



cogitativo

Gut Microbiomes and Machine Learning Join the Battle Against Opioid Use Disorder

Protecting the Health
of our Veterans



Evolving Addiction Risk Scores from Posteriori Reaction to a Priori Foresight

Introduction

Cogitativo recognizes the rising prevalence of opioid use disorder among Americans and the urgent need for effective preventative strategies.¹ We propose leveraging cutting-edge machine learning (ML) techniques to determine which individuals are at high risk for developing opioid addiction and using these insights to empower individuals and their providers. Specifically, ML can be used to identify patterns in highly dimensional data, including social determinants of health, medical records, as well as gut microbiomes, and genetic biomarkers.

Combining readily available biomarkers with ML can help clinicians guide at-risk patients toward appropriate interventions such as pain management therapeutics and provide an individualized, sophisticated strategy to help minimize the vexing, complex personal and national crisis of opioid use disorder. This preventative approach can improve clinical outcomes while reducing costs and utilization associated with the use of acute, urgent healthcare services.

Background

The rise in deaths due to opioid overdose (OOD) in the population of Veterans seeking treatment through the Veterans Health Administration (VHA) closely mirrors that of the US population.² Veterans may be at particular risk for OOD given that they have high rates of pain treated with prescription opioids: 247,000 VHA beneficiaries received prescription opioids in 2020.³ Thus, the VHA is an essential setting for studying addiction and untoward outcome risks resulting from prescription opioids.

UNMET NEED: We lack tools with high fidelity and sensitivity to elucidate each Veteran's opioid health risks and provide guidance on how to intervene rapidly to mitigate harm and improve health outcomes.

SOLUTION: New technology that combines the power of machine learning (ML) with the information embedded in large and growing biological datasets will allow evidence-driven care to begin before ordering prescription opioids while continuously monitoring potential addiction risk according to each Veteran's specific needs.

ASK: If granted access to existing federal data assets containing Veterans' biological information, Cogitativo will have the data artifacts required for its platform to reveal relationships between biological signatures and those with known opioid addiction. This unique ML solution will predict the individual-specific probability of addiction risk.

IMPACT: Armed with these new insights, the VA will have the opportunity to rapidly predict each Veteran's risks for opioid use disorder, which enables the opportunity to use other pain management therapies.

Prevalence & Significance of Opioid Addiction

Most drug overdose deaths in the US involve an opioid such as morphine, fentanyl, and heroin. In 2020, opioids accounted for three out of four drug overdose deaths in this country.⁴

Several genetic, physiological, psychological, and environmental factors play a role in the likelihood and severity of addiction.

Known risk factors for opioid misuse and addiction include:

- Poverty
- Unemployment
- Family history of substance abuse
- Personal history of substance abuse
- Young age
- History of criminal activity or legal problems, including DUIs
- Regular contact with high-risk people or high-risk environments
- Prior drug or alcohol rehabilitation
- Female sex

With respect to sex, women have a unique set of risk factors for opioid addiction. Women are more likely than men to suffer from chronic pain, which is a major catalyst for opioid use and addiction. Women are also more likely to be prescribed opioid medications, to be given higher doses, and to use opioids for longer durations. Compared to men, women may also have biological tendencies that facilitate more rapid dependence on prescription pain relievers.

Drug behavior can also impact drug-related risks. For example, crushing an opioid pill for snorting or injection can increase its effect, as well as the likelihood of overdose. Researchers have also found that taking opioid medications for more than a few days increases the risk of long-term use, which increases addiction risk. Specifically, after only five days on opioids, the odds of continuing opioid use beyond a year significantly increase.

Managing the Opioid Epidemic is a public health challenge, and understanding factors influencing opioid abuse potential is critical for developing appropriate therapeutic interventions.

Current Opioid Addiction Epidemic



The opioid epidemic has been increasing across decades, and over

2.5 MILLION

Americans had an opioid addiction in 2021.⁵



In 2021, over **106,000** Americans died of drug overdose.⁶



Opioid overdose has been considered a national emergency as

136 PEOPLE

die every day from an opioid-related overdose.⁷



In 2019, 46.8 opioid prescriptions were dispensed for every

100 AMERICANS.⁸



The current treatment for opioid abuse is **opioid replacement therapy** or other drugs that work on opioid receptors.



Even with the best therapeutics interventions available on the market, the long-term relapse rate for opioid use is

85%.



This highlights a major need to develop improved and innovative therapeutic interventions for opioid cessation.

Linkage to Genetics and the Gut Microbiome

Substance use disorder research has shown that opioid addiction is moderately heritable. In particular, genetic influences on addiction traits were elucidated decades ago via genetic epidemiology twin and adoption studies.⁹ This research was critical in establishing a basis for gene mapping in addiction. However, despite the twin study framework being well established a decade ago, it has advanced little relative to molecular gene mapping successes.

Genetic studies have been considered vital for identifying targets to develop more effective treatments. However, we are just starting to comprehend and dissect the highly polygenic architecture of these complex traits. The main steps forward in this field have occurred recently and over just a few years, which is attributable to the advent of large biobanks and consortia that are allowing the study of sample sizes that until recently were unimaginable. Large-scale genome-wide studies of complex traits illustrate several key propositions.

First, broad diversity in biological data leads to a deeper understanding of biology. Specifically, extensive racially-ethnically diverse genome-wide association studies (GWAS) may uncover novel biology. Second, similar to other complex traits, genetic findings from European-descent populations (for example, European American subjects) greatly exceed those from other populations (for example, African American subjects). Third, candidate genes selected based on known biology, which has a dismal record in the field,⁶ have been successfully replicated by large-scale addiction GWAS in only a few instances.

In addition to the genetic predisposition to addiction, new research is establishing links between the gut microbiome and the likelihood of addiction. The gut and the brain communicate across a bidirectional, biochemical, and neural highway¹¹ (the gut-brain axis).¹² Nerve endings below the intestinal epithelium receive metabolic signals from the gut microbiota, which may influence behaviors like stress or anxiety. In addition to other metabolites implicated in central nervous system (CNS) development and brain function, like short-chain fatty acids (SCFAs),¹³ gut microbes help produce an array of neurotransmitters associated with mood, cognition, and reward (e.g., serotonin and dopamine) and may therefore influence addiction risk.

Evaluating Addiction Risk

An alternative approach to our current prescription habits is to evaluate risk before prescribing opioids, using screening questionnaires. The most popular tool for this method is the Opioid Risk Tool (ORT). This tool quantifies the risk of developing an opioid use disorder (OUD). **The key assumption for the value of this tool is that those at risk for addiction will demonstrate easily identifiable predisposing factors**, including behavioral factors such as abuse, misuse, or diversion, and factors strictly related to the patient's history and experiences. However, these factors are often absent in those who will go on to develop opioid addiction. For instance, in clinical practice, many subjects with chronic pain syndromes that develop OUD do not have a prior history of addiction, which hampers the use of this posteriori tool.

The ORT suffers several other limitations, including that it is designed to assess the risk of opioid abuse only in adults and that it contains only five items and three potential outputs (low, moderate, or high risk for aberrant drug-related behavior), which do not provide deep insight into addiction risk. In addition, we have compared the performance of any risk prediction tools¹⁴ side by side, so there is no evidence of the superiority of the ORT tool. Despite its lack of proven effectiveness, the ORT is widely used, likely owing to the enormous unmet clinical need to characterize and quantify addiction risk.

Our Solution

We propose employing Cogitativo's Visión clinical risk machine learning (ML) platform to elucidate the mechanisms of opioid addiction, focusing on genetic polymorphisms and gut microbiome variation effects on addiction. In doing so, we will investigate the bidirectional communication between the gut and the brain through the biochemical and neural pathways of the gut-brain axis (i.e., the gut-brain axis), including how the nerve endings beneath the intestinal epithelium, receiving metabolic signals from the gut microbiota, may play a role in influencing addiction-relevant moods and behaviors such as stress, anxiety, cognition, and reward, mediated by neurotransmitters like serotonin and dopamine.

Visión is a continuous learning system that leverages state-of-the-art ML techniques and large-scale data sources to understand, predict, and manage adverse clinical outcomes through early diagnosis and treatment. Visión has been deployed in the Department of Veterans Affairs (VA) to predict and understand the impacts of deferred care for chronic conditions as well as decomposition risks for ICU patients.

Visión has a library of ML algorithms for approximately 40 endpoints encompass cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, COVID-19, human immunodeficiency virus (HIV), and kidney disease.

Visión uses ensemble learning to integrate proven ML techniques, reducing overfitting and facilitating transfer learning. It incorporates medical knowledge into the learning process at multiple stages to ensure the final model is consistent with established knowledge. Visión supports static and temporally varying features and captures the progressions of diseases through different stages, allowing for more timely interventions.

The outputs of Visión include (i) highly interpretable quantification of clinical risks, (ii) novel knowledge represented by correlative structures, and (iii) quantification of uncertainties in predictions as well as recommendations on how to reduce and manage uncertainties. We adopt a continuous improvement strategy to ensure reliable and relevant output in a constantly changing world. Visión's knowledge/data management system will incorporate new information and refresh training sets as opioid research and patient data evolve.

It is also important to note that identifying more vulnerable patients aligns with current federal efforts for pharma to develop less addictive pain medications. Using Cogitativo's approach to identifying high-risk individuals, these most vulnerable patients could become the initial candidates for taking new, less addictive pain medications. Given that

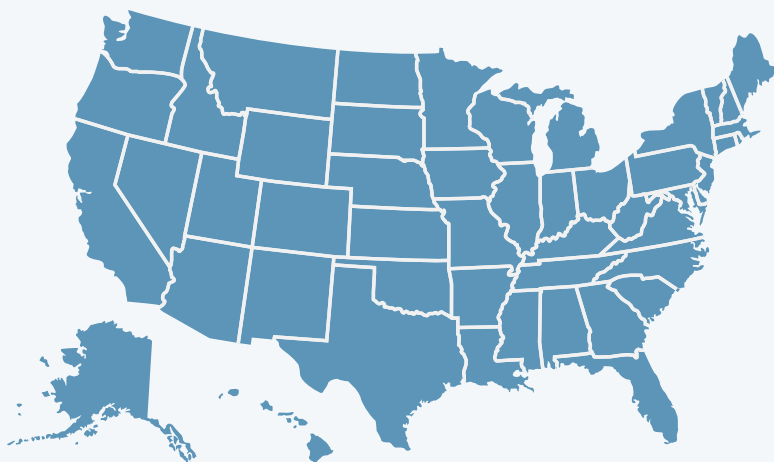
these efforts will be costly, pharma companies will need data on effectiveness to obtain reimbursement from payors. Cogitativo intends to assist in this effort to provide better pain management without the cost of addiction to individuals with addiction vulnerabilities.

Closing

Despite the efforts (and successes) of the VA to curb opioid and other substance-related mortality among Veterans, the opioid overdose public health crisis persists, with the highest number of overdose fatalities ever reported during 2020–2021 among the general population. Many veterans face complex challenges, combining problems of pain management, substance use, service-related mental and physical health problems, and the day-to-day challenges associated with housing, employment, and relationships, all of which can heighten the risk for opioid overdose.

Fortunately, we now have the data assets to identify the Veterans with the highest OUD risk through GWAS and large-scale gut microbiome databanks. These assets, when combined with machine learning tools, provide a prophylactic capability that identifies the most vulnerable opioid patients well before any predisposing factors are known.

Cogitativo's efforts to advance the identification of those vulnerable individuals enable the potential retargeting of pain management intervention therapies into more appropriate approaches.



136
PEOPLE

died each day from an
opioid overdose in 2021.

Source: National Center for Drug
Abuse Statistics

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