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Hangover

PERSPECTIVES

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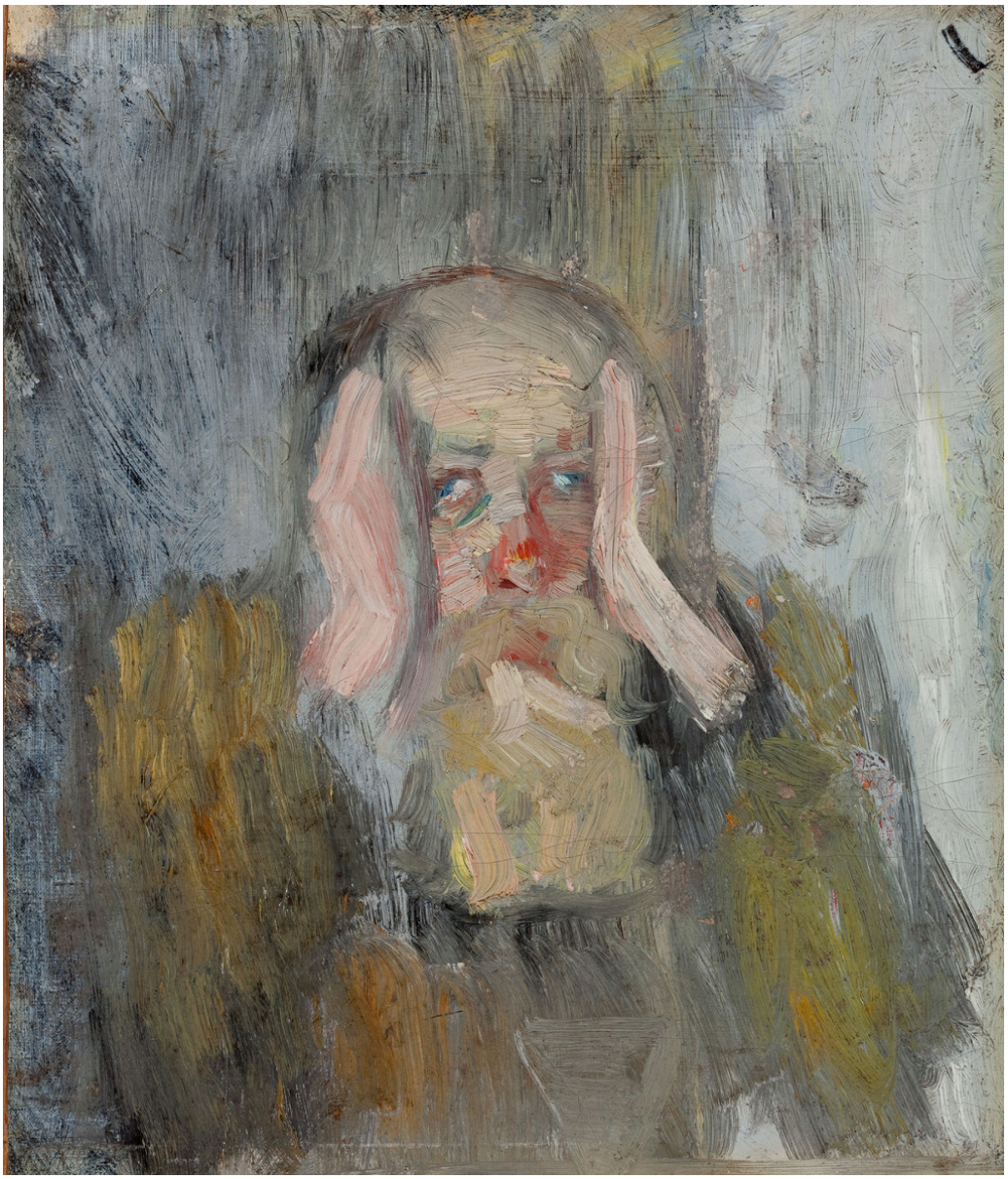
You wake up with a dry mouth and pounding headache. You are sweating, irritable and experiencing symptoms of anxiety. Inside, a relentlessly churning meat grinder is spiralling out of control, and you start to vomit. You ask yourself: 'What happened?'



*'Dagen derpå, selvportræt' (*The morning after, self-portrait*) (1883), Christian Krohg (1852–1925). In public ownership, via Wikimedia Commons.*

'Hangover' is known by a variety of colloquialisms in some languages (1) and the phenomenon is caused by excessive ethanol intake the day before. The hangover is a complex condition that can be viewed from various perspectives. Like any other illness, it not only involves a set of pathological mechanisms but must be seen in the context of the patient's subjective experiences and how external factors shape and moderate these. People's perceptions of hangovers differ based on factors such as time, place, culture and worldview. Perhaps the morning after the night before was grimmer for seventeenth-century Calvinists than for the Bacchae of ancient Roman? In other words, we are dealing with a *biopsychosocial-cultural* phenomenon. However, we will examine the hangover through the clinical lens of Michel Foucault, describing the effects and aftermath of ethanol in light of *physiological processes*. For a review of the cultural history of the hangover, *The Hangover: A Literary and Cultural History* by Jonathon Shears is recommended (2).

Metabolism

Ethanol is mainly metabolised in the liver by the enzyme alcohol dehydrogenase (ADH) (3), to produce acetaldehyde. First-pass metabolism also occurs in the stomach, particularly in men. This reduces bioavailability and may partly explain why men have a higher tolerance for alcohol than women, also when correlated to body weight (4). Additionally, men have a larger volume of distribution of hydrophilic drugs, which may further reduce the concentration of alcohol in plasma. However, tolerance and toxicity vary considerably in individuals, based on sex, age, body composition and tissue tolerance. The presence of food in the stomach delays the passage of alcohol to the intestine, prolongs first-pass metabolism and reduces exposure. In fact, bioavailability can be 3–10 times higher in someone in a fasted state (5).

Hepatic CYP (cytochrome P450 enzyme) 2E1 accounts for approximately 10 % of the total metabolism of ethanol to acetaldehyde. CYP2E1 is inducible and thus increases the elimination rate and alcohol tolerance if alcohol consumption is maintained over time. CYP2E1 induction increases by about 30 % with one week of daily alcohol consumption (40 g/day) (6). After four weeks, induction has been shown to be approximately three times greater, but with considerable variability among individuals. Three days after stopping drinking, the induction returned to the baseline.

Acetaldehyde is more toxic than ethanol, and several symptoms of alcohol poisoning following consumption (in the form of a hangover), as well as health risks associated with alcohol consumption, can be attributed to acetaldehyde. Acetaldehyde is further oxidised to acetate (acetic acid) in the body by the enzyme aldehyde dehydrogenase (ALDH). Acetate can be used as a nutrient by the body via acetyl-CoA and the citric acid cycle. Approximately 36 % of people of East Asian descent have an inactive or dysfunctional variant of the gene encoding ALDH, which can exacerbate symptoms of acetaldehyde poisoning following intake of ethanol (7). Disulfiram (Antabuse) inhibits ALDH and intensifies symptoms of alcohol poisoning through the accumulation of acetaldehyde.

Kinetics

In some countries, such as Norway, blood alcohol concentration (BAC) is measured by alcohol per mille (thousand millilitres) of blood. One per mille (1 ‰) corresponds to 1 gram of alcohol in 1 litre of blood. Symptoms and toxicity as a result of alcohol consumption correlate to the blood alcohol level. A rule of thumb is that one unit of alcohol (12–14 g of ethanol) will give an average increase of 0.2 per mille in a man, and 0.4 in a woman. The frequency of alcohol consumption determines the increase. Excretion (metabolism and elimination), and thus the reduction of blood alcohol level, is approximately 0.10–0.25 per mille/hour (8).

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Ethanol elimination follows both zero-order and first-order kinetics, but above a certain threshold, which is low for most people (around 0.2 per mille), zero-order kinetics prevail (9). This means that the need for elimination exceeds the capacity of the metabolic machinery (saturation kinetics), and the elimination rate therefore remains constant as opposed to increasing proportionally with the BAC. This, in turn, means that a relatively small increase in the dose can lead to a surprising, unpredictable and disproportionate increase in the BAC, similar to a 'narrow therapeutic window' for certain medications. In zero-order kinetics, the half-life also increases as the BAC rises.

Alcohol metabolism is both genetically determined and, to a large extent, adaptive. Elimination rates of 0.2–0.6 per mille/hour have been recorded in alcoholics (10). First-order kinetics over a broader range of BAC levels have also been observed in some individuals. This results in an exponential and non-linear fall in BAC over time, and thus potentially fewer symptomatic adverse effects linked to consumption (11). The BAC of two individuals with the same level of consumption can therefore differ by several fold. It cannot be ruled out that ultra-rapid metabolism can lead to milder hangovers (10).

Mechanisms, myths and remedies

The mechanisms underlying hangovers are not fully understood. It is reasonable to assume that a wide range of cellular and physiological disturbances and damage play a role, including oxidative stress, inflammation, apoptosis and reduced sleep quality, with immunological, endocrine and haemodynamic involvement (12, 13). Depending on the degree of toxicity, this damage will be either reversible or irreversible. Given the broad nature of the mechanisms underlying hangovers, it is unlikely that any intervention will completely eliminate them. Once the damage has been done, there is little else to do but wait, although analgesics can be given for symptom relief. Drinking water can prevent dehydration resulting from alcohol-induced inhibition of vasopressin, but it does not reduce the hangover to any great extent. The intake of electrolytes, glucose, minerals or antioxidants has little or no clinical effect (14). Myths such as 'beer before wine and you'll feel fine; wine before beer and you'll feel queer' have been debunked in clinical trials (15). Thus, it is not the order of the different alcohol types that matters, but the total amount consumed and the rate of consumption that are the determining factors. Consuming different types of alcohol can potentially lead to larger quantities being drunk overall. It has been speculated that certain types of alcohol may cause worse hangovers due to the presence of other constituents (congeners), in the suggested order of pure spirit, beer, white wine, red wine, whisky and brandy. There is some evidence to support this (16), but again, it is the total alcohol exposure that is the determining factor.

A variety of remedies and measures have been proposed over the years to treat hangovers, but they lack documentation in the form of randomised controlled clinical trials, even after 8000 years of exposure. The trials that have been conducted often entail weaknesses and small sample populations. One of the main problems is that they cannot effectively blind participants to whether they are consuming alcohol or not, and are thus unable to eliminate the expectation of becoming hungover as a factor (17). Ernest Hemingway's cure for a hangover was tomato juice and beer. Consuming more alcohol to ward off a hangover can, at best, offer a temporary reprieve; at worst, it could exacerbate the situation. Some research also suggests that those who suffer worse hangovers than others are more likely to reach for the bottle the next day, thus facing a higher risk of developing alcoholism (18). However, the causal relationship between hangovers and alcoholism is probably more complex than that. To paraphrase the Norwegian playwright, Ludvig Holberg: 'Everybody says that Jeppe drinks, but nobody asks why Jeppe drinks'.

A pilot study found that isocapnic hyperpnea can accelerate ethanol elimination via the lungs, thereby achieving first-order kinetics alongside hepatic zero-order kinetics. Although this pilot study only had five participants, the mean half-life of elimination was dramatically reduced from 139 to 39 minutes without and with isocapnic hyperpnea (19). While there are no studies on the impact of this method on hangover symptoms, it is reasonable to assume that forced elimination and the resulting reduction in potential metabolites could have a positive effect. Respiratory alkalosis could limit usability for 'recreational purposes'.

Another pilot study shows that defecation can reduce intestinal alcohol absorption, thereby moderating hangover symptoms (20). In other words, alcohol should not be consumed on an empty stomach, but unnecessary blockages that could prolong alcohol absorption at the other end should also be avoided. NSAID medications and prostaglandin inhibition (21), or taking L-cysteine (22) (which binds to acetaldehyde), may have a role to play in symptom relief, but the evidence base is limited. Some data exist for clove extract, vitamin B_6 and yeast-based supplements, but overall, the quality of the evidence base is generally low (23, 24).

> ***«If an effective hangover cure existed, people might drink even more»***

Conclusion

Meta-analyses (23, 24) have concluded that the most effective method for reducing the incidence of hangovers is to *avoid* them altogether, i.e. drink less alcohol. A rational and prosaic piece of advice that highlights an important point: not all conditions can or should be treated. If an effective hangover cure existed, people might drink even more. Discomfort may therefore have a certain preventive effect, thus promoting good health. However, moderation is often easier said than done in many areas of life. It is now time to listen to

Foucault and broaden our perspective. People who deviate from the norm should be treated with empathy, not condemnation. From this perspective, prevention and treatment should be aimed at those who may develop, or already have, a pathological relationship with alcohol. For most people, however, hangovers are primarily a philosophical rather than a physiological issue, on a par with the question of how to exit a party when you have had enough: with a polite farewell, attracting everyone's attention to thank them for a pleasant evening, or with an 'Irish goodbye', quietly slipping into the night.

Trond Methi works at the pharmaceutical company Novo Nordisk, but the opinions expressed in this feature article are his own.

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