$50M Wellcome Leap Program
Untangling Addiction

Worldwide, someone dies from drug or alcohol addiction every 4 minutes.

Globally, 108 million people are estimated to be addicted to alcohol, and nearly 40 million are addicted to illicit drugs. In 2019, alcohol use disorder (AUD) killed 168,000 people worldwide and was a risk factor in an additional 2.44 million deaths. In the same year, substance use disorder (SUD)—partly defined by continued use of substances despite negative consequences—killed over 128,000 people worldwide[i]. And the numbers are getting worse.

The number of people with SUDs between 2009 and 2019 increased by 45%–from 27.3 million to 39.5 million globally. In the United States alone, an estimated 29.5 million people *12 years old* or older met the criteria for having an AUD in 2021; 24 million for an SUD. Globally, AUD and SUD cause an estimated 131 million years lived with disability (YLDs), resulting in an annual cost of over $740 billion in healthcare, lost work productivity, and crime. No country or region is immune. The prevalence of AUDs is highest in Europe (14.8% of the population), followed by the Americas (10.6%) and Africa (5.1%), and the prevalence of illicit SUDs is highest in North America (2.7% of the population), followed by Oceania (2.3%) and Europe (1.5%)[ii].

Addiction continues to rise despite increased expenditures.

Reliable values of global expenditures on drug abuse prevention and treatment are difficult to obtain. However, the US spent $24 billion to prevent and treat alcohol and drug abuse in 2009[iii] and $32.6 billion in 2019[iv]. These expenditures represent an increase of 35% over ten years. In that same period, the proportion of US adults who met the AUD and SUD criteria rose from 8.5% in 2013 to 12.5% in 2021. Efforts and resources devoted to addressing addiction have risen, but it's not working.

"Most people with addictions try to quit. Most can't quit."

In 2021, in the US, fewer than 4 million of the more than 46 million people with an AUD or SUD received treatment[v]. In total, that's **less than 9% of the US population with AUD or SUD having received treatment**. Percentages in the UK are a bit better for SUD treatment, with 20% of people meeting the criteria of SUD receiving treatment. However, the numbers for AUD are comparable to those seen in the US, with only 5% of those meeting the criteria of AUD receiving treatment[vi].

> "Drug Addiction is a chronic, relapsing brain disorder characterized by compulsive drug seeking and use despite harmful consequences."
>
> — National Institute on Drug Abuse (NIDA)

Among those treated, the statistics for relapse are equally alarming. For alcohol addiction, studies have shown relapse rates of approximately 50% within the first three months after completion of intensive inpatient programs. One study showed a 91% relapse rate for opiates, with 59% relapsing within the first week and 80% within a month.

This calls for a radical rethinking of our current approaches. A new approach that measures and characterizes the underlying neural and physiological factors that are affected and altered by addiction and incorporates that understanding into the treatment and tracking of recovery.

Why are we stuck?

Worldwide efforts at reducing and treating addiction have been ineffective primarily because (1) only a fraction of people with addictions get treatment; (2) treatment approaches are one-size-fits-all with minimal, if any, matching of treatment to the underlying physiology of the person with addiction; and (3) there are no standard relapse prevention programs with the result that more than half of those treated to achieve abstinence reverting to their addiction within 90 days. To make matters worse, potentially addictive substances are increasing in number and potency.

Prescription opiates: A new source of addiction.

'Super meth' and other mixed uses of illicit drugs are on the rise, but perhaps most troubling has been the emergence of prescription opioids. Historically, most substance abuse stems from the recreational use of illicit drugs and alcohol. Nevertheless, in the past 20 years, the rise in the legitimate prescription of potent opioid pain relievers has spurred an alarming new wave of misuse and addiction. Naturally occurring opiates, like opium and morphine, have been used for medicinal purposes for millennia to relieve pain and induce sleep. More recently, synthetic opioids, like fentanyl and sufentanil, have become available that are 100x and 500x more potent, respectively, than morphine.

Opioids are the most effective pain relievers available and have become indispensable to the practice of medicine, particularly for relieving severe pain, such as that caused by cancer, surgery, or trauma. However, opioids can also evoke feelings of intense euphoria and are highly addictive, such that about 10% of patients prescribed opioids for chronic pain begin to abuse them[vii]. In 2019, nearly 10 million Americans misused prescription opioids, and the number of overdose deaths directly resulting from prescription opioids was four times higher than a decade earlier[vi]. In 2021, 9.2 million people in the US over the age of 12 misused opioids[v], and 8.7 million misused prescription opioid pain relievers[v]. Opioids currently contribute to over 70% of overdose deaths in both the US[i] and the EU[ii]. Alarmingly, a 2014 study found that **75% of recent heroin users first abused prescription opioids**[viii]. *Thus, opioids are not only a growing source of addiction but increasingly the dominant cause of death in addiction.*

What needs to change?

We have a critical gap in our understanding and treatment of substance use disorders. Despite the myriad of factors that can influence treatment outcomes, it remains unclear which or even whether, any of these interventions can be considered universally effective, underscoring the need to consider personalized approaches to substance abuse treatment[ix]. By applying knowledge gained from neuroscience, genetics, and pharmacology, we aim to set a new standard for patient outcomes in substance abuse. Indeed, if we are to make impactful change in how substance use disorders are prevented and treated, we need to re-envision two important paradigms.

Establish standards of care based on biology, not tradition.

The majority of drug rehabilitation programs have traditionally followed a 30-day model, an approach established in the early years of addiction treatment and influenced by practical considerations. This framework, predicated on the belief that a one-month program is sufficient for detoxification (now termed medically supervised withdrawal) and initiating recovery, has been perpetuated due to its alignment with insurance and funding structures. However, contrasting this traditional approach with contemporary research highlights its limitations. Although 30-day programs can initiate recovery for some individuals, research shows that following such standard treatment, **patients, on average, relapse five times** before achieving abstinence or regaining control over their drinking habits[x]. This high rate of recurrence not only induces feelings of guilt, shame, and despair in patients and their families[xi], but also underscores the

shortcomings of a treatment model devoid of quantitative, individualized measures of efficacy and risk reduction.

The National Institute on Drug Abuse (NIDA) acknowledges the necessity of extended treatment, lasting at least 90 days, to facilitate sustained recovery[xii]. This stance is bolstered by clinical evidence indicating that various neural pathways, such as mesocortical pathways, impaired by addiction often necessitate a healing period exceeding the initial 30 days of sobriety or abstinence. It is imperative to transcend the antiquated rigid 30-day treatment model if we are to mitigate the distressing cycle of relapse and foster more lasting recovery. Adopting a model that comprehensively addresses addiction's neurobiological complexities allows for the customization of treatment durations to align with the unique needs and specific biological states of patients. Comprehending the factors that influence and affect recovery could lead to novel strategies for hastening recovery, evaluating relapse risk, and enhancing the reliability of sustained recovery. This shift, guided by cutting-edge neuroscientific developments and extensive longitudinal studies, promises a more empathetic and efficacious route toward healing.

Integrate Neurobiological Methods in SUD Diagnosis and Prognosis.

SUD diagnostics are presently grounded in standardized criteria, aiming for uniformity across diverse populations. These diagnostic practices rely heavily on self-reported information and can provide important subjective insights into a patient's experiences and challenges. Nevertheless, the degree of subjectivity inherent in self-reports introduces errors in underreporting use and severity, particularly when patients may minimize their symptoms due to stigma—a concern notably highlighted in adolescent groups[xiii] and in patients that misuse prescription drugs[xiv].

Diagnostic tools, such as patient self-reports and clinical interviews, are valuable for rapid screening and diagnosing substance abuse. However, predictive models based solely on patient self-reports and clinical interviews are not effective for reducing the risk of addiction emerging or for identifying patients at risk of relapse after treatment. In a study of alcohol-dependent patients, a model built from such clinical data alone had limited predictive accuracy for relapse in alcohol-dependent patients, achieving a 63.8% sensitivity and a 49.4% specificity. When neuroimaging imaging data was added, the same model achieved 90.0% sensitivity and 68.8% specificity[xv]. This notable increase emphasizes the substantial role of quantitative, patient-specific, biological data provided by neuroimaging in refining the predictive capacity of the models.

The evolution of neurobiological methodologies offers new opportunities to use more precise and objective measurement data, such as neuroimaging and biomarkers, to improve the accuracy of diagnosis and treatment. Combining neurobiological data with patient narratives will enhance our understanding with a quantifiable dimension of their condition. Moreover, for patients undergoing treatment with medications that have abuse potential, like opioid-based pain relievers or benzodiazepines, neurobiological monitoring could provide a critical, objective tool to track increased risk or progression toward drug abuse. As we look towards prognosis, these neurobiological tools may not only aid in the initial diagnosis but also have the potential to inform more precise prognostic models. By understanding the neurobiological underpinnings of an individual's use of known addictive substances, clinicians can make more informed predictions about initial addiction risks, recovery trajectories, and relapse risks, which can be pivotal in crafting successful and personalized treatment plans.

Why now?

The persistent opioid crisis, coupled with the emergence of new potentially addictive substances and the global resurgence of cocaine abuse[xvi], underscores the urgent need for innovative approaches to addiction prevention and treatment. Given that lives and communities are at stake, it is critical to adopt and integrate new technologies and methodologies. At this pivotal moment, the field of addiction research and treatment finds itself at a transformative juncture, shaped by recent advances in our understanding of the biological underpinnings of addiction and by novel technological breakthroughs.

What we've learned about the biological indicators of abuse.

The process of addiction is a complex brain disorder that disrupts the function of at least 16 major neural circuits within the human brain[vii]. Addictive substances induce a spectrum of functional and structural neuroadaptive changes within the central nervous system, most prominently within the brain's reward circuitry. This circuitry is an integrated network of brain structures central to motivation, associative learning, and the generation of pleasurable emotions, such as euphoria.

The core of the impacted reward system resides within the cortico-basal ganglia-thalamo-cortical loop. Recent studies have offered new insights, indicating that critical neuroadaptations are occurring in the circuits connecting the Nucleus Accumbens (NAc), Ventral Tegmental Area (VTA), and prefrontal cortex (PFC). These adaptations

play a significant role in the onset and progression of substance abuse disorders and, as such, may be highly suitable for developing biomarkers.

Reward circuits have evolved to ensure survival by reinforcing behaviors critical for life, including eating, drinking, and reproducing. Dopamine is the primary neurotransmitter of the reward circuit, and alterations in dopaminergic and glutamatergic neurotransmission are critically linked to the development of addictions. Indeed, the dopaminergic neurons projecting from the VTA to the NAc constitute the mesolimbic dopamine pathway, a well-characterized reward circuit essential for experiencing both natural and drug-induced rewards. Repeated and intense activation of this circuit by drugs can alter connectivity[xvii,xviii], and studies have shown that the level and persistence of dopamine released in response to drugs of abuse and alcohol greatly surpass those released by natural rewards. These factors, alongside other indicators such as changes in gene expression (e.g., *CREB, ΔfosB*, *PECAM*, *IL4*, etc.), epigenetics (including alterations in DNA methylation patterns), and metabolomics shifts (notably in neurotransmitter synthesis), as well as physiological responses, are integral to the various mechanisms that 'hijack' reward circuits and contribute significantly to the development of addiction-like behaviors. These findings imply the potential for quantifying the degree of addictive potency and the extent of substance-induced alteration in this circuit.

Additionally, a quantitative assessment of alterations in crucial brain circuits, such as mesolimbic and mesocortical connections, may aid in evaluating the risk of developing a substance use disorder. Consequently, detecting and quantifying pathophysiological changes in brain circuits occurring during addiction could offer crucial biological metrics. Assessing dynamic changes in circuit structure or function might enable a more objective and quantitative method for managing drug and alcohol use, similar to how glycated hemoglobin (HbA1c) underpins objective management strategies for diabetes risk in individuals and populations.

Drug Cravings. Managing cravings—the intense urge to consume a drug during abstinence—is the primary neurobiological challenge to maintaining abstinence. The perceived intensity and frequency of cravings are significant predictors of relapse among individuals in recovery. Typically, individuals who experience higher levels of cravings are more than twice as likely to use drugs or relapse compared to those with lower levels of these indicators[xix]. Thus, addressing cravings is a primary focus of intervention efforts[xx].

Emerging clinical trials suggest that the insular cortex—a brain region involved in emotional regulation and decision-making—strongly influences cravings by modulating the interplay between emotional responses and the compelling urges that drive substance use. The role of the insula in drug craving was serendipitously discovered in a study of stroke patients who were able to quit smoking effortlessly and without relapse when the stroke had caused damage to the insula[xxi]. The insula's role in nicotine cravings, extensively validated by human and animal studies, is now understood to extend to cravings for a variety of addictive substances.

Recent studies have additionally discovered that structural alterations in the insula, particularly projections to the NAc, could more accurately forecast relapse than conventional clinical models in a group of individuals recovering from methamphetamine addiction[xxii].

Crucially, recent human studies have shown that the insula and other brain regions can be effectively targeted by non-invasive brain stimulation techniques like deep repetitive transcranial magnetic stimulation (rTMS)[xxiii]. In one notable study, it was found that among nicotine-dependent individuals, rTMS led to a 75% reduction in daily cigarette consumption and increased the percentage of individuals maintaining abstinence six months after treatment by 33%[xxiv]. Comparable results have been observed in preliminary studies involving patients with cocaine use disorder, focusing on the prefrontal cortex[xxiii] as well as studies targeting both the insula and the prefrontal cortex[xxv]. These studies imply that non-invasive brain stimulation could be effective in addressing a wide range of substance use disorders.

New technological advances.

Advanced neuroimaging techniques, including fMRI and PET scans, used alone or in conjunction with EEG recordings, now yield detailed insights into brain activity and structure, facilitating more targeted and effective treatment approaches[xxvi]. Recent advancements in deep brain stimulation (DBS) technology have shown promising results in identifying electrophysiological markers linked to cravings. This technology—particularly its ability to identify and modulate specific neural signals in the NAc associated with loss-of-control eating—suggests potential methods for similar interventions in managing cravings related to substance abuse disorders. These innovations are laying the groundwork for future research and the creation of precision-targeted treatments for addiction[xxvii].

Integrating big data and machine learning allows the ability to analyze or reanalyze extensive health datasets, revealing previously undetectable patterns and predictive factors in addiction from longitudinal bio banked data. This approach could significantly improve the accuracy of prognosis and the personalization of treatment strategies[xxviii]. Additionally, advancements in digital health aids are opening up new possibilities with wearable devices and telehealth solutions, enabling patient-led monitoring and support that could lead to more proactive, collaborative, and responsive strategies in managing recovery[xxix].

Recent developments *in vitro* modeling of brain circuits and the utilization of neurons derived from human-induced pluripotent stem cells (iPSCs) of postmortem overdose subjects present a promising yet underexplored avenue in SUD research. This method has the potential to elucidate the cellular mechanisms underlying addiction and may lead to the identification of novel therapeutic strategies[xxx].

The Promise of Psychedelics.

Anecdotal evidence has consistently emphasized the potential therapeutic benefits of various psychedelic compounds, including but not limited to LSD and ketamine, in aiding recovery from substance abuse disorders. Reports from individuals and further anecdotal evidence consistently indicate that psychedelics lead to reduced cravings, lower relapse rates, and diminished overall substance dependence. Moreover, individuals in recovery, frequently with therapeutic support, have reported significant breakthroughs in their healing journey attributed to psychedelic use. Such experiences highlight a promising avenue in the realm of addiction treatment.

In a controlled clinical trial involving 95 participants diagnosed with AUD, the combined administration of psilocybin and psychotherapy led to a significant reduction in heavy drinking days. Specifically, patients who were administered psilocybin exhibited a 13.9% greater decrease in heavy drinking days over 32 weeks compared to those given a placebo[xxxi]. This preliminary evidence suggests that psilocybin may also be useful in treating substance abuse disorders.

Although, the precise mechanisms through which these substances exert their effects are still largely speculative, a dominant theory proposes that they may induce neuroplastic changes, thereby facilitating the rewiring of crucial neural pathways[xxxii]. This hypothesis emphasizes the urgent need for more comprehensive and rigorous scientific research to validate these preliminary observations and unravel the therapeutic processes involved.

Program goals.

The escalating rates of global substance use, addiction, and overdose-related deaths highlight an urgent need for innovative methods to prevent, diagnose, and treat substance use disorders (SUD) and alcohol use disorders (AUD). The myriad of biological factors that determine individual susceptibility to addiction and their responsiveness to intervention is poorly understood. A primary objective of this program is to identify biomarkers that can be detected through non-invasive or minimally invasive methods (e.g., blood tests, somatosensory evoked potentials, etc.) to facilitate quantitative assessment of the fundamental changes and neurobiological underpinnings of drug abuse and, ultimately, to demonstrate increased efficacy of prevention and treatment approaches using these quantitative methods.

To that end, our goals are to:

1. **Develop scalable measures to assess individual addiction susceptibility to a range of addictive and potentially addictive substances.** Approaches may include, but are not limited to, analysis of longitudinal samples from existing biobanks, *in vitro* experiments with patient-derived hiPSCs, or computational methods such as predictive modeling and machine learning algorithms. Measures should demonstrate an accuracy of ≥ 80% in the prediction of progression to addiction.

2. **Quantify addiction risk and progression during prescription drug use.** We are particularly focused on prescription opioids with a goal to demonstrate the ability to reduce misuse and subsequent addiction in patient populations by 50%, from an estimated 1 out of 10 patients to 1 out of 20.

3. **Develop innovative treatments and quantifiably assess recovery using new or existing treatments, on a personalized basis, such that the risk of relapse is reduced by a factor of 2 post treatment.** Estimated abstinence rates for AUD is ~50% 90 days after treatment, and ~25% 1 year after treatment[xxxiii]. The 90-day abstinence rate for SUD varies by drug but is estimated to be between 15-30% for opioids.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over 3 years in one or more of the following thrust areas. Proposers should clearly relate work in these thrust areas to one or more of the program goals.

It is not necessary to form a large consortium or teams to address all facets of the program. The strength of this approach will manifest through program-level integration of efforts from individuals and small agile teams with deep (and sometimes narrow) expertise. Across all projects, Wellcome Leap will facilitate iterative and collaborative integration of findings to refine models and improve and validate predictive measures and adapt approaches as teams make progress towards shared goals.

Thrust Area 1: Comprehensive Neurobiological and Behavioral Measurement and Modeling of Addiction Risk and Recovery.

This thrust area seeks the development and test of advanced predictive models that incorporate a broad spectrum of new and existing neurobiological and behavioral biomarkers to assess the risk of addiction and the efficacy of recovery interventions. Of particular interest are characterization approaches that develop models incorporating multiple measurement domains to stratify patients by risk or indicate transitions toward substance abuse or relapse.

Interest Areas:

- Development of new and existing biomarkers including neurotransmitters, hormones, neurotrophic factors, genetic/epigenetic markers.
- Employment of neuroimaging techniques (e.g., fMRI, PET, DTI).
- Real-time/longitudinal data collection of physiological biomarkers such as heart rate variability (HRV), blood pressure, and sleep patterns. Of particular interest are non- or minimally-invasive techniques, such as blood draws and saliva tests, or wearable technologies.
- Behavioral and cognitive biomarkers: e.g., performance on cognitive tasks, reaction times, and behavioral patterns captured through digital means, including apps, or wearables.
- Metabolomics and proteomics for comprehensive profiling of metabolites and proteins.

- Cross-modality integration approaches using artificial intelligence and machine learning techniques to create a holistic view of an individual's addiction status and response to treatment.

Developments within this area are expected to target demonstrations of predictive models with at least 90% sensitivity and 70% specificity, capable of supporting a 50% reduction in progression to opioid misuse, specifically, and/or a 50% reduction in relapse rate at 90 days post-treatment, generally.

Thrust Area 2: Validation and Optimization of Neurobiological Biomarkers for Substance Use Disorders and Alcohol Use Disorders.

This thrust area is focused on the demonstration and validation of the neurobiological, behavioral, and digital biomarkers identified in Thrust Area 1 in diverse cohorts, communities, and settings with the goal of predicting the onset, progression, and/or relapse rate post treatment for Substance Use Disorders (SUD) and Alcohol Use Disorders (AUD) with sufficient sensitivity and specificity to meet the program goals.

Interest Areas:

- Use of controlled studies sufficiently powered to validate biomarkers related to SUD and AUD across various stages and responses to treatment.
- Biomarker assessment and harmonization for use in clinical settings: Development, adaptation, and demonstration of optimized, select biomarkers that facilitate patient-specific, and user-friendly use in clinical and personal settings.

Thrust Area 3: Longitudinal Studies of Prescription Opioid Use, Addiction Risk Trajectories, and Prevention Strategies.

This thrust area is intended to develop new and/or validate existing longitudinal studies that specifically trace the progression from prescription opioid use to potential misuse and addiction. Key interests focus on the early detection of an individual's addiction risk or misuse indicators as well as the efficacy of prevention and recovery interventions.

Interest Areas:

- Longitudinal monitoring: Comprehensive studies using quantitative markers to track individuals prescribed with opioid pain relievers to diagnose early misuse signs and addiction predispositions.
- Intervention effectiveness: Optimization and evaluation of the sustained impact of various prevention or recovery interventions on patient outcomes, aiming to prevent onset of addiction and/or relapse post treatment.
- Data integration: Amalgamation of diverse data types, such as patient health records and self-reported outcomes, neurobiological and behavioral data, from diverse clinical, healthcare, and research settings.

Thrust Area 4: Retrospective Analysis of Broad Existing Datasets for Addiction Risk.

This thrust area focuses on the use of retrospective research methodologies to analyze existing biological datasets. The focus is on identifying distinctive neurobiological markers that may signal susceptibility to Substance Use Disorders (SUD) or Alcohol Use Disorders (AUD).

Interest Areas:

- Retrospective studies: Employ case-control and cross-sectional study designs to dissect existing datasets, seeking neurobiological markers that separate those affected by SUD or AUD from unaffected individuals.
- Data analysis compatibility: Identification and use of historical datasets that are amenable to application of state-of-the-art analytical methods—including artificial intelligence and machine learning, and 'omics technologies—to detect underlying patterns and associations of addiction or relapse risk.

It is anticipated that proposals in this area will employ integration and innovation strategies including, but not limited to, cross-dataset synthesis of information from disparate datasets; advances in data processing tools to manage and analyze large-scale, diverse-content datasets; and retrospective to prospective bridging that leverages retrospective data to inform prospective studies to refine predictive modeling. Finally, proposals directed to this thrust are expected to demonstrate capabilities for retrospective analysis that align with

the sensitivity and specificity targets set forth in the prior thrust areas.

Thrust Area 5: Novel Interventions.

This thrust seeks the development and validation of innovative treatments for Alcohol Use Disorders (AUD) and Substance Use Disorders (SUD).

Interest Areas:

- Development of new pharmacotherapeutic and non-invasive neuromodulation therapies for AUD and SUD. Of particular interest is the use of psychedelic compounds backed by recent anecdotal evidence and study evidence in animals, along with repurposing of FDA-approved compounds with prior evidence of potential for AUD or SUD efficacy in humans. Compounds currently utilized off-label for treating AUD/SUD, including Baclofen, Topiramate, and Gabapentin, as well as over-the-counter supplements, are outside the scope of interest.
- Assessment and optimization of treatments based on their potential to significantly reduce relapse rates and surpass existing treatment efficacies. Such treatments include, but are not limited to: Transcranial Direct Current Stimulation (tDCS), Transcranial Alternating Current Stimulation (tACS), Focused Ultrasound (FUS), Temporal Interference (TI) Stimulation, and Low-Intensity Focused Ultrasound Pulsation (LIFU)

Proposals should demonstrate a clear path towards doubling the efficacy of current treatments for AUD and SUD. They are expected to present a robust methodology for measuring treatment outcomes, with a focus on reducing relapse rates. Proposals should also illustrate a commitment to the advancement of safe and effective recovery interventions, with a goal to establish new standards in addiction treatment practices. Human studies will be given the highest priority, followed by pre-clinical studies in non-human primates, and rodents.

REFERENCES:

[i] Global Burden of Disease (GBD). https://www.healthdata.org/research-analysis/gbd.

[ii] World Drug Report 2023 - Special Points of Interests. *United Nations : Office on Drugs and Crime* //www.unodc.org/unodc/en/data-and-analysis/wdr-2023_Special_Points.html.

[iii] White, A. G. *et al.* Direct Costs of Opioid Abuse in an Insured Population in the United States. *J. Manag. Care Spec. Pharm.* **26**, 1188-1198 (2020).

[iv] Substance Abuse and Mental health Services Administration.(2019). https://www.samhsa.gov/sites/default/files/samhsa_fy2019_operating_plan_508.pdf

[v] Section 5 PE Tables – Results from the 2021 National Survey on Drug Use and Health: Detailed Tables, SAMHSA, CBHSQ. https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect5pe2021.htm - tab5.6a

[vi] Adult substance misuse treatment statistics 2021 to 2022: report. *GOV.UK* https://www.gov.uk/government/statistics/substance-misuse-treatment-for-adults-statistics-2021-to-2022/adult-substance-misuse-treatment-statistics-2021-to-2022-report.

[vii] Vowles, K. E. *et al.* Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* **156**, 569–576 (2015).

[viii] Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014 Jul 1;71(7):821-6. doi: 10.1001/jamapsychiatry.2014.366. PMID: 24871348.

[ix] Els, C. *et al.* High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* **2017**, CD012299 (2017).

[x] Kelly, D. E., John. People recover from addiction. They also go on to do good things. *STAT* https://www.statnews.com/2021/05/03/people-recover-from-addiction-they-also-go-on-to-do-good-things/ (2021).

[xi] Batchelder, A. W. *et al.* The shame spiral of addiction: Negative self-conscious emotion and substance use. *PloS One* **17**, e0265480 (2022).

[xii] National Institute on Drug Abuse. (2012). *Principles of Drug Addiction Treatment: A Research-Based Guide: Third Edition*. https://doi.org/10.1037/e686332012-001.

[xiii] Percy, A., McAlister, S., Higgins, K., McCrystal, P. & Thornton, M. Response consistency in young adolescents' drug use self-reports: a recanting rate analysis. *Addiction* **100**, 189–196 (2005).

[xiv] Broman, M. J., Bista, S. & Broman, C. L. Inconsistency in Self-Reporting the Use of Substances over Time. *Subst. Use Misuse* **57**, 1356–1364 (2022).

[xv] Seo, S. *et al.* Predicting the future relapse of alcohol-dependent patients from structural and functional brain images. *Addict. Biol.* **20**, 1042–1055 (2015).

[xvi] UNODC, Global report on Cocaine 2023 – Local dynamics, global challenges (United Nations publications, 2023).

[xvii] Samaha, A.-N., Khoo, S. Y.-S., Ferrario, C. R. & Robinson, T. E. Dopamine 'ups and downs' in addiction revisited. *Trends Neurosci.* **44**, 516–526 (2021).

[xviii] Feltenstein, M. W., See, R. E. & Fuchs, R. A. Neural Substrates and Circuits of Drug Addiction. *Cold Spring Harb. Perspect. Med.* **11**, a039628 (2021).

[xix] Vafaie, N. & Kober, H. Association of Drug Cues and Craving With Drug Use and Relapse A Systematic Review and Meta-analysis. *JAMA PSYCHIATRY* **79**, 641–650 (2022).

[xx] Tiffany, S. T. & Wray, J. M. The clinical significance of drug craving. *Ann. N. Y. Acad. Sci.* **1248**, 1–17 (2012).

[xxi] Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. Science. 2007 Jan 26;315(5811):531-4. doi: 10.1126/science.1135926. PMID: 17255515; PMCID: PMC3698854.

[xxii] Tisdall, L., MacNiven, K. H., Padula, C. B., Leong, J. K. & Knutson, B. Brain tract structure predicts relapse to stimulant drug use. *Proc. Natl. Acad. Sci.* **119**, e2116703119 (2022).

[xxiii] Bolloni, C. *et al.* Bilateral Transcranial Magnetic Stimulation of the Prefrontal Cortex Reduces Cocaine Intake: A Pilot Study. *Front. Psychiatry* **7**, (2016).

[xxiv] Dinur-Klein, Limor et al. 2014. "Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial." Biological Psychiatry 76(9): 742–49.

[xxv] Sanna, A. *et al.* Intermittent Theta Burst Stimulation of the Prefrontal Cortex in Cocaine Use Disorder: A Pilot Study. *Front. Neurosci.* **13**, (2019).

[xxvi] Garrison, K. A. & Potenza, M. N. Neuroimaging and Biomarkers in Addiction Treatment. *Curr. Psychiatry Rep.* **16**, 513 (2014).

[xxvii] Shivacharan, R. S. *et al.* Pilot study of responsive nucleus accumbens deep brain stimulation for loss-of-control eating. *Nat. Med.* **28**, 1791–1796 (2022).

[xxviii] Mak, K. K., Lee, K. & Park, C. Applications of machine learning in addiction studies: A systematic review. *Psychiatry Res.* **275**, 53–60 (2019).

[xxix] Marsch, L. A. Digital Health and Addiction. *Curr. Opin. Syst. Biol.* **20**, 1–7 (2020).

[xxx] Mendez, E. F. *et al.* A human stem cell-derived neuronal model of morphine exposure reflects brain dysregulation in opioid use disorder: Transcriptomic and epigenetic characterization of postmortem-derived iPSC neurons. *Front. Psychiatry* **14**, (2023).

[xxxi] Bogenschutz, M. P. *et al.* Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* **79**, 953–962 (2022).

[xxxii] Vargas, M. V., Meyer, R., Avanes, A. A., Rus, M. & Olson, D. E. Psychedelics and Other Psychoplastogens for Treating Mental Illness. *Front. Psychiatry* **12**, (2021).

[xxxiii] Krupitsky, E. M. & Grinenko, A. Y. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J. Psychoactive Drugs* **29**, 165–183 (1997).

