Independent Research & further reading

Guest: Sarah Wakeman

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Global Drug-Related Mortality: The Crisis in the United States and Scotland

> *"So when we look at kind of drug related deaths across the country, the US leads the globe. So we have more people die from overdose deaths than anywhere else in the world. Number two is actually Scotland."*

The United States has the highest rate of overdose deaths in the world, with more than 100,000 lives lost annually in recent years and a rate of over 300 deaths per million people. Drug-related mortality has increased sharply since 2019, driven largely by synthetic opioids like fentanyl and exacerbated by widespread polysubstance use. Scotland follows closely behind, with the highest drug-related death rate in Europe and one of the highest globally among sovereign nations. Despite a slight decline in recent figures, Scotland continues to face a severe opioid crisis, marked by high levels of opioid use disorder, hospital admissions, and fatalities. Together, the United States and Scotland represent two of the most acute examples of drug mortality in the developed world.

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Moderate Alcohol Use: Reported Benefits

"Not that long ago, and even still, I think people thought like, oh, if I drink wine, red wine with dinner every night, that's actually good for me. That's like a health-promoting behavior. And yet we have this whole new body of research that shows really that's not how we should be thinking about alcohol (...) in most of the studies, what people do is they take like a massive population, tens of thousands of people where we have some data where they're reporting how much alcohol they used, and then we look at health risks over time. And scientists would [group] people into non-drinkers versus light drinkers, moderate drinkers or heavy drinkers. And what they were finding is that people who were drinking even up to the moderate level were actually doing better than the people who weren't drinking at all. And so that was where that concept that drinking is good for your health came from. And so people talk about this J-shaped curve, meaning that moderate drinkers actually have lower risks of health problems and it's really only when you start drinking very high levels that you start having more risk of health problems than people who don't drink at all. What they realized was wrong with that is that the people who don't drink at all, many of those people are not drinking 'cause they're actually really unhealthy for another reason. (...) So they've already had some damage from alcohol and they're not drinking because of that. And so when you change the reference group to people who very rarely drink (...) Then you start to see that those health benefits of alcohol go away, especially if you look across all conditions."

Moderate alcohol consumption, such as a daily glass of red wine, has been associated with certain health benefits in some research, particularly relating to cardiovascular health and longevity. Studies have noted a potential reduction in the risk of heart disease, type 2 diabetes, and

neurodegenerative conditions among moderate drinkers, with these effects often cited within the context of the Mediterranean diet. This evidence has contributed to the idea of a J-shaped relationship, where moderate drinkers appear to have better health outcomes than both abstainers and heavy drinkers. However, these potential benefits are not universal. Even moderate alcohol use has been linked to an increased risk of certain cancers and may pose additional health risks for individuals with specific medical conditions, a history of addiction, or during pregnancy. The health impact of moderate drinking varies depending on personal risk factors, and it is not universally recommended.

Limitations of Research on Moderate Drinking and Health Outcomes

Many of the reported health benefits of moderate drinking arise from observational studies, which are prone to significant methodological limitations. A key concern is confounding—where factors like income, education, diet, and overall lifestyle influence both drinking habits and health outcomes, making it difficult to isolate the specific effect of alcohol. Another issue is reverse causation, where individuals with poor health may abstain from drinking, skewing comparisons and giving the illusion that moderate drinkers are healthier by contrast. Inconsistent definitions of alcohol use and measurement inaccuracies further complicate interpretations, as does the lack of standardization in how drinking behavior is assessed across studies. While some findings suggest a J-shaped curve, other studies show different patterns or no clear association at all. Importantly, advanced methods designed to infer causality, such as Mendelian randomization, often reveal weaker or null associations. Taken together, these limitations cast doubt on the extent to which moderate alcohol consumption can be deemed directly beneficial to health.

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Alcohol and Cancer Risk: Lower Thresholds and Greater Sensitivity Than Cardiovascular Disease

> *"one is that your risk of cancer starts to increase at a much lower level of alcohol than your risk of heart problems, for example (...) so even drinking at levels that most people would probably consider totally normal, you start to see an increase in your risk of cancer (...) the association at low levels of alcohol and cancer risk is strongest for breast cancer (...)* ***So if I have this glass of wine every day, then I'd be over the UK limit of lower risk drinking*** *(...) You'd be in what we call moderate risk, which is associated with pretty much every form of cancer (...) if you were to drink fewer than seven drinks (...) or in the UK is below that 14 units (...) we still see a slight increase in the risk of breast cancer. It's about a 5% increase."*

Cancer risk begins to increase at much lower levels of alcohol consumption than cardiovascular risk. Even small amounts of alcohol have been linked to an elevated risk of various cancers, including breast, liver, and colorectal cancer, with no clearly safe threshold identified. The association between low levels of alcohol consumption and increased cancer risk is especially strong and well-established for breast cancer. Research consistently shows that even light to moderate alcohol intake is linked to a

measurable increase in breast cancer risk. In contrast, cardiovascular risk tends to follow a J-shaped pattern, with some studies suggesting that very light to moderate drinking may offer limited protective effects, though this has been increasingly questioned by newer research. As alcohol intake rises, both cancer and heart-related risks increase, but the onset of elevated cancer risk occurs earlier, often with consumption as low as one or two drinks per week.

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High Alcohol Consumption and Cancer Risk

> *"these big cancer studies categorize people as sort of low risk or light drinkers, moderate or heavy, and for pretty much every cancer, once you get to the moderate category, we start seeing increases and there's what we call a dose response relationship (...) in the heavy drinking category (...) roughly we're talking like a 40% increase in cancer [risk] depending on the cancer type. And the more you drink, the more that's gonna go up."*

Dose-Response Relationship: The risk of cancer increases steadily with higher alcohol intake, and some studies show a significant rise in cancer risk at consumption levels above 25 grams per week (about 2 standard drinks).

Heavy alcohol consumption is linked to a significant increase in cancer risk, though the extent varies by cancer type. In many cases, the rise in risk is well above 40%. Cancers of the head and neck,

such as oral, pharyngeal, and esophageal cancers, show the steepest increases, with risk elevated by as much as 400% to 500% in heavy drinkers compared to non-drinkers. For other common cancers like breast and colorectal, the increase is around 50%, while stomach and pancreatic cancers show more modest but still notable increases of 26% to 30%. Overall, cancer mortality is substantially higher among heavy drinkers, and risk is further magnified when alcohol use is combined with smoking. These figures underscore the breadth of harm associated with sustained heavy drinking across multiple cancer types.

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How Alcohol Increases Cancer Risk

> *"most cancers, because the way alcohol impacts your risk of cancer is not really on a specific organ outside of the liver. It's really about how it changes our DNA. So it's about inflammation and what are called reactive oxygen, um, species that sort of change our cells and increase the risk over time of the mutations that lead to cancer (...) ethanol gets broken down into what's called acetyl aldehyde. That molecule is really important because it's the thing that causes a lot of the toxics effects, including cancer (...) your body wants to get rid of that toxic compound as quickly as it can, and then it converts it into something called acetate and then you can pee that out and breathe that out and get rid of it. So to eliminate the alcohol in your body, you have to go through this process and part of that process includes this toxic molecule that's gonna be floating around and causing damage to your cells."*

Alcohol increases cancer risk through multiple biological pathways, the most prominent of which involve the generation of acetaldehyde and the promotion of chronic inflammation. As alcohol is

metabolized in the body, it is first converted into acetaldehyde, a toxic and carcinogenic compound that can bind to DNA, disrupt repair processes, and lead to mutations. This metabolic byproduct floats through the body before being further broken down into less harmful substances, but during its presence it causes significant cellular damage. In addition to this direct chemical pathway, alcohol metabolism also produces reactive oxygen species and triggers inflammation—two processes known to promote DNA instability and support the conditions for cancer development. Together, these mechanisms alter cellular function over time and increase the risk of malignancy in multiple organs, even beyond those directly exposed to alcohol.

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Synergistic Effects of Alcohol and Comorbidities on Cancer Risk

> *"**And then if I have other comorbidities?** (...) Alcohol actually makes you more susceptible to the cancer causing effects of tobacco. So if you drink and smoke, your risk of cancer is gonna be even higher (...) and then obesity is the other big one. So your risk goes up if you (...) have an increase in your body mass (...) if you have very low body fat, you probably have more body water. And so, you know, two drinks for you is gonna diffuse into a larger amount of water."*

Synergistic Effects of Alcohol and Tobacco on Cancer Risk

Alcohol significantly enhances the carcinogenic impact of tobacco, particularly for cancers of the head, neck, and esophagus. When used together, these substances act synergistically, producing a combined cancer risk far greater than the sum of their individual effects. This elevated risk is attributed to biological interactions such as increased permeability of mucosal tissues caused by alcohol, which allows tobacco carcinogens to penetrate more deeply, along with compounded DNA damage and inflammation. Individuals who drink and smoke heavily may face a many-fold higher risk of developing

oral and esophageal cancers compared to those who do neither, underscoring the disproportionately harmful impact of co-use.

Obesity as an Amplifier of Alcohol-Related Cancer Risk

Obesity can intensify the cancer risk associated with alcohol consumption, particularly in the case of liver cancer. The combination of high body fat and regular alcohol use exerts a multiplying effect on the likelihood of developing hepatocellular carcinoma, beyond what would be expected from either risk factor alone. While the strongest synergy is observed for liver cancer, elevated risks may also occur for other cancers, such as colorectal cancer, though the evidence is more variable. On a population level, individuals who are both obese and drink above recommended guidelines consistently show higher rates of alcohol- and obesity-related cancers.

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The Impact of Language on Stigma and Addiction Treatment

> *"there's a lot of data showing that the public has more stigma if they hear someone described as an addict or an alcoholic, and that even highly trained clinicians have more stigma and recommend more punishing treatment if someone's described as a substance abuser or an addict (...) there have been these elegant studies that took like PhD level psychologists really highly trained clinicians, and they described a person as either a substance abuser or as a person with a substance use disorder. And the clinician was actually more likely to recommend a punitive intervention for the person described as a substance abuser."*

Language plays a significant role in shaping public and professional attitudes toward people with addictions. Terms like "addict" or "substance abuser" reinforce harmful stereotypes by framing substance use as a moral failing rather than a medical condition, which increases stigma and social distance. Research shows that both the public and clinicians are more likely to assign blame, support punitive responses, and view individuals as less deserving of care when such labels are used. This stigma can deter people from seeking treatment and lead to poorer health outcomes. In contrast, person-first language—such as "person with a substance use disorder"—helps reduce stigma, fosters empathy, and supports a more compassionate, evidence-based approach to treatment and recovery.

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The Neurobiology of Addiction: Dopamine, GABA, Endogenous Opioids

> *"how addictive a substance is is really related to sort of how much dopamine is released in the brain (...) any substance that can cause addiction is gonna release dopamine. That's sort of a primary driver of many things that we find rewarding, whether it's sex or food or alcohol or drugs (...) alcohol also binds to a system called GABA, which is sort of our anti-anxiety system. So it's the same system that anxiety medications, like Ativan or Lorazepam or Xanax (...) alcohol acts on that part of the brain and it actually then causes a release of your endogenous opioids in your brain."*

Dopamine and the Neurobiology of Addiction

Dopamine plays a central role in the development and persistence of substance addiction. Most addictive drugs sharply increase dopamine levels in brain regions associated with reward, particularly the

striatum and nucleus accumbens. These surges create powerful reinforcement, motivating repeated use by producing a sense of intense pleasure and reward far beyond that of natural stimuli. Over time, dopamine also drives craving and compulsive drug-seeking by strengthening associations between environmental cues and drug effects. As addiction progresses, the brain becomes less responsive to natural rewards and more reliant on substances for pleasure and motivation. Chronic use eventually leads to a decline in dopamine function and activity in brain areas linked to self-control, contributing to compulsive behavior and vulnerability to relapse.

Alcohol, GABA, and the Release of Endogenous Opioids

Alcohol interacts with multiple brain systems, including GABA and the endogenous opioid system, to produce its rewarding and reinforcing effects. GABA (gamma-aminobutyric acid) is the brain's primary inhibitory neurotransmitter, responsible for calming neural activity and regulating anxiety. Alcohol enhances GABAergic activity, which contributes to its sedative and anti-anxiety effects. In certain brain regions, like the ventral tegmental area, this activity can inhibit inhibitory neurons, indirectly stimulating dopamine release. At the same time, alcohol triggers the release of endogenous opioids—naturally occurring chemicals like β-endorphins that produce feelings of pleasure and reinforcement. This process is tightly linked to alcohol's actions on GABAergic circuits. The interaction between alcohol, GABA, and endogenous opioids is a key component of its addictive potential and helps explain why opioid-blocking medications such as naltrexone are effective in reducing alcohol consumption.

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Global Burden of Alcohol and Drug Use

> *"2.6 million people every year die from alcohol related causes (...) Another 600,000 people die from drug related deaths annually (...) And then when we look at the criteria for meeting a substance use disorder or addiction, it's about 400 million people worldwide for alcohol and 80 million people for drug use."*

In 2019, approximately 2.6 million deaths globally were attributable to alcohol consumption, while an additional 600,000 deaths were linked to psychoactive drug use. Alcohol-related deaths accounted for 4.7% of all global deaths that year, with a disproportionate burden among men. The impact of substance use extends beyond mortality: an estimated 400 million people globally were living with alcohol use disorders, including 209 million with alcohol dependence. In comparison, approximately 39.5 million people were living with drug use disorders globally in 2021, with opioids accounting for the majority of drug-related deaths. These figures reflect a substantial global health burden from both alcohol and drug use, compounded by significant treatment gaps and widespread stigma that hinder access to care.

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Lifetime Prevalence of Alcohol Addiction

> *"If you think about alcohol, some studies estimate that the lifetime prevalence, meaning over the course of your life, how likely are you to at some point develop alcohol addiction, somewhere between 15 and 30% in some studies. So one in three people may have a problem with alcohol at some point in their life."*

Lifetime prevalence estimates for alcohol use disorder vary significantly by region, but large-scale studies indicate that between 8% and 30% of adults globally may meet criteria for AUD at some point in their lives. In the United States, the figure reaches nearly 30%, suggesting that roughly one in three adults may struggle with alcohol use over the course of their life. Lower prevalence rates have been reported in regions such as East Asia and parts of Europe, where cultural patterns around drinking differ. Men are consistently found to be at higher risk than women, and most cases of AUD emerge in young adulthood.

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The Impact of the COVID-19 Pandemic on Alcohol and Drug-Related Mortality

> *"the pandemic was not kind to addiction, so we saw rates of alcohol and drug use and deaths related to those increased significantly after the onset of the Covid pandemic (...) immediately following the onset of the pandemic (...) we saw a 23% increase in alcohol related mortality, and we saw the highest rates ever we've seen of drug related overdose deaths."*

Following the onset of the COVID-19 pandemic, rates of alcohol- and drug-related mortality rose significantly, with the most pronounced increases observed in the United States. Alcohol-related deaths

surged across multiple causes, including liver disease and pancreatitis, with overall mortality rising by 17.6% between 2020 and 2021. Among young adults aged 25–44, the increase was even steeper, reaching 34.6% annually. In some European regions, such as the Baltic states, alcohol-attributable mortality rose by as much as 46%. Drug overdose deaths also reached record highs during the pandemic, driven largely by synthetic opioids like fentanyl, but also involving alcohol, heroin, cocaine, and stimulants. These increases were especially acute among men and marginalized populations, and were compounded by service disruptions and reduced access to addiction treatment during the pandemic.

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Genetic and Childhood Risk Factors for Addiction

> *"There are two different things that drive someone's risk of addiction. One is genetics. It's about 40 to 60% genetics similar to diabetes in terms of someone's risk (...) the other half of the equation is based on your exposures and your experiences. And one of the number one drivers is what we call adverse childhood experiences."*

Addiction risk is shaped by a complex interplay of genetic and environmental factors. Genetic heritability accounts for approximately 30% to 70% of an individual's vulnerability to addiction, with variation depending on the specific substance and population studied. This genetic influence is

polygenic, involving numerous genes that interact with life experiences such as stress, trauma, and social environment. One of the most well-established environmental risk factors is exposure to adverse childhood experiences (ACEs), including abuse, neglect, and household dysfunction. There is a strong dose-response relationship between the number of ACEs and the likelihood of developing a substance use disorder, with each additional ACE increasing the odds of addiction by up to 18%. ACEs not only elevate the risk of early initiation and more severe patterns of substance use but also contribute to long-term changes in brain development and emotional regulation. Together, genetics and childhood adversity represent two of the most significant drivers of addiction risk.

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Evidence-Based Treatments for Addiction: Medications and Psychotherapy

> *"So the things that we know are most effective for addiction, one, are medications, which there's a lot of stigma, misunderstanding about. And then two are evidence-based psychotherapy. So things like cognitive behavioral therapy, motivational enhancement therapy, you know, working on your underlying trauma."*

The most effective treatments for addiction are a combination of medications and evidence-based psychotherapies. Medications such as methadone, buprenorphine, and naltrexone are well-established for treating opioid use disorder, reducing illicit use, improving treatment retention, and lowering overdose risk. For alcohol and nicotine addiction, FDA-approved medications like acamprosate, bupropion, and nicotine replacement therapies have also shown strong efficacy in reducing cravings and supporting abstinence. While no consistently effective medications yet exist for stimulant use disorders, ongoing research continues to explore new pharmacological options. In parallel, several psychotherapies are backed by strong evidence. Cognitive behavioral therapy (CBT) and motivational enhancement therapy (MET) are among the most effective, especially when used alongside medications. Other validated approaches include contingency management, family-based therapies, group interventions, and brief motivational strategies. Treatment outcomes are strongest when these methods are combined and tailored to the individual's needs, reinforcing the importance of integrated care in addressing addiction.

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The Protective Power of Positive Childhood Experiences in Preventing Addiction

> *"you can reduce the risks that someone develops addiction by increasing the number of positive childhood experiences. So take someone who's experienced some terrible adversity, their parent has died, or they have a parent who's in prison, or they have addiction in their family. If that kid has one single adult figure that they believe cares about them, that reduces their risk of addiction."*

Positive childhood experiences (PCEs) play a critical role in reducing the risk of developing addiction, even among children exposed to significant adversity. Supportive relationships, particularly with a caring adult, have been shown to buffer the negative effects of adverse childhood experiences and are associated with lower rates of substance use and addiction in later life. Children who report strong bonds with parents, caregivers, or mentors are less likely to engage in smoking, heavy drinking, or

drug use, even when they have experienced trauma, loss, or household dysfunction. PCEs also contribute to broader protective effects, including better mental health, academic achievement, and resilience—factors that further reduce vulnerability to addiction. These findings underscore the power of even a single stable, nurturing relationship in shaping long-term outcomes and protecting against the intergenerational cycle of addiction.

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Long-Term Relapse Risk and the Chronic Nature of Addiction

> *"After five years of recovery, a person's risk of subsequently developing addiction is no higher than the general public. So your brain actually does change."*

While the risk of relapse decreases significantly with time in recovery, it does not fully return to the level seen in individuals with no history of addiction. Long-term studies have shown that even after five or more years of abstinence, individuals remain at an elevated risk of relapse, particularly when exposed to stress, substance-related cues, or other triggering circumstances. Although the brain undergoes meaningful changes in recovery, and many people sustain long-term sobriety, addiction is best understood as a chronic condition that may require ongoing support and management. Protective factors—such as social connection, purpose, and psychological resilience—can reduce vulnerability.

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Alcohol, Obesity, and Patterns of Use: Key Drivers of Liver Disease

> *"once you get to a level where you have a lot of scar tissue in your liver, we call that cirrhosis, you sort of reach a point of no return, where at that point the liver can't heal itself (...) now the two leading causes of liver disease, one are obesity and two is alcohol (...) For liver damage, it does tend to be the moderate to higher amounts that cause damage (...) having these massive binge episodes is probably more harmful than drinking at a moderate level for a long period of time."*

Cirrhosis as the Irreversible Stage of Alcohol-Related Liver Disease

Once cirrhosis develops—a condition marked by extensive scarring and structural damage—the liver typically cannot heal itself, and the changes are largely irreversible. Earlier stages of alcohol-related liver disease, such as fatty liver and alcoholic hepatitis, are reversible with complete abstinence from alcohol, often allowing for significant recovery of liver function. However, cirrhosis represents a critical threshold beyond which the liver's capacity to regenerate is severely compromised. While abstinence can halt further progression and improve symptoms, and in some cases lead to modest functional improvement, the scarring itself remains. For those with advanced cirrhosis, liver transplantation is the only curative option. Early diagnosis and intervention are therefore essential to prevent reaching this point of no return.

Obesity and Alcohol as the Leading Drivers of Liver Disease

Obesity and alcohol use are now the two most significant contributors to liver disease worldwide, each capable of independently causing chronic liver damage, and often compounding one another's effects. Obesity is the primary driver of non-alcoholic fatty liver disease (NAFLD), which is now

the most common form of liver disease globally and a major cause of cirrhosis and liver transplantation. Alcohol remains the central cause of alcoholic liver disease (ALD), another leading source of liver-related mortality. These risk factors frequently coexist, particularly in Western populations, where metabolic syndrome and hazardous drinking overlap. Their combined presence not only accelerates liver inflammation and fibrosis but also blurs the traditional distinctions between alcoholic and non-alcoholic liver disease. Together, they represent the dominant challenge in contemporary liver health.

Binge Drinking as a Greater Threat to Liver Health Than Moderate Use

Binge drinking poses a more serious threat to liver health than consistent moderate alcohol use, even when total alcohol intake is similar. This pattern of drinking, characterized by heavy consumption over a short period, leads to rapid spikes in blood alcohol levels that overwhelm the liver's ability to metabolize alcohol, resulting in acute stress and damage. Binge drinking is associated with a markedly increased risk of liver-related events and mortality, as well as elevated liver enzymes and early signs of liver dysfunction. These harmful effects are often more severe than those seen with regular moderate drinking. Public health data show that rising rates of binge drinking—particularly among young people—are driving an increase in liver disease and related complications. Addressing binge drinking is therefore vital for protecting liver function and preventing long-term liver damage.

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Acetaminophen, Alcohol, and Liver Toxicity

> *"acetaminophen or Tylenol, which is a very common over the counter pain reliever above a certain threshold can cause serious liver damage. So sometimes we'll see cases where someone didn't realize that, like their cold medicine plus the Tylenol they were taking both had that ingredient and then they go out and drink heavily. And that kind of combination effect can cause liver damage."*

Acetaminophen (paracetamol), while safe when used as directed, can cause severe liver damage when taken in high doses. It is the leading cause of acute liver failure in several countries, including the United States. Even moderate, repeated overuse—exceeding 4 grams per day—can result in toxic liver injury. The risk increases significantly when acetaminophen is combined with alcohol, particularly in people who drink heavily or binge drink. Alcohol induces liver enzymes that convert acetaminophen into a toxic metabolite while simultaneously depleting glutathione, a compound that normally protects liver cells. This combination heightens the risk of liver cell death, especially when acetaminophen is taken during or shortly after a period of heavy drinking. Unintentional overdoses can occur when individuals take multiple medications containing acetaminophen, such as cold remedies and pain relievers, without realizing the cumulative dose—posing a serious but preventable health risk..

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Alcohol and the Brain

> *"a form of dementia is related to alcohol use. And so your brain can be hugely impacted with alcohol (...) your brain can be hugely impacted with alcohol (...) The other thing that can accelerate the brain damage we see with alcohol is actually nutritional deficiencies"*

The Neurological Impact of Alcohol on Brain Structure and Function

Alcohol has wide-ranging effects on the brain, altering both its structure and function in ways that can impair cognition, behavior, and long-term neurological health. Chronic alcohol consumption leads to shrinkage and damage in critical brain regions, including the hippocampus and frontal lobes, which govern memory, decision-making, and impulse control. These structural changes correlate with declines in attention, memory, and executive functioning, and contribute to the progression of alcohol dependence. Alcohol also triggers neuroinflammation, disrupts mitochondrial function, and damages the brain's ability to produce new neurons—mechanisms that may underlie lasting cognitive deficits and increased risk of neurodegenerative disorders. The impact is especially severe during key developmental periods such as adolescence and prenatal stages, when alcohol exposure can permanently disrupt brain maturation. While some damage may be reversible with sustained abstinence, long-term heavy use can result in enduring impairments.

Alcohol-Related Dementia: A Preventable Form of Cognitive Decline

Alcohol-related dementia (ARD) is a distinct form of cognitive impairment that develops from long-term, excessive alcohol use. It is characterized by persistent memory problems, impaired executive function, and deficits in attention and visuospatial processing. ARD arises from both the direct toxic effects of alcohol on brain tissue and indirect effects such as thiamine (vitamin B1) deficiency, which is common in chronic drinkers and further exacerbates brain injury. Accounting for a significant portion of early-onset dementia cases, ARD typically emerges at a younger age than other forms of dementia and disproportionately affects men and socially isolated individuals. The condition may stabilize or even partially reverse if alcohol use stops and nutritional deficiencies are addressed early. Unlike Alzheimer's disease, ARD does not involve characteristic protein changes and may show cognitive improvement with appropriate intervention, making early recognition and abstinence from alcohol critical.

Nutritional Deficiencies as Accelerants of Alcohol-Related Brain Injury

Nutritional deficiencies—particularly thiamine (vitamin B1) deficiency—significantly intensify the brain-damaging effects of chronic alcohol use. Thiamine is essential for brain energy metabolism, and its deficiency can lead to serious neuropsychiatric conditions such as Wernicke Encephalopathy and Korsakoff Syndrome, both of which are marked by confusion, memory loss, and severe cognitive impairment. The neurotoxic synergy between alcohol and thiamine deficiency results in more extensive brain damage than either factor alone, affecting gene expression, brain cell insulation, and structural integrity. Thiamine deficiency not only exacerbates alcohol-induced neuronal injury but also impairs the brain's capacity to recover. While other nutritional deficits may also contribute to brain vulnerability, thiamine remains the most critical and well-studied. Addressing malnutrition and supplementing thiamine in individuals with alcohol use disorders is essential for preventing irreversible brain damage and supporting recovery.

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Alcohol and the Stomach

> *"So alcohol can cause [stomach] ulcers (...) You can even get a bleeding ulcer, which can be very dangerous (...) you can get cancer (...) bleeding."*

Alcohol can cause a range of injuries to the stomach and gastrointestinal (GI) tract, from inflammation and ulcers to more serious complications like bleeding and cancer. Chronic alcohol use damages the protective lining of the stomach, leading to gastritis and gastric ulcers, which can result in painful symptoms and, in severe cases, dangerous bleeding. It also weakens the lower esophageal sphincter and disrupts normal gut motility, increasing the risk of acid reflux and delayed gastric emptying. Beyond mechanical irritation, alcohol induces oxidative stress, disrupts enzyme activity, and alters gut microbiota, all of which contribute to inflammation and compromised intestinal integrity. This damage increases gut permeability, allowing toxins and bacteria to enter the bloodstream and placing additional strain on the liver and other organs. Long-term alcohol use also raises the risk of gastrointestinal cancers, particularly in the esophagus, stomach, and colon, due in part to the carcinogenic metabolite acetaldehyde. While some alcohol-related GI damage can improve with abstinence and appropriate care, persistent use can lead to lasting or life-threatening complications.

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Alcohol and the Heart

> *"the heart is affected by alcohol (...) at low risk levels there doesn't seem to be harm from alcohol. But once you get into the moderate and high, we see harms (...) one is something called atrial fibrillation (...) And then over time, if you're drinking at high levels, your heart actually dilates and you can end up with congestive heart failure from a cardiomyopathy."*

Alcohol affects the heart in a dose-dependent manner, with harm increasing markedly at moderate and high levels of consumption. While some studies suggest that low levels of alcohol may be associated with reduced cardiovascular risk, these findings are contested, and more rigorous genetic and epidemiological studies question whether any protective effect is truly causal. What is well-established, however, is that higher levels of alcohol intake increase the risk of a range of cardiovascular problems, including atrial fibrillation—a common arrhythmia characterized by an irregular and often rapid heartbeat that can lead to stroke and other complications. Chronic heavy drinking can also cause alcoholic cardiomyopathy, a condition in which the heart muscle becomes weakened and dilated, impairing its ability to pump blood effectively and potentially leading to congestive heart failure. The risk of these conditions rises steadily with alcohol consumption, and heavy or binge drinking is particularly damaging. While short-term cardiovascular stress may follow even moderate drinking, the long-term effects of sustained high intake can be progressive and life-threatening, underscoring the importance of limiting alcohol to protect heart health.

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Hangovers

> *"Hangover (...) seems to be most related to how high the ethanol concentration in your brain gets."*

The severity of a hangover is closely linked to the concentration of ethanol in the brain and bloodstream, with higher levels generally resulting in more pronounced symptoms. Ethanol crosses the blood–brain barrier and exerts effects on cognitive and physiological functions even after blood alcohol concentration (BAC) begins to fall. Research shows that hangovers are more severe following episodes of high BAC, particularly when drinking exceeds an individual's usual pattern. As the body metabolizes ethanol, the brain experiences inflammation, oxidative stress, and disrupted neurotransmitter function, all of which contribute to the headaches, fatigue, nausea, and cognitive deficits typical of a hangover. While a specific BAC threshold for hangovers varies by person, the risk and intensity clearly rise with greater ethanol exposure, supporting the idea that how much alcohol reaches the brain is a key determinant of hangover severity..

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Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder

> *"One of the most like groundbreaking trials in the last couple of years for alcohol use disorder was psilocybin. So there's a big study of psilocybin assisted psychotherapy for alcohol use disorder, which showed really remarkable effects. So people took psilocybin and actually compared it. Folks came in and they either got a big dose of Benadryl or psilocybin and then they sat with the therapist for like eight hours for this guided psilocybin journey and they found that people drank much less after it. So it does seem to have some effect. And the thought is that part of the way psychedelics work is they increase neuroplasticity, meaning the ability for the brain to form new pathways and kind of retrain itself."*

Psilocybin, a naturally occurring psychedelic compound found in "magic mushrooms," acts primarily on serotonin 2A receptors and has been studied for its ability to promote neuroplasticity and facilitate profound psychological experiences. In a landmark double-blind randomized clinical trial published in JAMA Psychiatry, researchers evaluated the efficacy of psilocybin-assisted psychotherapy in adults with alcohol use disorder (AUD). The study involved 95 participants diagnosed with alcohol dependence. Each participant received 12 weeks of manualized psychotherapy (including cognitive behavioral therapy and motivational enhancement therapy) and was randomly assigned to receive either high-dose psilocybin or an active placebo (diphenhydramine) during two all-day therapy sessions at weeks 4 and 8.

The results demonstrated that participants who received psilocybin showed significantly greater reductions in heavy drinking compared to the placebo group. Specifically, the percentage of heavy drinking days over a 32-week follow-up was 9.7% in the psilocybin group versus 23.6% in the placebo group—a substantial difference with moderate effect size. Additionally, the psilocybin group showed

greater likelihood of achieving abstinence, greater reductions in drinking-related problems, and greater improvements in World Health Organization (WHO) risk level classifications. The treatment was well tolerated, with no serious adverse events reported in the psilocybin group.

Proposed mechanisms underlying psilocybin's therapeutic effects include enhanced neuroplasticity—i.e., the brain's ability to reorganize and form new neural connections—alongside emotionally significant subjective experiences facilitated by the psychedelic state. These mechanisms may allow individuals to

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GLP-1 Receptor Agonists and Their Potential to Reduce Alcohol Use

> *"wegovy, ozempic, that whole class of GLP-1 medications seems to also reduce alcohol use"*

Glucagon-like peptide-1 (GLP-1) receptor agonists—such as semaglutide (Wegovy) and liraglutide (Saxenda)—are best known for their roles in treating type 2 diabetes and obesity, but recent research suggests they may also help reduce alcohol consumption. Preclinical studies in animals consistently show that these medications suppress alcohol intake, likely by acting on brain regions involved in reward and addiction, such as the ventral tegmental area and nucleus accumbens. These compounds appear to reduce alcohol's reinforcing effects and may also enhance inhibitory neurotransmission, contributing to diminished cravings. Early human studies and observational data offer some support for these effects, particularly among individuals with obesity, though clinical trials have produced mixed results and remain inconclusive overall. While more research is needed to determine their therapeutic efficacy in alcohol use disorder, GLP-1 receptor agonists represent a promising new direction in pharmacological addiction treatment.

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Role of Prescription Opioids in the Epidemic

> *"the worst overdose crisis ever in the history of the world has been happening in the US over the past 10 years or so (...) I would say the upstream drivers are, are largely a lot of what we've talked about. Lack of connection (...) lack of family support and meaning (...) But what happened also, and people have probably heard of this, was this dramatic shift in the use of prescription opioids."*

The current U.S. overdose crisis—widely regarded as the most severe in history—was catalyzed by a dramatic increase in the prescribing of opioid medications beginning in the late 1990s. Influenced by evolving standards in pain management, aggressive marketing by pharmaceutical companies, and the underestimation of addiction risks, prescription opioid use surged nationwide. By 2012, over 250 million opioid prescriptions were written in a single year—enough for every adult in the U.S.—resulting in widespread misuse, dependence, and a sharp rise in overdose deaths. From 1999 to 2015, prescription opioids were responsible for more than 183,000 deaths. Many individuals initially exposed to opioids through legal prescriptions eventually transitioned to heroin or illicit fentanyl, further compounding the crisis. Although prescription rates have since declined, the epidemic's roots remain deeply tied to the early oversupply and overuse of these drugs. Combined with social drivers such as isolation, lack of support, and existential distress, this pharmacological shift helped ignite a public health emergency that continues to evolve.

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Therapist Empathy as a Key Predictor of Substance Use Recovery

> *"there's been a lot of interesting studies looking at how empathetic your therapist is probably the strongest predictor of whether you make changes to your alcohol or drug use."*

Empathy is one of the most robust and consistent predictors of positive outcomes in substance use disorder (SUD) treatment. Research, including large clinical trials and meta-analyses, shows that when therapists demonstrate high levels of empathy, clients experience significantly greater reductions in alcohol and drug use, improved coping skills, and enhanced self-efficacy. These effects are observed across various treatment models and persist even when controlling for other therapeutic techniques. Empathic therapists foster stronger therapeutic alliances, which in turn increase treatment retention and decrease relapse risk. In contrast, low-empathy or confrontational approaches are associated with poorer outcomes, including higher dropout rates and less behavioral change. Importantly, it is not only the therapist's empathy but the client's perception of that empathy that drives these outcomes—highlighting the relational and attuned nature of effective addiction treatment..

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Post-Incarceration Overdose Risk

> *"There's 130 times increased risk of dying from a drug related cause after people leave prison"*

Text.

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