

# Are sweetened drinks a gateway to alcohol addiction? review of shared morbidity, neurocircuitry and therapy

## Abstract

Alcohol addiction is a chronic, relapsing disorder with genetic, biochemical and psychosocial antecedents. Persistent alcohol use results in changes in the mesolimbic pathway of the brain including reduced extracellular dopamine levels and down regulation of dopamine 2 receptors. The same biochemical changes are seen with persistent high dose sugar use. Cross-sensitization between sugar and alcohol is seen in rat models. This raises the possibility that sugar drinks could act as a gateway to alcohol addiction. Furthermore, both sugar and alcohol exerts toxic effects via steatohepatitis (fatty liver), resulting in insulin resistance, hypertension, dyslipidaemia, obesity and increased risk of cancers. This article reviews the links between sugar and alcohol abuse, suggests potential therapeutic approaches, and suggests potential therapeutic approaches and comments on appropriate taxation and warnings on containers.

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## Introduction

Widespread use of sugar commenced in the mid-19<sup>th</sup> century in Europe, when production moved from an annual harvesting of sugar cane in the Caribbean (transported by ship), to year round extraction from sugar beet grown locally<sup>1</sup> this change of production partly forced due to England and France blockading each other's ports during the Napoleonic wars. Since then, sugar has been used in a whole range of foods and drinks (alcoholic and non alcoholic) to increase palatability. Currently, the average Briton consumes 248 teaspoons of sugar a week; the average American 3 pounds a week.<sup>2</sup> This has resulted in the re-introduction of taxation on sugary soft drinks due to increasing awareness of linked health issues including a condition called non-alcoholic steatohepatitis or NASH,<sup>3</sup> described as the world's commonest silent killer, due to its potential to cause unexpected myocardial infarcts and strokes.

NASH is also associated with a range of conditions collectively known as the 'metabolic syndrome', including obesity, dyslipidaemia, hypertension and insulin resistance which is the precursor to 'sugar diabetes' (Type II Diabetes). There is increasing concern about the metabolic syndrome presenting in young children, who also happen to be heavy consumers of sugary drinks.<sup>4</sup> Furthermore, recent epidemiological research has linked NASH with bowel and breast cancer<sup>5</sup> a concern for younger adults. In older adults the major concern is the potential conversion of mild memory problems to dementia; the main known risk factor being insulin resistance, most likely linked to NASH.<sup>6</sup>

Alcohol has been recognised over the last 100 years of being a potentially addictive substance. The first documented alcohol dependency epidemic was in the 1760's called the 'Gin craze' leading to legislation to control production and use<sup>7</sup> as people became less productive and paid less tax. Thereafter, social and medical concerns led to the formation of self-help groups like Alcoholics Anonymous (AA), based on the idea that alcohol dependency was a 'disease' on which the affected individual was powerless to control or stop, needing back up from similarly affected peers (a 'buddy' system) along with belief in a 'higher power' to provide redemption. Evidence

for effectiveness of AA in terms of relapse is mixed, with persistent attenders at AA meetings appearing more likely to remain abstinent.<sup>8</sup> Abstinent AA attenders are noted to use coffee and cigarettes significantly in excess of the general population, in order to avoid subjective anxiety and depression,<sup>9</sup> but is unclear if coffee was sweetened as well. Certainly, AA does not discourage excess sugar or coffee use among its attendees.

## Why is the sugar-alcohol link important?

The main consequence of alcohol abuse involves the liver, its main clearing house. Unlike Glucose (50% of sugar molecules), which the liver can readily convert to Glycogen, alcohol and the other half of sugar Fructose is converted with difficulty via acetaldehyde to lipids stored in the liver, or transferred to body fat stores. The superficial fat stores are limited in capacity, and use the hormone Leptin to warn the brain that its capacity is full. Thereafter, most of the alcohol related lipids get stored in visceral fat, surrounding the abdominal structures or within adipocytes within the liver, leading to steato hepatitis (commonly known as alcohol related fatty liver.<sup>9</sup> Similar to NASH, there is an association between alcoholic fatty liver and the metabolic syndrome. However, alcohol is more likely to cause fibrotic infiltration of the liver; alcoholic cirrhosis; an end of life condition with untoward effects ranging between upper gastrointestinal bleeding secondary to 'portal hypertension', through to cognitive deterioration due to 'alcoholic dementia' caused by nitrogenous toxins which the liver has failed to clear due to 'hepatic encephalopathy'.<sup>10</sup>

## Defining addiction and its stages?

The 2 models accepted by addiction specialists are presented below.

### Box 1

- I. Stages of addiction – World Health Organisation Definitions<sup>11</sup>
- II. Binging–escalation of intake frequency, with a high proportion of intake at one time, usually after a period of voluntary abstinence or forced deprivation. Associated with,

- a. Sensitisation-increased responsiveness to a repeated stimulus, leading to
  - b. Tolerance-decreased responsiveness, more substance needed to produce same effect.
- III. Withdrawal—a somatic symptom complex; associated with anxiety, when the abused substance is unavailable or chemically blocked (for example with Naloxone in opiates). The somatic symptom complexes appear to differ; for example between alcohol and opiate withdrawal; however anxiety is a common feature.
- IV. Craving—a cognitive feature; increased efforts and planning to obtain a substance of abuse as a result of addiction and subsequent abstinence. Evidence of enhanced motivation to search for substance (including planning day according to use)
- V. Cross sensitisation-observed in animals sensitised to amphetamine for example, showing bingeing behaviour towards cocaine. In humans sensitised to alcohol use of excess benzodiazepines.

## Box 2

The alternative behavioural staging described by Kalivas and Volkov<sup>12</sup>

- a. Acute drug effects (thrill, pleasure, and excitement)
- b. Transition from recreational use to repetitive use,
- c. End-stage addiction characterized by an overwhelming desire to use the drug,
- d. Diminished ability to control drug-seeking, reduced pleasure from other daily rewards.

## Is sugar also an addictive substance?

Gordon and colleagues<sup>13</sup> have recently completed a meta-analysis on publications proposing sugar as an addictive substance. They found most evidence emanating from neuroscience, with a few from epidemiology. Nevertheless, the notion that sugar can be addictive similar to the conventional drugs of abuse (such as alcohol, amphetamines and opiates) has not been uniformly accepted, especially among clinicians in the field of addictions. This is partly related to a debate on semantics as to whether sugar is a food or a substance.

However, there is also the issue as to the causative agent for addiction; whether it is sugar specifically, or people getting addicted to the sensation of intense sweetness. These substances appears to be equally addictive as cocaine,<sup>14</sup> and include sucralose, aspartame, HFCS, all associated with obesity, and stevia leaves, currently showing no morbid effects, although a recent entry to the sweetener market. Furthermore, recently a gene termed CREM has been found, which is associated with impulsiveness and multiple substance abuse.<sup>15</sup> This would be consistent with multiple cross sensitivities found in the addiction field. Neuroanatomical research has led to the concept of the Brain Reward Circuit,<sup>16</sup> centred on the shell of the Nucleus Accumbence (NAc); sited dorsal to the Thalamus, with the main input via Dopaminergic neurones from the Ventral Tegmental Area (VTA); a circuit known as the Mesolimbic Pathway (MLP) described by Blum and colleagues.<sup>17</sup> The NAc shell has both Dopamine 1 and 2 receptors. The VTA receives inhibitory input from the Lateral Hypothalamus (which controls both feeding for hunger and for recreational purposes

via 2 different circuits) via Serotonin (5HT) neurones. The NAc also has connections to the dorsomedial prefrontal cortex<sup>18</sup> well known for compulsive checking and searching in obsessional compulsive disorders.

On specific receptor subtypes, Dopamine receptors, the NAc based D2 receptors appear to have a damping effect on drug consumption, with D1 receptors related to increased use. Consistent with this, drugs of abuse appears to down regulate D2 and up regulate D1.<sup>19</sup> Furthermore, genetic polymorphism of the D2 receptors is associated with hypo-dopaminergic functioning in the NAc.<sup>20</sup>

From a neurochemical perspective, the lateral Hypothalamus (LH) commences the process with release of 5HT (serotonin) in the hypothalamus, leading to endogenous opiate release (via mu receptors) in the VTA leading to inhibition of Dopamine supply to the NAc.<sup>21</sup> However, in situations of drug and sugar abuse, additional GABA input to the VTA disinhibits the release of dopamine to the MLP, increasing concentration of dopamine at the NAc shell. Furthermore, there is evidence in rats of escalating consumption of readily available sugar to achieve a phasic dopamine release in the NAc shell<sup>22</sup> the process leading to sensitisation and consequent tolerance. On cross sensitisation, Rada and colleagues<sup>23</sup> have demonstrated in rats given daily access to sugar show dopamine sensitisation and opioid dependence including alterations of Dopamine and mu-opioid receptors, cross sensitisation with amphetamine and alcohol, as well as behavioural/neurochemical signs of naloxone precipitated withdrawal. Compared to control rats not given daily sugar solution, the experimental rats increased their daily consumption by three times, with extracellular Dopamine rising by 130%. There was also evidence of a delayed satiation response generated by acetylcholine, compared to rapid satiation in control rats.

Human studies on sugar addiction have been limited, possibly because of limited commercial interest. The medical community in North America have come around to describing sugar as 'toxic', encouraged by activist academics in California such as Dr Robin Lustig.<sup>24</sup> In addition, governments are constantly seeking targets for augmenting their income, and have set up sugar taxation on soft drinks, under pressure from academics, the general public and, manufacturers of alcohol based drinks (who have up to now borne the brunt of drink taxation). Food and drink manufacturers have already pre-emptively moved towards 'low sugar' alternatives to go below the threshold set up by governments in order to avoid the sugar tax via artificial sweeteners (like Sucralose and Aspartame). The cheaper alternative has been to use 'high fructose corn syrup' (HFCS) which provides a similar (possibly more intense) sweet sensation, as well as acting as a food preservative to increase shelf life of processed food. HFCS is not currently taxed, despite being equally damaging to the liver as sugar.<sup>25</sup>

## Therapeutic approaches (opinion)

In terms of harm reduction, it is hoped that the sugary drinks tax would reduce consumption. However, HFCS is not taxed, despite similar morbidity rates compared to sugar and alcohol. This needs urgent review by governments, despite the predictable negative reaction by food and drink manufacturers. Public awareness of steatohepatitis produced by alcohol, sugar and HFCS remains low. This might be tackled via vivid pictorial representations on sugary drinks (and so called alcopops) to try and get younger consumers to think again. Unfortunately, 'diet' soda drinks with artificial sweeteners has also shown to increase weight; most likely as the brain misinterprets

the sweetener as a precursor to a big meal and produces large amounts of insulin leading to insulin resistance.<sup>26</sup> It would be beneficial to publicise this finding on diet drinks. The public health tutorials in schools should include the dangers of Fatty Liver (especially Non Alcoholic steato Hepatitis or NASH), so that children are aware of the longer term harm of processed foods and sugary drinks.

Considering the imbalance between Dopamine 1 and Dopamine 2 receptors in the mesolimbic pathway (MLP), it is possible that specific D1 antagonists would have a beneficial impact on reducing craving for both sugar and alcohol. However, D1 antagonists have dyskinetic and dystonic effects, with younger people especially at risk. D2 receptor agonists (like Bromocriptine) has been used as an adjunct in Diabetes control, but there are side effects such as hypertension and migraine. Aripiprazole is a partial D2 agonist, therefore potentially of value, perhaps in lower dosage to maximise its agonist properties. The main non-drug approach used has been surgical reduction gastric volume. A consequence of ingesting sugar following surgery can be the 'dumping syndrome' where sugar is moved rapidly to the small intestine, resulting in dizziness, nausea, bloating and diarrhoea. Consequently the post-operative advice is to avoid sugar entirely. It is unlikely that this procedure would be acceptable for a large population of people with alcohol and sugar intake issues, unless complicated by life threatening obesity.

The latest non-drug approach has been non-invasive Transcranial Direct Current Stimulation involving direct current applied to the pre frontal areas of the brain (right prefrontal anode and left prefrontal cathode). Although the numbers are small, there has been promising results in terms of reduced impulsivity towards a range of addictive behaviours (including food) during and shortly after applying current.<sup>27</sup> However, the dose, frequency of application and the duration of treatment remains unclear. Finally, from a metabolic medicine perspective, it appears that unsaturated fatty acids (supplied nasogastrically) provide satiety of food intake.<sup>28</sup> This is consistent with the idea that humans can live healthily without much carbohydrates (including sugar) by catabolising fat derived ketones for energy (including use by the brain). The associated diet is called the 'Ketogenic diet' which involves a high fat, moderate protein and low carbohydrate content so that plasma levels of ketone bodies (acetoacetate and  $\beta$ -hydroxybutyrate) rise and serve as an alternative oxidative fuel.<sup>29</sup>

Furthermore, this diet mainly using saturated fats (meat, butter) and unsaturated fats (sardines, olive oil), and appears to reduce weight alongside improvements in insulin and leptin resistance.<sup>30</sup> On side effects, the main problem is constipation, managed by using low calorie fibre preparations, magnesium supplementation and olive oil. Magnesium supplementation has the additional attraction of improving cardiovascular protection,<sup>31</sup> and can help alcohol related Magnesium depletion. On concurrent alcohol usage, a Ketone diet can lead to quicker detoxification via the liver, resulting in stronger 'hangovers',<sup>32</sup> perhaps best seen as an inducement to reduce regular and heavy use. Sweeteners consistent with a ketone diet include Stevia, and approved alcohols being low calorie gins and other spirits, rather than wines and beers.

### Box 3

#### Action points

- a. Public awareness of sugary and non-sugar sweetened drinks, alcopops (pictures, phrases). Also TV advertisements similar to HIV/AIDS

- b. Legislation on taxation of sweetened drinks (including HFCS); money ring fenced for the NHS.
- c. Cross over (6 months each) double blind randomised controlled trial of CBD 1 antagonists vs Dopamine 1 partial agonists in heavy sugar users; looking at weight change, consumption of alcohol/sugar (self-report) and insulin resistance, liver function changes, with addressing confounders (locus of control, smoking)
- d. Screening for the CREM gene (addiction/impulsivity) beneficial in heavy sugar/alcohol users to help achieve abstinence? This could also be an observational study.
- e. Personalise to politicians on the dangers of them getting a heart attack/stroke, bowel/breast cancer based on their sugar/alcohol consumption, lack of exercise.
- f. Encourage High intensity Interval Training at work in group sessions

### Box 4

#### Key points

- a. Excessive daily use of sugar and alcohol liquids appears to increase the likelihood of addictive behaviour and cross sensitisation; confirmed by neuroscience research.
- b. Both alcohol and sugary drinks have been implicated in Fatty Liver, the associated metabolic syndrome and sudden death due to cardiac infarcts and strokes.
- c. Therapeutic agents include dopamine 1 receptor agonists, CBD 1 antagonists and Trans Cranial Magnetic Stimulation. The alternative solution is to move to a Ketogenic diet, which has the benefit of weight loss, and reduced alcohol usage because of stronger hangovers.
- d. However, it is possible that the basic addictive potential is due to highly sweet substances in general, and a genetic predisposition to impulsivity and addiction to dopamine, consistent with multiple cross sensitisations observed in rats and humans.
- e. Taxation extended to non-sugar sweeteners (including High fructose Corn surup) needs to be urgently legislated in Britain, as it is in North America, due to clear evidence of obesity, fatty liver and insulin resistance (pre diabetes).

### Conclusions

Increased use of sugar and its alternatives (like High Fructose Corn Syrup or HFCS) is the largest contributor to the so called silent killer Non-Alcoholic Steato Hepatitis (NASH) via unexpected cardiovascular thrombotic events, diabetes, hypertension, dyslipidaemia, and possibly, colon and breast cancers. Alcohol also produces Fatty Liver, with similar consequences. Therefore combining sugar in alcoholic drinks provides a 'double whammy' in terms of morbidity and premature sudden death.

Sugar consumption (especially as a binge), similar to alcohol, cocaine and amphetamine increases dopamine release at the Nucleus Accumbens (NAc) in rat modals. This release is considered to be the basis of the short lasting (but intense) reward experienced by animals and humans, resulting in repeated / escalating behaviour to search for and imbibe the substance. There is evidence from Rat modals of



cross sensitisation between sugar and alcohol. Therefore, it could be considered that sugar is a gateway to alcohol abuse, for example the so called ‘alcolpops’ used by young adult in social settings.

Apart from the usual harm reduction measures (such as taxation and pictorial reminders on containers), there are therapeutic approaches involving dopamine agonists and transcranial brain stimulation, although larger trials are needed in people who overuse both sugar and alcohol. The alternative solution may be moving to a Ketogenic diet. Nevertheless, the concept of sugar addiction remains in some doubt, due to findings of addiction to non-sugar sweeteners (including Sucralose and Aspartame), as well as recent identification of a gene (CRME) which links multi substance abuse and impulsivity.

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## Conflicts of interest

Author declares that there are no conflicts of interest.

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