

## REVIEW

### THE ALCOHOL HANGOVER—A PUZZLING PHENOMENON

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The alcohol hangover develops when blood alcohol concentration (BAC) returns to zero and is characterized by a feeling of general misery that may last more than 24 h. It comprises a variety of symptoms including drowsiness, concentration problems, dry mouth, dizziness, gastro-intestinal complaints, sweating, nausea, hyper-excitability, and anxiety. The alcohol hangover is an intriguing issue since it is unknown why these symptoms are present *after* alcohol and its metabolites are eliminated from the body.

Although numerous scientific papers cover the acute effects of alcohol consumption, researchers largely neglected the issue of alcohol hangover. This lack of scientific interest is remarkable, since almost everybody is familiar with the unpleasant hangover effects that may arise the day after an evening of excessive drinking, and with the ways these symptoms may affect performance of planned activities.

Many people favour the (unproven) popular belief that dehydration is the main cause of alcohol hangover symptoms. However, taking a closer look at the present research on biological changes during alcohol hangovers suggests otherwise. A limited number of experiments have studied biological changes that are present the day after excessive drinking (for a review, see Ylikahri and Huttunen, 1977). Significant changes were reported on endocrine parameters (increased concentrations of vasopressin, aldosterone, and renin) and metabolic acidosis (reduced blood pH values due to increased concentrations of lactate, ketone bodies, and free fatty acids). These effects are related to dehydration and cause symptoms such as dry mouth and thirst. In addition, changes in immune system parameters (increased concentrations of pro-inflammatory cytokine [IL-12] and interferon-gamma [IFN $\gamma$ ]) have been reported (Kim *et al.*, 2003). It is likely that these changes in immune system parameters cause the more 'cognitive' alcohol hangover effects such as memory impairment and mood changes. Moreover, these findings suggest that alcohol hangover and dehydration are two independent yet co-occurring processes that have different underlying mechanisms. The idea that alcohol hangover symptoms (i.e. memory impairment) are related to immune system activation is strengthened by a relatively new discovery that the immune system and central nervous system (CNS) operate in close communication with each other (Maier and Watkins, 1998; Maier, 2003).

The first line of evidence for the hypothesis that effects of immune activity on the CNS may be the cause of alcohol hangover comes from studies showing that cytokines

communicate with the brain. The nervus vagus pathway is the main afferent pathway mediating the effects of peripherally released cytokines in the CNS (Dantzer *et al.*, 1998). Peripherally released cytokines thus have central effects, by signaling the brain to up-regulate cerebral cytokine production (Parnet *et al.*, 1994). Cytokine receptors have been localized on glia cells and neurons throughout the brain, but are especially dense in the hippocampus, a brain structure that is vital in memory functioning.

Second, the effects caused by cytokines are very similar to the core symptoms of alcohol hangover, suggesting that underlying processes might be the same. Cerebral cytokines (IL-1 $\beta$ , IL-6, and tumour necrosis factor [TNF- $\alpha$ ]) are involved in sickness behaviour (Dantzer *et al.*, 1998). In animals, symptoms of sickness behaviour include weakness, inability to concentrate, decreased appetite, reduced activity, sleepiness, and loss of interest in usual activities. In humans, the same symptoms are all commonly reported during alcohol hangover.

Third, in humans, a relationship between the presence of cytokines and memory impairment has been demonstrated (Reichenberg *et al.*, 2001). Endotoxin, injected to provoke sickness behaviour in healthy volunteers significantly increased cytokine concentrations (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ). Psychomotor functioning and attention were not affected, but memory was significantly impaired on a word learning test, story recall test, and figure recall test up to 10 h after injection. Thus, the effects on memory functioning during sickness behaviour are strikingly similar to those observed during alcohol hangover.

There have been a few studies that proposed that dehydration itself is a cause of memory impairment (e.g. Cian *et al.*, 2001; Tomporowski, 2003; Lieberman *et al.*, 2005). However, intense stressors (e.g. simulated combat or heavy prolonged exercise) were used to cause dehydration. Hence, it can be argued that these stressors have mobilized the immune system that in return causes memory impairment, independent of the dehydration effects that accompany these stressors. In support for this idea, in passive circumstances *without* a stressor (e.g. using abstinence from water for 11 h) no significant effects were reported on tests examining memory functions (Neave *et al.*, 2001). Thus, these findings support the hypothesis that not dehydration, but a stressor causes an immune response which results in memory problems. Future research should verify this hypothesis.

In this issue of Alcohol & Alcoholism, the article by Stephens and colleagues clearly discusses the difficulties and pitfalls of hangover research. Hangover research showed conflicting results: half the studies report significant performance effects whereas the other half do not. The most important

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cause of this is the fact that the pathology of alcohol hangover has not been elucidated. This is illustrated by the fact that whereas numerous hangover cures are available, only few of them are scientifically investigated and none of them prevents or relieves hangovers in a significant way (Pittler *et al.*, 2005). Since the biology of hangovers is not well understood, it is not surprising that the design of experiments and the included psychological tests lack an evidence-based rationale.

Blinding, i.e. preventing participants from knowing which is the hangover or placebo test day, is especially difficult in alcohol hangover research. Considerable amounts of alcohol (>1.0 g/kg) need to be consumed to produce a hangover. Alcohol intoxication and its after-effects are impossible to mimic by a placebo condition. Hence, participants can easily recognize the hangover and placebo condition. Alcohol (hangover) expectancies may thus affect performance. The authors address this shortcoming to naturalistic experiments, but due to blinding difficulties this is equally true for laboratory-controlled experiments.

As pointed out by Stephens and colleagues, the small sample size of many hangover experiments is another issue that resulted in conflicting results. Several studies tested less than 10 subjects, and thus, do not have enough statistical power to draw strong conclusions from the outcome measures. Moreover, in most studies only young healthy men participated. It is well known that men and women differ in alcohol metabolism, and thus, may differ in the presence and severity of hangover symptoms. More recent studies (Verster *et al.*, 2003; McKinney *et al.*, 2004) acknowledged this and did use larger groups of subjects consisting of both men and women.

To make matters complicated, the presence and severity of alcohol hangovers is influenced by many factors other than the amount of alcohol. One of these factors is the presence of congeners in alcoholic drinks. Congeners are substances that flavour and colour drinks. In laboratory experiments mixing pure alcohol with orange juice can prevent the presence of congeners. However, in real life (and naturalistic experiments) people consume a variety of different alcoholic drinks which all have different congener content. Stephens and colleagues shortly discuss the impact of congeners on performance measures during alcohol hangover, but acknowledge that not much research has been done in this area. As summarized in Figure 1, it can be concluded that alcoholic drinks that contain more congeners produce more severe alcohol hangovers. Moreover, a recent survey showed it takes fewer high-congener drinks to get a hangover, while at the same time the severity of these hangovers is most pronounced (Verster, 2006).

A second factor that is often not incorporated in research is the effect of sleep duration and quality on the hangover state. Whereas in laboratory studies participants are often allowed a full night of sleep, in real life drinking time often goes at the expense of sleep time. The results of a recent survey, summarized in Figure 2, show that some of the symptoms that are experienced the day after excessive drinking are significantly related to sleep duration and quality and not to the amount of alcohol that was consumed (Verster and Roehrs, 2007). The resulting daytime sleepiness is significantly related to several affects that are generally ascribed to be alcohol hangover symptoms.

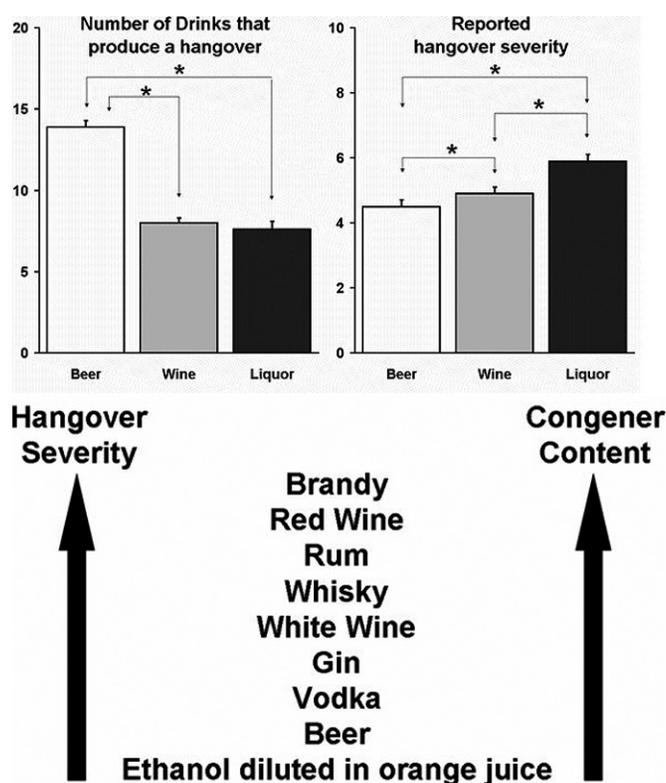


Fig. 1. Number of drinks that produce a hangover and the reported corresponding hangover severity for beer, wine and liquor. Hangover severity ranges from 0 (no hangover) to 8 (extreme hangover). Significant differences ( $P < 0.05$ ) are indicated by \*. Note: In The Netherlands a standardized drink of beer, wine or liquor all contain the same amount of alcohol.

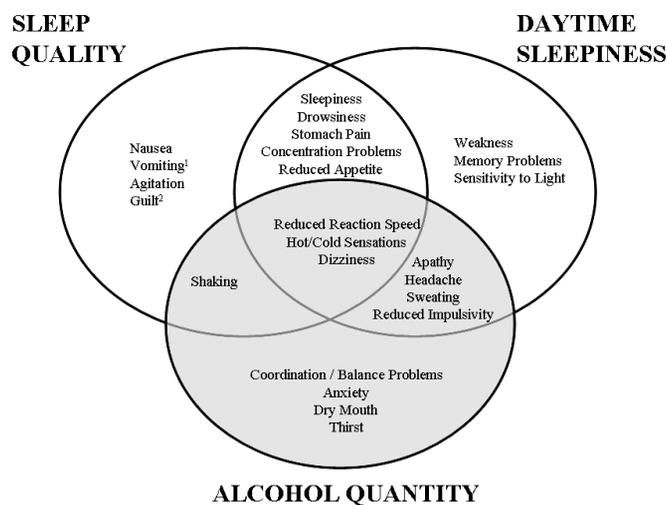


Fig. 2. Schematic representation of the relationship between individual hangover symptoms and sleep quality, daytime sleepiness and alcohol quantity. Please note that only alcohol quantity and daytime sleepiness correlated significantly with overall hangover severity. All depicted correlations were significant ( $P < 0.05$ ), except vomiting ( $P < 0.06$ ) and guilt ( $P < 0.07$ ).

The results from this survey underline the fact that many factors influence the hangover state. On the other hand, it is essential to keep in mind that several factors co-occur with

the hangover state including dehydration effects and sleep deprivation. Disentangling these factors is very important and requires future research. Other factors such as the impact of food and smoking on hangover severity also deserve attention from hangover researchers. Although it is of scientific interest to investigate these factors in isolation, in real life they are experienced together. Therefore, the importance of naturalistic studies in which subjects can freely drink, smoke, and eat is evident.

Although there are many methodological shortcomings in alcohol hangover research, it is evident that alcohol hangovers do have an impact on daily activities such as on-the-job performance. This is illustrated by a study of Ames *et al.* (1997).

They conducted structured interviews among 800 assembly workers in order to examine the relationship between hangovers and work-related problems. Although less than half the workers reported being at work while having a hangover, those who experienced hangovers reported significantly often feeling sick at work, been criticized by a supervisor, having conflicts or fights with co-workers, had significantly more problems in completing the job, and reported falling asleep more often at work. Statistical analyses showed that having a hangover during work actually predicts these work-related problems: the frequency of problems increases when people more often reported having hangovers at work.

Interestingly, no significant differences were found in absenteeism between workers reporting hangovers and those who did not. A possible explanation may be that workers with a hangover feel that having a hangover is 'their own fault', and the obligation they have to go to work may prevent calling sick. The fact that workers do go to work when having a hangover is of concern, especially since some in jobs making the wrong decisions may have serious consequences.

The article by Stephens and colleagues calls for additional hangover research, using more sophisticated research methods. In this context, researchers should ask themselves the question 'what is the alcohol hangover?'. It is evident that besides the alcohol amount many other factors play a role in determining the presence and severity of hangovers. To complicate matters, co-occurring dehydration and sleep deprivation have an impact on the next-day effect of excessive alcohol consumption as well. Until future research elucidates its pathology, the alcohol hangover remains a puzzling phenomenon.

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