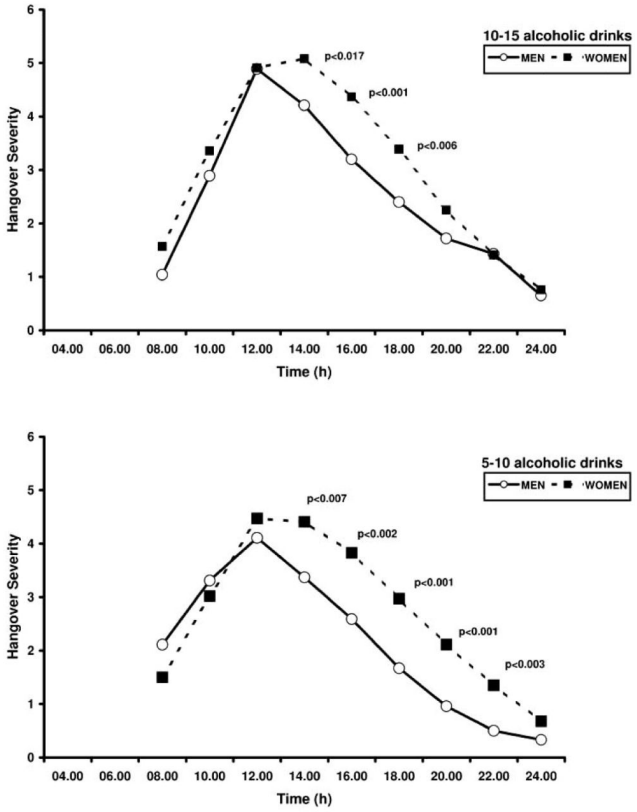

Fig. 3.

Hangover severity reported by men and women after consumption of 10 to 15 alcoholic drinks (top) and 5 to 10 alcoholic drinks (bottom) by time of day [53]. Significant sex differences in hangover severity were found at 14.00h, 16.00h, and 18.00 h.

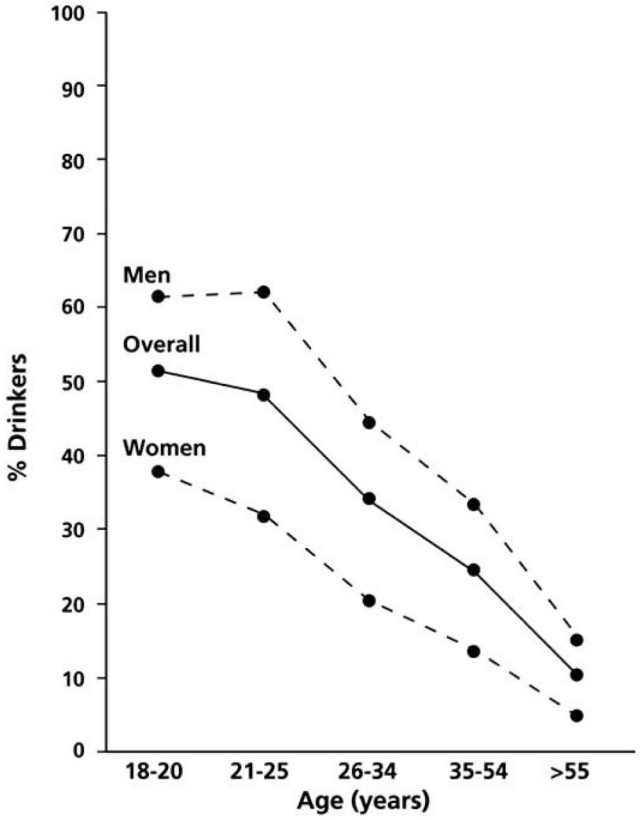

Fig. 4.

Percentage of heavy episodic drinkers among different age groups (5+/4+ alcoholic drinks on a single occasion by men/women, respectively). Note the significant difference between men and women, and the rapid decline as age increases (data from [65]).

Table 1

Top-10 Alcohol-Related Consequences Among Dutch Students [5]. Percentages Represent Subjects that Experienced the Particular Event at Least Once During the Past Year.

1	**Hangover**	**74.3%**
2*	Less energy or felt tired.	63.9%
3	While drinking, I have said or done embarrassing things.	38.0%
4*	Felt very sick to my stomach or thrown up after drinking.	34.1%
5	Ended up drinking on nights when I had planned not to drink.	29.2%
6*	Not gone to work or missed classes at school.	28.0%
7	Blackouts.	26.8%
8	Taken foolish risks when I have been drinking.	24.7%
9*	Quality of work or school has suffered because of my drinking.	21.7%
10	When drinking, I have done impulsive things I regretted later.	21.4%

Events that may be Related to Alcohol Hangover are Indicated by *