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## The elusive hangover cure

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Recently the news reported that the best remedy for a hangover is common soft drink. This was, however, only a hypothesis based on the *in vitro* finding of accelerated metabolism of ethanol and its toxic product, acetaldehyde.<sup>1</sup> With winter holidays approaching, pharmacists are likely to encounter patients seeking relief from alcohol overindulgence.

### ***Veisalgia - aka hangover***

A hangover can mean any of a constellation of unpleasant signs and symptoms that occur when the blood alcohol concentration (BAC) falls. It usually begins 6 to 8 hours after consumption of an intoxicating amount of alcohol, peaks when the BAC reaches zero, and lasts about 24 hours.<sup>2</sup> There is no consensus on what constitutes a hangover.<sup>2-5</sup> In the largest survey of hangover symptoms, fatigue was the most common symptom (reported by almost 96%), followed by thirst, drowsiness, sleepiness, headache, dry mouth, nausea, weakness, reduced alertness and concentration problems (symptoms reported by at least 75%).<sup>5</sup> They were usually the most severe symptoms too, in addition to vomiting, apathy, and reduced appetite.

The pathophysiology of hangovers is not fully understood. During hangovers there are a number of abnormalities - dehydration, pH and electrolyte imbalance, hypoglycemia, sleep disturbances; alteration in hormones including serotonin, histamine, prostaglandins and cytokines; and inflammation such as gastric irritation.<sup>2-5</sup> There is no clear correlation between these abnormalities and symptoms. - "no two hangovers are the same".<sup>6</sup> The relative role of ethanol, its metabolite acetaldehyde, congeners (other alcohols and organic compounds produced during fermentation or introduced during beverage production), co-exposures such as tobacco smoke, other substances, and dancing is also unclear. Psychosocial factors, personality traits, and individual biology may play a role. An estimated 25 - 30% of adults are resistant to developing hangovers.<sup>7</sup>

The economic burden of hangovers is significant. One estimate of the cost to the Canadian economy of alcohol-related short-term disability (days in bed or with reduced activity) is \$40 million per year.<sup>8</sup> The estimated cost of lost productivity in other countries is in the billions.<sup>9</sup> Studies have shown impaired cognitive and psychomotor performance in the hangover state. In one study the decrease in attention performance was similar between the acute intoxication and hangover states while reaction times were worse in the hangover state, raising safety concerns.<sup>10</sup>

### ***Treatments***

There is no experimental evidence of an effective treatment for hangovers, the only sure-fire prevention is abstinence. Home treatments, folk-cures, herbal and homeopathic hangover remedies abound, as do tales of their effectiveness. While rehydrating, refuelling, and resting are good things, very few specific hangover treatments have been scientifically studied (Table 1). The few published are small and methodologically flawed (a consensus document on best practices in hangover research has recently been published<sup>11</sup>).

**Table 1. Purported mechanisms and effects of some hangover treatments**

Soft drinks (Sprite); fructose or glucose beverages (Outox®, RU21, others)	Raises activity of alcohol dehydrogenase and aldehyde dehydrogenase, increasing clearance of ethanol and acetaldehyde. Fructose enhances regeneration of NAD <sup>+</sup> , a cofactor in the metabolism of ethanol. Clinical studies; effect on hangover symptoms unknown. <sup>1,12</sup>
Borage oil	Basis of treatment unclear - likely related to mediation of prostaglandin synthesis. No effect on overall hangover symptom score. (RCT n=18) <sup>9</sup>
Artichoke extract	Antioxidant and choleric activity. No effect on physiological changes, cognitive function test scores or symptom ratings; subjects could not reliably identify treatment vs. placebo. (xo RCT n=15) <sup>13</sup>
Prickly pear ( <i>Opuntia ficus indica</i> ) (NOHO, PreToxx, others)	Antioxidant; increases protective stress proteins. Extract reduced nausea, anorexia, and dry mouth but had no effect on other symptoms. Reduced risk of a severe hangover and markers of inflammation. (xo RCT n=55) <sup>14</sup>
After Effect® (borage oil, prickly pear, milk thistle extract, fish oil, vitamins and magnesium)	Combined antioxidant, prostaglandin, immune system and miscellaneous effects. Symptom score: appeared to show benefit, but there was no placebo control (only subjects' expected severity score was used). (n=103) <sup>15</sup>
Party Smart® (Himalayan Drug Company)	Mechanism unknown. Contains date palm, chicory, Indian gooseberry, grape, and other Ayurvedic herbs. Four small trials (n=10 to 19) conducted by the manufacturer showed better mood and reduced hangover symptoms compared to competing products (various vitamins, minerals, extracts etc.). Ethanol and acetaldehyde clearance also increased. Another Himalayan Drug Co product, Liv.52, is also reported to do the same. <sup>16-20</sup>
Tangerine pith/ginger/ sugar	Unclear; traditional Chinese remedy, regulates "qi". Reduced gastrointestinal symptoms when taken before alcohol consumption but no effect if used after (xo RCT n=10). <sup>21</sup>
Kudzu ( <i>Pueraria lobata</i> ; Drinkwel, Last Round, others)	Kudzu <i>flower</i> increases elimination of acetaldehyde. However, some remedies contain kudzu <i>root</i> which reduces acetaldehyde clearance similar to disulfiram. No clinical studies on hangover symptoms. <sup>22</sup>
B vitamins and derivatives (pyridoxine, metadoxine, pyritinol) (Hangover Guardian, Modjo Synergy, others)	Pyridoxine and metadoxine are purported to increase alcohol metabolism, protect the liver and balance the immune system. Equivocal effects on alcohol clearance but largest studies show pyridoxine does not affect ethanol clearance or level of consciousness during intoxication; hangover symptoms not assessed. Pyritinol is a pyridoxine derivative touted as nootropic; may reduce prostaglandins, promote glucose uptake into the brain. One small study reported reduced hangover symptoms. <sup>23</sup>
Cysteine and other "biologically active" sulphur compounds (Xo3, others)	Cysteine, N-acetylcysteine, and glutathione are supposed to replenish hepatic glutathione stores, but relation to hangover symptoms is unclear. One patent application for methylsulfonylmethane (MSM) as a hangover cure purports that MSM softens cell walls, allowing alcohol to be flushed out faster by increasing cell oxygenation. No clinical trials on relieving hangover symptoms. <sup>24</sup>
Caffeine	Caffeine has alerting and analgesic effects. Subjects given caffeinated beer reported better perceived sleep quality, but there were no significant differences in morning sleepiness, hangover incidence or overall hangover severity. (RCT n=54) <sup>25</sup>
Propranolol	Increased adrenergic tone may cause hangover symptoms. 160 mg long-acting propranolol taken before drinking reduced HR but no effect on BP; no benefit for tremor, headache, overall severity or sleep quality. (RCT n=10). <sup>26</sup>
NSAIDs	Inhibition of prostaglandin synthesis. 200 mg tolfenamic acid taken before drinking and before bed reduced headache, dry mouth, thirst, tremor, nausea and vomiting. (xo RCT n=30) <sup>27</sup>
Tropisetron (plus diazepam)	Tropisetron aimed at GI symptoms; diazepam for withdrawal. Tropisetron did not have any effect on hangover symptoms or headache. (RCT, n=11) <sup>28</sup>

xo = crossover RCT = randomized controlled trial

## Safety concerns

While most remedies are likely harmless, some treatments are potentially hazardous. "Hair of the dog" (more alcohol) only delays the onset of hangover symptoms, may enhance the existing toxicity of alcohol already consumed, and increases the likelihood of continued drinking. Analgesics may provide relief from headache, but care must be taken not to overuse. Some hangover remedies available for purchase on the internet contain analgesics - patients should check labels. NSAIDs may worsen gastric irritation, and the rare patient may be at increased risk of liver toxicity from acetaminophen due to depleted glutathione stores and induction of hepatic metabolism. Caffeine may create a false sense of safety, but data shows that judgement and psychomotor performance remain impaired during acute intoxication, and there is no evidence of improved performance during hangovers.



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We are grateful to all the First Nations who have cared for and nurtured the lands and waters around us for all time, including the x?m??k??y??m (Musqueam), Sk?wx?wu?7mesh U?xwumixw (Squamish Nation), and s?l?ilw?ta? (Tsleil-Waututh Nation) on whose unceded and ancestral territory our centre is located.

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