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Meeting Report

Proceedings of the 11th Alcohol Hangover Research Group Meeting, in Nadi, Fiji

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Abstract: The present proceedings offer a summary of the 11th meeting of the Alcohol Hangover Research Group held in April 2019 in Nadi, Fiji. The aim of the meeting was to gather the world's leading experts in the field of alcohol hangover and share advances and ideas to help better understand the underlying pathology, consequences, and potential therapeutics. Several aspects of alcohol hangover research were discussed, including hangover-associated impairments of cognitive performance and health, novel and best research practice, the validation and use of wearable technology and online tools for off-site data collection, effects of hangover on physical strength performance, new evidence on sex differences in the occurrence and severity of alcohol hangover, and exciting future projects and directions.

Keywords: hangover; alcohol; cognitive performance; hangover treatments

1. Introduction

Alcohol hangover is defined as "the combination of mental and physical symptoms, experienced the day after a single episode of heavy drinking, starting when blood alcohol concentration approaches zero." [1]. A recent WHO report indicated that 18.2% of the worldwide population has consumed alcohol to a sufficient level to induce hangover [2]. Alcohol hangover has also been linked to neurocognitive impairments [3], an increased risk of accidents [4], and reduced (workplace) productivity [5]. It is therefore unsurprising that in addition to having a health and social impact, alcohol hangovers were predicted to have cost the US economy approximately $179 billion in 2010 alone [6]. Further research on the effects and causes of hangover is therefore required to develop a better understanding of the short-term effects of high alcohol consumption and the development of a potential treatment of hangovers.

The Alcohol Hangover Research Group was established in 2010 to encourage both the international collaboration of researchers in this field and the development of a better understanding of the implications of alcohol hangover. The present proceedings offer a summary of the 11th meeting held on the 25th of April 2019 in Nadi, Fiji.

2. The Physiological Impact of Alcohol Hangovers

Michelle van Wijk (Utrecht University, the Netherlands) reported the outcomes of a naturalistic alcohol hangover study among n = 22 Dutch students who went on a seven-day skiing holiday. The aim of the study was to examine physical performance during alcohol hangover. While previous research devoted to this topic is limited [7], the reporting of physical hangover symptoms is common [8]. In this study, a number of measures were taken across each day. Every morning, for example, the grip strength of each participant was assessed in addition to hangover severity and past evening alcohol consumption. In the afternoon, after a day of skiing, breath alcohol tests were completed, and subjects reported on their skiing performance. The results showed that alcohol intake, and the presence and severity of alcohol hangover (symptoms) varied from day to day. The data revealed that cumulative alcohol intake over the week was significantly associated with a steady reduction in reported perceived immune fitness. Surprisingly, the first results of this study suggest that having hangovers did not affect the self-reported quality, frequency, and duration of skiing performance, and no significant changes associated with the grip-strength test were observed. Further analyses should reveal whether specific factors have moderated the observed effects, such as the total amount of alcohol intake, and also reveal whether psychological factors such as group pressure to participate in skiing activities, desire for conformity, and other motivational aspects have an impact. The observation that grip strength was unaffected during alcohol hangover is in line with previous research [9].

Charmaine van Rossum (Utrecht University, the Netherlands) discussed the impact of sleep on the presence and severity of alcohol hangover. Several studies have investigated this previously, but most of these studies relied on self-reports [8,10] and showed that sleeping time is often lost at the expense of drinking time. Additionally, total sleeping time and sleep quality have been found to be significantly reduced after an evening of heavy alcohol consumption. Recently, Devenney et al. [11] published a study using a GENEactiv watch (Activinsights, Cambridgeshire, UK) to continuously monitor sleep and daytime activity on a drinking night and an alcohol-free control day. The findings confirmed previous self-reports, but also found differences in the GENEactiv recordings, stressing the importance of including objective recordings in naturalistic study designs. Current mobile technology allows for real-time assessment of different factors, including sleep/wake activity [12]. GENEactiv watches were worn by 22 students for seven days, during which daytime activity levels and sleep outcomes were assessed. The first results showed a day-to-day variation in total sleeping time and time-to-bed outcomes that paralleled that day's alcohol intake. Heavier drinking days alternated with non- or low-alcohol days, on which participants tried to catch up/compensate for previous sleep loss. The data showed that subjects slept longer the night before a hangover day, and reported significantly poorer sleep quality compared to non-hangover days.

Stephanie Balikji (Utrecht University, Utrecht, The Netherlands) discussed the potential relationship between changes in the microbiome and alcohol hangover. A study was conducted to examine the changes in the microbiome composition of young, healthy volunteers after an evening of heavy alcohol consumption. Data from n = 15 healthy social drinkers (18–30 years old) who regularly experienced hangovers were analyzed. They participated in a naturalistic study, consisting of an alcohol day and an alcohol-free control day. Stool and saliva samples of these individuals were collected on each test day (the morning after alcohol consumption), and the microbiome composition was investigated. Alcohol hangover severity was rated on a scale ranging from 0 (absent) to 10 (extreme). After alcohol consumption, there were significant changes in the microbiota composition of the saliva, but not of the faeces. Saliva analysis showed that the relative abundance of *Rothia*, *Streptococcus*, and *Veillonella* was significantly increased after alcohol consumption, as compared to the control day. This was coupled with significantly decreased relative abundance of *Prevotella*,

Fusobacterium, *Campylobacter*, and *Leptotrichia*. The biggest change in microbiome was the increase of *Rothia*, which was significantly negatively correlated with reported hangover severity. Changes in other microbiota did not correlate significantly with hangover severity. In conclusion, a higher abundance of oral *Rothia* is associated with experiencing less severe hangovers. This finding may be explained by the notion that *Rothia* presence is associated with production of large amounts of acetaldehyde (Moritani et al. [13], and thereby can influence the rate of alcohol metabolism. The latter might then influence the presence and severity of next-day alcohol hangover symptoms.

Aurora van de Loo (Utrecht University, Utrecht, The Netherlands) discussed the role of the immune system in the development of alcohol hangover. Immune status and perceived immune functioning have been suggested to play a role in the pathology of alcohol hangover. Previous research has found that drinkers with poorer self-reported immune status are more vulnerable to experiencing alcohol hangovers [14], although no direct relationship between the severity of hangovers and immune status has been found [15]. Aurora van de Loo discussed the results from three different studies that assessed cytokine concentrations in saliva at different time points after alcohol consumption. In the first controlled study, salivary cytokine concentrations were measured hourly for 8 h after participants consumed alcohol to an estimated blood alcohol concentration (BAC) of 0.08%. Cytokines that could be detected reliably were IL-1β, IL-8, TNF-α. Compared to the alcohol-free control day, a significant increase was found for IL-1β at several time points throughout the alcohol test day.

In the second naturalistic study presented by van de Loo, salivary cytokine responses on the morning after an evening of alcohol consumption and on the morning of a control day were measured. In the third study, the same naturalistic design was followed as in study 2, however, cytokines were assessed hourly during the hangover and on a control day. In the second study, IL-1β, IL-6, IL-8, TNF-α, and IL-10 could be reliably detected. Significant hangover-associated increases in salivary cytokine concentrations were found for IL-6 and Il-10, and the increase of TNF-α approached significance. In the third study, no significant changes in cytokine concentrations were found, but as this was preliminary data from only $n = 9$ subjects, the low sample size likely accounted for the absence of statistically significant changes in cytokines. Taken together, these studies demonstrate that the immune system responds to heavy alcohol consumption. These findings suggest that the immune response may be related to the presence of alcohol hangover. Hangover severity was, however, not found to significantly correlate with any of the salivary cytokine changes described above.

Albertine van Lawick van Pabst (Utrecht University, Utrecht, The Netherlands) presented data on possible sex differences in the presence and severity of alcohol hangover symptoms [16]. Investigating sex differences is important, as their presence may have implications for the functional consequences of having a hangover. For example, men and women may differ with regard to the magnitude of performance impairments, and in the degree of negative alcohol hangover influences on daily activities such as driving and job performance. Furthermore, if sex differences existed in the presence and severity of hangover symptoms, this might have implications for the development of an effective hangover treatment. Perhaps new treatments should be sex-specific and target different hangover symptoms in men and women.

Data from two previous surveys was combined for the analysis of van Lawick van Pabst [8,17]. In both studies, subjects reported details on their most recent hangover experience within the past month. Participants rated the presence and severity of 23 hangover symptoms. The data ($n = 2446$, 1094 male and 1352 female) were used to examine potential sex differences among the presence and severity of these 23 hangover symptoms. Data were grouped according to estimated blood alcohol concentration (BAC) ranges, to ensure a fair comparison between males and females. The analysis revealed that across the BAC groups (up to an estimated BAC of 0.4%), severity scores of nausea and tiredness were higher in females than in males. Although the differences were statistically significant, they were of small magnitude and therefore, likely to have only little clinical relevance.

3. The Cognitive Impact of Alcohol Hangovers

Lizanne Arnoldy (Utrecht University, Utrecht, The Netherlands) discussed a study of the psychological factors that may have an impact on hangover severity. Previous research found that psychological state while drinking has a significant effect on next-day hangover severity [18,19]. For example, feelings of anger and anxiety could increase hangover severity, as compared to drinkers with a neutral mood state. A survey was conducted among an international sample of young adults (18–30 years old) who were on holiday or working in Nadi, Fiji. The analysis could not replicate a significant effect of various mood states, including anxiety, depression, stress, and fatigue during drinking on hangover severity. In other words, when correcting for estimated BAC, mood during drinking had no relevant impact on hangover severity the next day. Instead, regression analysis revealed that subjective intoxication was the best predictor of next-day hangover severity, accounting for about 21% of variance. Finally, the results showed that the hangover state itself is accompanied by mood changes, including increased levels of stress and guilt about drinking.

Chantal Terpstra (Swinburne University of Technology, Melbourne, Australia) described the validation of an online version of the Trail-Making-Task-B (TMT-B). The TMT-B is a neuropsychological task that measures attention and working memory with an executive component. The task is known to be sensitive to cognitive impairments due to disease and pharmacological interventions. To make this traditional pen-and-paper task more accessible, an online version, the eTMT-B, was created and validated for future research purposes. Twenty-four participants were included (Mean age = 30.29, SD = 5.03) and no significant differences were found in response times between the pen-and-paper version and online platforms. There was a significant correlation between completion time on the two platforms (errors were rare on either platform). After validation of the online version, a larger study was conducted where breath alcohol concentration (BrAC) and self-reported drinking behavior were collected from social drinkers at exit points of an entertainment district. These were then related to hangover severity and cognitive function, as measured over the internet in the same subjects the following morning. Of n = 346 individuals who were breathalyzed and indicated that they may be prepared to participate in the next-day phase of the study, n = 105 provided complete online datasets (this retention rate is similar to those reported for naturalistic hangover studies). Participants completed a number of measures including an online version of the Alcohol Hangover Severity Scale (AHSS), questions regarding alcohol consumption, and the eTMT-B. Hangover severity was significantly correlated with one drinking measure only, namely the previous night's BrAC. The previous night's BrACs were statistically similar between those who did (0.11%) and those who did not (0.11%) complete next-day measures, which strongly suggests that level of intoxication did not affect consent to the extent that the sample were 'self-selecting' in this context. Completion time on the eTMT-B was significantly correlated with hangover severity, the previous night's BrAC, and time spent drinking. These findings confirm that alcohol hangover negatively affects cognitive functioning and that poorer working memory and executive performance correlate with hangover severity. The results also support the use of online measures in (future) hangover research.

Elizabeth Ayre (Swinburne University of Technology, Melbourne, Australia) described the findings of a recently published study measuring the cognitive effects of alcohol hangover and related this to a current review of literature, which compares cognitive impairments during alcohol hangover and acute intoxication. Firstly, a recent field/internet study explored the relationship between BrAC, hangover severity, and performance on an executive function task. Participants were breathalyzed after a normal night out drinking in Brisbane's central entertainment district and reminded to complete an online version of the (TMT-B) the next morning when experiencing alcohol hangover. Findings showed that hangover severity positively predicted the time to complete the TMT-B, but not task accuracy. These results indicate a potential trade-off between speed and accuracy that opposes the relationship evident during acute intoxication. To investigate this further, a literature review is currently being conducted to compare cognitive impairments caused by alcohol intoxication and alcohol hangover and to explore the path of impairment across the blood-alcohol curve. Separate literature searches for "alcohol-hangover" and "acute intoxication" studies have been

completed. Studies were included if the stage of the blood-alcohol curve was identified and aspects of attention, memory, or psychomotor performance were measured. Preliminary findings from 10 alcohol hangover studies and 20 acute intoxication studies show similar trends in poorer reaction times (and not accuracy). Further analyses of findings in other cognitive domains may determine the suitability of alcohol-hangover as a third phase in the already established "biphasic" effects of alcohol.

4. The Future for the Research and Treatment of Alcohol Hangovers

Emily Palmer (Imperial College London, London, UK) discussed the key limitations and methods for establishing a representative animal model of alcohol hangover. Critically, all models of hangover should be based on the current definition of alcohol hangover, which is outlined above. Firstly, it is important to determine the onset of hangover within the animal model. This is achieved by measuring the ethanol concentration within the blood, with hangover onset occurring once the blood ethanol concentration returns to zero [1]. A second critical consideration for the development of an animal model is the complex symptomology experienced in a hangover: over 47 symptoms [17], including both psychological and physical symptoms, can be best modelled in animals by completing multiple and varied behavioral tasks that cover a range of symptoms. In previous studies, behavioral tests such as the tightrope [20] and rotarod [21] have been used to measure physical detriments in response to ethanol. Additional paradigms such as the open field or Elevated Plus Maze have been employed to assess psychological functions such as anxiety [22]. When considering which behavioral tests to include in a model of alcohol hangover, it is important to consider the wide symptomatic variety that accompanies the alcohol hangover. Of note, there is even a wide variety of inter-individual symptoms depending on the specific hangover occurrence. So, in contrast to human research, a primary endpoint (reported overall hangover severity) is not possible in animal research, but is a combination of outcomes of various behavioral tests. Finally, both the dose and route of ethanol administration should be carefully considered. The human experience of alcohol hangover follows a single dose of heavy drinking in which high levels of intoxication are normally experienced. Literature has found that between 3–6 g/kg have successfully induced intoxication in mice and rats, which can be confirmed by the loss of the righting reflex [21]. The intragastric route mimics heavy drinking in humans and is therefore the best route to use in an animal model of alcohol hangover.

Joris Verster (Utrecht University, Utrecht, The Netherlands) discussed current developments in the search for effective and safe hangover treatments. Although there is a high demand for an effective hangover treatment [23], most of the currently marketed hangover treatments lack scientific evidence to support their efficacy. For other compounds that have been evaluated by clinical trials, the effectiveness is normally limited to either mitigating a single hangover symptom or absent completely [24–26]. The primary cause for the lack of an effective hangover treatment is the fact that limited investments are made in the development of such treatments, and that the pathology of the alcohol hangover is not yet fully elucidated [25,27,28]. Two approaches dominate hangover treatment development. The first approach aims to accelerate alcohol metabolism, while the second approach aims to moderate the immune response elicited by heavy alcohol consumption. For both approaches, there is emerging support from scientific evidence. Several newly developed compounds have been shown to speed up alcohol metabolism [29], reduce blood cytokine levels that were raised by alcohol consumption [30], or both. More research is needed to investigate the possible effectiveness of several natural compounds and nutrients that have been suggested to alter the rate of alcohol metabolism (e.g., micronutrients such as zinc), or counteract the immune response elicited by heavy drinking [31,32].

Fu Chen (More Labs, Los Angeles, CA, USA) described a product developed by More Labs called Morning Recovery. Morning Recovery is a dietary supplement product marketed in US for liver support during drinking. It contains multiple herb extracts and vitamins in the formula, especially *Hovenia Dulcis* extract, which has been used traditionally for hangover symptom relief for thousands of years. One of the active components found in *Hovenia Dulcis* extract is dihydromyricetin (DHM). In this study, the liver protection effect of DHM and its ability to upregulate alcohol dehydrogenase

(ADH) and acetaldehyde dehydrogenase (ALDH) have been demonstrated in live cell models. Results showed that DHM can effectively increase ADH and ALDH expression, which may in turn facilitate alcohol metabolism. It also reduced alcohol-induced cytotoxicity by reducing oxidative stress and mitochondrial stress. Morning Recovery also uses a patent-pending technology to increase DHM solubility more than threefold, which is important for its bioavailability.

Sarah Benson (Swinburne University of Technology, Melbourne, Australia) discussed a study which investigated whether administration of an l-cysteine and B- and C-group vitamin supplement would reduce hangover symptom severity. Although the precise pathogenesis of alcohol hangover is unknown, it has been suggested that the accumulation of highly toxic acetaldehyde plays a significant role in hangover symptom presence and severity (although empirical data are lacking). Acetaldehyde is metabolized by acetaldehyde dehydrogenase and glutathione, with efficient metabolism resulting in less damage. However, glutathione stores are quickly depleted following excessive alcohol intake, allowing acetaldehyde levels to build up. Since glutathione contains high levels of cysteine, cysteine supplementation may help avoid or reduce hangover symptoms. Twenty young and healthy adults completed a counterbalanced, placebo-controlled, and semi-naturalistic study. During intoxication visits, the laboratory was set-up as a bar and participants had free access to alcohol to a maximum of 1.3 g/kg. Participants' alcohol consumption on the second testing visit was identical to that on their first in timing and number of drinks consumed. Participants attended the laboratory the morning following the intoxication visit and were breathalyzed to ensure a BrAC of 0.00% before undergoing a blood sample for high sensitivity C-reactive protein (hs-CRP) and gamma-glutamyl transferase (GGT) analyses, and completing several questionnaires assessing hangover symptom severity, sleep quality, and current sleepiness. BrACs obtained over the two testing conditions did not significantly differ (0.097% on the placebo visit and 0.096% on the treatment visit). There were no significant differences between placebo and the active treatment on any of the measures. In conclusion, this study failed to find any evidence for l-cysteine supplementation to reduce hangover symptom severity. Furthermore, these findings suggest that hs-CRP and GGT levels are not affected by alcohol hangover.

Sean O'Neill (Toast! Supplements, Boston, MA, USA) explained the story and the science behind Toast! Before You Drink gummies. Beginning with an erroneous diagnosis of cirrhosis of his liver, Mr. O'Neill explained how researching alcohol's interactions with the body led him to clinical research showing how various compounds could potentially reduce alcohol's damaging effects, including preventing a hangover. Toast! is based on the hypothesis that hangovers result from an immune response to the inflammatory effects of metabolizing alcohol, the latter through some combination of both acetaldehyde as well as other compounds such as congeners. Starting with a simple test of n-acetylcysteine and milk thistle as a proof of concept, that combination was tested. Receiving a positive, if not uniform, response, Toast! then followed an iterative, naturalistic approach internally testing various formulations. Tests were conducted to investigate multiple variants to single individuals, with subjects reporting data back the following day after using Toast!. Toast! experimented with a large number of ingredients, before coming to a final formulation which was then used by over 200 consumers. Fatigue was the only symptom reported with any frequency, with subjects otherwise reporting no hangover symptoms. Since commercializing the product, reviews have remained excellent, with fatigue again the only symptom reported with any consistency. Independent double-blind placebo-controlled studies are planned to further investigate the efficacy of Toast! Before You Drink gummies.

Gillian Bruce (the University of the West of Scotland) discussed a study conducted to examine differences in alexithymia between hangover-sensitive and hangover-resistant individuals. Recent studies have identified relationships between alexithymia and both heavier social drinking as well as problem drinking. Furthermore, heavier drinking has also been associated with hangover resistant drinkers, i.e. drinkers who do no report hangover symptoms in spite of drinking at levels where hangover would be expected. Interestingly, recent studies have demonstrated differences in hangover-resistant and hangover-sensitive drinkers in a number of areas, including some personality characteristics and psychological profiles. As part of a large online survey distributed to students in

The Netherlands, demographics, alcohol consumption patterns, hangover characteristics, and personality were recorded. In addition, participants completed the Toronto Alexithymia Scale (TAS-20). In order to ensure participants consumed enough alcohol to expect alcohol hangover participants were only included in the statistical analysis if they had an estimated BAC of ≥0.11% on their heaviest past month drinking occasion. Those who claimed to be hangover-resistant over the past year were compared with drinkers who did experience hangovers (the hangover-sensitive group). The results indicated that hangover-resistant drinkers scored significantly higher on the alexithymia subscales for 'difficulty describing feelings' and 'externally oriented thinking'. This could imply that drinkers who claim to have no hangovers might not be truly hangover-resistant, but have more difficulty describing biopsychological changes that occur during the hangover state. Alternatively, they may have poorer meta-cognition than their hangover-sensitive counterparts.

5. Discussion

Several important aspects of alcohol hangover were discussed during the 11th Alcohol Hangover Research Group Meeting. Specifically, a focus was put on improving the understanding of how hangover impairs different aspects of human health, how it should ideally be assessed, and which hangover treatment options could prove promising in the future. In this context, the increased use of new wearable technologies such as the GENEactiv watch was pointed out to be of particular interest in hangover research. Using this technology has the potential to bridge the gap between carefully controlled laboratory studies and the more naturalistic studies commonly used in alcohol hangover research. This provides researchers with the opportunity to accurately capture data whilst allowing participants to engage in their natural drinking behaviors. Another aspect of great relevance is the recent introduction of wearable BAC tracking devices, which can objectively monitor ethanol levels in real time during an evening of unsupervised alcohol consumption in naturalistic study designs. Results from studies investigating the cognitive effects of alcohol hangover have been mixed [3]. They also present methodological challenges, since alcohol hangover research often relies on self-reports of the alcohol consumption leading to hangover [33]. Another research development helping to bridge the gap between naturalistic and laboratory research is the validation and use of the online version of the TMT-B. Online tasks have the capacity to provide accurate cognitive testing to participants in the comfort of their own homes. This has the capacity to dramatically reduce participant drop-out in hangover studies, which will allow for a more accurate representation of the impact of alcohol hangovers. This use of online cognitive tasks sets an exciting precedent for future alcohol hangover investigations.

Several speakers reported exciting findings that contradicted those reported in previous literature. Firstly, it was found that that skiing performance is not affected by hangover severity, which is in contrast to what previous studies might suggest [34]. However, further research on a larger, more age-diverse demographic group may be an interesting direction for future research. It was also found that sex differences were minimal in the occurrence and severity of alcohol hangover symptoms. This suggests that future hangover research can (and should) assess men and women equally, thus providing the opportunity for easier study recruitment in the future. Another finding that contradicted previous findings was that mood during drinking had no relevant impact on next-day hangover severity [35]. These collective contradictory findings are indicative of improvements in research methodologies and developments in study designs, including prospective studies and larger sample sizes.

A promising future direction was outlined, as several members stressed their intention to conduct a large (international) survey to assess psychological, behavioral, and biological factors that contribute to alcohol hangover occurrence and severity. This survey aims to measure factors that are expected to contribute to hangover, including family history of alcohol misuse, lifestyle, coping, emotional state/stress, metacognitions, mental resilience, and personality traits. This survey is partially exploratory and to the best of our knowledge, it will be the first project to assess alcohol hangovers across various cultures. Findings will determine whether there are any cross-cultural

differences in the causes and experience of a hangover and will enhance current understanding of the fundamental factors that cause alcohol hangover.

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Conflicts of Interest: Fu Chen is the Head of Product Development at More Labs, USA. Sean O'Neill is the founder of Toast! Supplements. Sarah Benson has received funding from Red Bull GmbH, Kemin Foods, Sanofi Aventis, Phoenix Pharmaceutical and GlaxoSmithKline. Andrew Scholey has held research grants from Abbott Nutrition, Arla Foods, Bayer Healthcare, Cognis, Cyvex, DuPont, GlaxoSmithKline, Martek, Masterfoods, Naturex, Nestle, Red Bull, Wrigley, and has acted as a consultant/expert advisor to Abbott Nutrition, Barilla, Bayer Healthcare, Danone, Flordis, GlaxoSmithKline Healthcare, Masterfoods, Martek, Novartis, Unilever, and Wrigley. Over the past three years, J.C.V. has received grants/research support from the Dutch Ministry of Infrastructure and the Environment, Janssen, Nutricia, and Sequential, and has acted as a consultant for Clinilabs, More Labs, Red Bull, Sen-Jam Pharmaceutical, Toast!, and ZBiotics. The other authors have no potential conflicts of interest to disclose.

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