Social determinants as biomarkers of structural vulnerability in minoritized people with substance use disorders: implications for translational addiction science

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ABSTRACT

Like traditional biomarkers, sociomarkers (social biomarkers) reflect disease etiology, severity, course, and prognosis. This thesis synthesizes selected peer-reviewed publications to reframe social determinants of health as clinically meaningful biomarkers of structural vulnerability, defined as an individual's or population's risk for adverse health outcomes arising from exposure to intersecting socioeconomic, political, and cultural hierarchies.

In the United States, minoritized communities have been disproportionately impacted by inequities in access to evidence-based treatments for substance use disorders and by an emerging racial shift in drug overdose deaths, within the context of a structurally inequitable health care system. Although existing literature identifies structural vulnerability as a final common pathway shaping health outcomes among people with substance use disorders, this construct remains poorly operationalized, and a coherent, sustainable translational framework is lacking. It is therefore critically important for public health to develop frameworks that can predict risk, inform the design of equitable interventions, and address upstream structural drivers of persistent racial and ethnic inequities.

This thesis addresses this gap by developing a translational framework that conceptualizes social determinants of health as clinically meaningful biomarkers influencing substance use disorder risk, course, and outcomes. Included studies document population-level inequities in overdose and treatment within a changing drug supply; demonstrate systemic racism-related distress as a measurable and persistent exposure associated with substance-related psychopathology; and show that social and structural factors shape remission trajectories, treatment pathways, and diagnostic

complexity. Epidemiologic analyses highlight persistent disparities and within-group heterogeneity, complemented by qualitative evidence of lived structural barriers to care. Conceptual papers translate these findings into implications for harm reduction, policy, and addiction workforce development. Collectively, this body of work advances a translational framework positioning social determinants as biomarkers of structural vulnerability in addiction science.

This thesis further operationalizes interactions among social elements across multiple socioecological levels and health care system infrastructures, arguing that achieving health equity requires centering social determinants of health within culturally responsive, dynamic, and self-correcting health systems. The social determinants of health framework is expanded to include metastructural determinants, an original conceptual contribution introduced as a scaffold within a tiered system encompassing social and structural determinants. Metastructural determinants capture global, overarching forces that sustain, legitimize, and reproduce inequities while shaping structural arrangements beyond the control of any single ecological level, including colonialism, capitalism, globalization, climate change, displacement, and nativism. Reframing social determinants of health as biomarkers of structural vulnerability extends traditional biomedical models and creates new opportunities for prevention, intervention, and policy. Operationalizing social variables as weighted social indices, latent constructs, and risk vectors enables clinical risk stratification and the systematic incorporation of structural forces into predictive and causal models of substance use disorder.

Although the selection, conceptual organization, and framing of this thesis form a coherent body of scientific evidence, limitations include the inability to draw causal inferences from predominantly cross-sectional research designs and limited generalizability across diverse contexts. Conceptualizing social determinants of health as biomarkers is therefore intended to establish a translational paradigm rather than provide definitive causal proof; further conceptual refinement, empirical validation, and implementation research will be required before this framework can be regarded as standard clinical practice.

Finally, embedding socio-structural context into computational and analytic architectures in addiction research and clinical care has the potential to improve predictive validity, enhance algorithmic fairness, and increase contextual precision.

Keywords: Social determinants of health, Structural vulnerability, Substance use disorders, Health inequities, Translational addiction science

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Glossary of Terms

This glossary defines key conceptual terms as used in this thesis, recognizing that several constructs are employed in ways that extend or refine existing definitions within addiction and health equity research.

Biomarkers

Objectively measurable indicators of biological processes, pathogenic processes, or responses to an exposure or intervention. In this thesis, the term is extended to include social biomarkers that capture patterned exposure to structural conditions influencing health.

Health Disparities

Differences in health outcomes and access to care that are closely linked with social, economic, and environmental disadvantage, particularly among historically marginalized populations.

Health Inequities

Systematic, avoidable, and unjust differences in health outcomes that arise from structural and social arrangements rather than biological variation.

Metastructural Determinants

Upstream, historically embedded forces—such as colonialism, capitalism, globalization, climate change, displacement, and nativism—that shape social structures and downstream social determinants of health across populations and generations.

Minoritized Populations

Groups that are socially, politically, or economically marginalized through structural processes, regardless of numerical representation, resulting in disproportionate exposure to health risks and reduced access to protective resources.

Race

A socially constructed classification system used to categorize individuals and groups based on perceived physical characteristics and ancestry. In this thesis, race is conceptualized not as a biological attribute but as a social and political construct that structures differential exposure to resources, risks, and opportunities through systems such as structural racism, thereby shaping health outcomes and contributing to structural vulnerability.

Social (or Socio-) Biomarkers

Operationalized social determinants of health conceptualized as stable, measurable, and reproducible indicators of structural vulnerability that reflect disease risk, severity, course, and prognosis, analogous to traditional biological biomarkers.

Social Determinants of Health (SDOH)

The non-medical conditions in which people are born, grow, live, work, and age—including socioeconomic position, education, housing, employment, and access to health care—which significantly influence health outcomes.

Structural Racism

The architecture or configuration of historically rooted laws, public policies, institutional arrangements, and cultural norms that collectively shape and constrain opportunities along racial lines, producing patterned and durable racial inequities across multiple domains, including health.

Structural Vulnerability

An individual's or population's condition of increased risk for adverse health outcomes resulting from sustained exposure to intersecting socioeconomic, political, and cultural hierarchies that constrain agency and access to resources.

Substance Use Disorder (SUD)

A chronic, relapsing medical condition characterized by a maladaptive pattern of substance use leading to clinically significant impairment or distress, including impaired control over use, social or occupational dysfunction, risky use, tolerance, and withdrawal, as defined by established diagnostic criteria.

Systemic Racism

The pervasive, self-reinforcing operation of racial inequity through routine institutional practices, decision-making processes, and interactions across interconnected systems that, even in the absence of explicit intent, reproduce unequal outcomes for racialized groups over time, including in health.

Translational Addiction Science

An interdisciplinary approach that integrates basic, clinical, public health, and implementation research to move evidence-based addiction knowledge into equitable real-world practice and policy.

Vulnerable Populations

Groups at increased risk for poor health outcomes due to structural, social, or environmental disadvantage; in this thesis, vulnerability is conceptualized as structurally produced rather than individually inherent.

LIST OF ABBREVIATIONS

AAAP- American Academy of Addiction Psychiatry

ACES- Adverse Childhood Experiences

ACGME- Accreditation Council of Graduate Medical Education

ASAM- American Society of Addiction Medicine

AUDADIS-5- Alcohol Use Disorder and Associated Disabilities Interview Schedule-5

Bup- Buprenorphine

COD- Co-occurring Disorders

COWS- Clinical Opiate Withdrawal Scale

CSA- Controlled Substances Act

DMHAS- Department of Mental Health and Addiction Services

DSM- Diagnostic and Statistical Manual

DUD- Drug use disorder

FDA- United States Food and Drug Administration

FSA- Fair Sentencing Act

HPSO- High potency synthetic opioids

ISEL- Interpersonal Support Evaluation List

LDI- Low Dose Initiation

LMHA- Local Mental Health Authority

MAT- Medication for Addiction Treatment

MOR- Mu Opioid Receptor

MOUD- Medication for Opioid Use Disorder

NCS- National Comorbidity Survey

NESARC- National Epidemiologic Survey on Alcohol and Related Conditions

NHRVS- National Health and Resilience in Veterans Study

NIDA- National Institute on Drug Abuse

NIAAA- National Institute on Alcohol Abuse and Alcoholism

NSDUH- National Survey on Drug Use and Health

OTP- Opioid Treatment Program

OUD- Opioid use disorder

PRISMA-ScR- Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews

QOL- Quality of Life

REACH- Recognizing and Eliminating Addiction through a Culturally informed Healthcare

SAMHSA- Substance Abuse and Mental Health Administration

SDOH- Social determinants of health

SMI- Serious Mental Illness

SUD- substance use disorder

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DEDICATION

To my late father, Michael Ojo Olumuyiwa, and to his grandsons, my sons, Opeyemi and Oluwatobi.

Chapter 1

1.1 Introduction and Overview

The body of work presented in this thesis presents data at the intersection of translational addiction science, public health and social medicine. It represents a comprehensive narrative highlighting the conceptual salience of social determinants of health (SDOH) as biomarkers of structural vulnerability among minoritized people with substance use disorder (SUD). This thesis operationalizes social determinants as measurable, stable and actionable proxies of structural vulnerability, a construct that determines health outcomes, while hypothesizing biological, psychological, and social constructs as etiological pathways to structural vulnerability among minoritized people with SUD. In terms of public health significance, understanding social biomarkers may provide equitable evidence-based and tailored interventions for historically racialized and ethnically minoritized people who use drugs. This will be achieved by informing policies that advance a multidisciplinary understanding of SUD, mitigate structural vulnerabilities, thus improving health outcomes.

Statement of Research Problem

Existing frameworks inadequately account for structural vulnerability leading to persistent racial inequities in substance use disorder outcomes highlighting the failure to operationalize social and structural forces as clinically meaningful constructs. Framing social determinants of health as biomarkers capable of informing risk stratification, intervention design, or predictive modeling is clinical useful and likely to fill this existing gap. This gap constrains translational progress and undermines efforts to achieve health equity across different contexts in addiction care.

Thesis Aim:

The central aim of this thesis is to develop a conceptual framework that operationalizes SDOH as biomarkers of structural vulnerability in minoritized people with SUD and use that biomarker framing to strengthen translational addiction science—supporting risk stratification, prevention/intervention design, and equity-oriented policy/clinical systems change.

This thesis consists of twelve (12) original publications (**Table 1.1**) with direct relevance to the United States of America (US) but nonetheless, the implications are translatable to global healthcare systems. The candidate served as first author on six of the publications; six are secondary analyses of large data sets, one is a systematic review, one is qualitative research and four are invited expert reviews of current data in the field. The publications are presented sequentially in Chapters 2-4 (**Figure 1.1**): Chapter 2 is an overview of racial inequities in addiction treatment based on six publications that describe drug overdose mortality, the impact of high potency synthetic opioids (HPSO) as drivers of the fourth wave of drug-related mortality, the association between racial distress and psychopathology, systemic and structural racism as determinants of substance use, and racial disparities in diagnostic remission and disparities in the rates and correlates of SUD treatments.

Chapter 3 focuses on social determinants of health and structural vulnerability among minoritized people with SUD. Three publications are presented that address service utilization of the diverse Black sub-populations in the US, systemic racism as a determinant of substance use and a qualitative study of the challenges of medications

for opioid use disorder (MOUD) among people with SUD who are experiencing homelessness.

Chapter 4 consists of three publications that present the complexity of SUD and SUD treatments within the current US healthcare system. The papers examine co-occurring disorders (dual diagnosis), harm reduction, and the importance of public health frameworks to inform diversity in the addiction field.

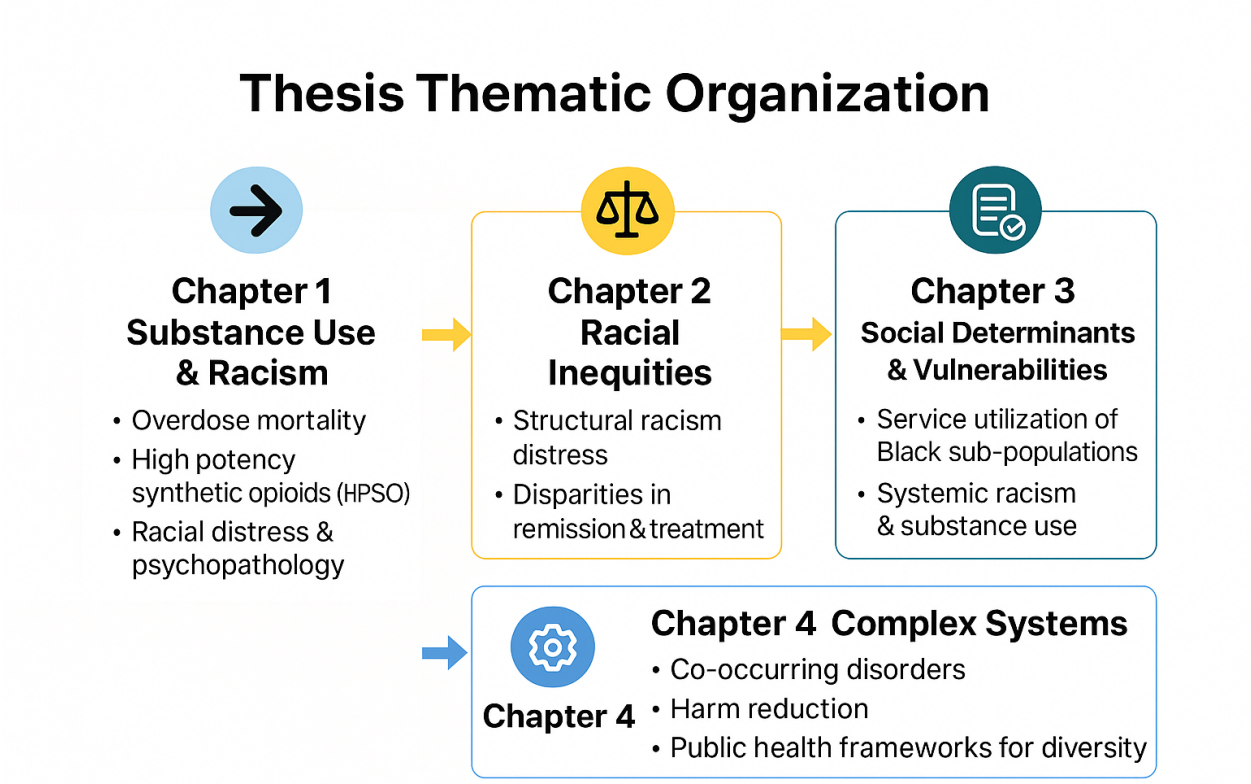


Figure 1.1: Thematic organization of the thesis. Core sections are organized in Chapters. Each Chapter begins with an overview of the published manuscripts, publication title, role and contribution of the Ph.D. candidate to each publication, broad commentary of each chapter and detailed commentary of each publication.

1.2 Candidate's Autobiographical Context:

I am an Assistant Professor of Psychiatry at Yale University School of Medicine with triple board certifications in General Psychiatry, Addiction Psychiatry and Addiction Medicine. The intersection of my academic, clinical, and research training and a lived experience as an African immigrant in the US not only informed my choice of profession and medical specialty but also provided me with the requisite background which enabled me to ask pertinent, community-driven and clinically meaningful research questions. During my psychiatry residency training, I became acutely aware of the impact of social determinants of health (SDOH) among historically minoritized people with mental illness and substance use disorder (SUD) who also struggled with homelessness, poverty, racial discrimination and a healthcare system historically designed to exclude their needs.

This experience fostered my interest in understanding more about health disparities and led me to a yearlong scholarship at the SAMHSA (Substance Abuse and Mental Health Administration)-sponsored REACH program (Recognizing and Eliminating disparities in Addiction through Culturally informed Healthcare [grant no. 5H79TI081358]). This led me to further advanced training in Addiction Psychiatry at Yale University and I have since focused my scholarly work on addiction science, health equity, and the promotion of evidence-based interventions for structurally marginalized populations with SUD. The thematic focus of my work includes examining the various dimensions of complexity that SUD presents at the individual and population levels, the social determinants of SUD, and health equity in the field of addiction science, with the aim to expand evidence-based addiction treatments for minoritized populations.

My research is rooted in addiction science, with an emphasis on health disparities in mental health outcomes, particularly among underserved populations, and explores how structural vulnerabilities—such as racial, socioeconomic, and systemic inequalities—affect access to and the quality of mental health and addiction services. I focus on identifying and addressing the barriers that marginalized groups face in seeking addiction treatment, aiming to improve the effectiveness and reach of care interventions. Through my research, I seek to develop clinical and policy solutions that promote equity in addiction and mental health services.

My academic and clinical interests have led me to examine interactions between SUD and psychiatric disorders within the ecosystem of inequitable healthcare superstructures, particularly in populations that experience higher rates of health disparities. By exploring these relationships, my research contributes to a broader understanding of how SDOH influence addiction and mental health treatment outcomes. I am particularly interested in how healthcare systems can address the unique needs of minoritized populations by developing tailored, accessible, and culturally sensitive approaches to addiction treatment.

A significant aspect of my work involves collaborating with multidisciplinary teams to advance addiction medicine and public health policies, with the goal of shaping healthcare delivery in ways that minimize health disparities. My long-term goal is to inform the development of integrated care models that address both SUD and mental health disorders, to provide comprehensive support to marginalized communities and enhance their overall quality of life. Through evidence-based research, I advocate for systemic, structural and metastructural changes that will lead to more equitable health outcomes in the field of addiction science.

1.3 Background: Substance use prevalence, determinants of health and biomarkers

There has been a global surge in substance use and substance-related disorders (SUD) over the past several years. Substance use remains a major public health concern across every racial and social demographic. Globally, 296 million people (aged 15-64) used illicit drugs in 2021 (1 in every 17 people) reflecting a 23 percent increase from 240 million people in 2011 [1]. SUD contributed an estimated 30 million years lived with disability in 2017 [2]. In the United States, latest reports in 2023, show that among individuals aged 12 or older, 70.5 million people (24.9 percent) used illicit drugs in the past year, and 48.5 million people (17.1 percent) had diagnosable SUD [3]. Despite years of research on the impact of social factors on SUD treatment outcomes in minoritized communities, adequate attention has not been placed on social determinants of substance use both in scientific literature and popular media. Emerging literature however shows social determinants as central to the etiology, treatment access, trajectory and clinical outcomes of SUD especially in minoritized populations [4-6].

The renewed interest in the social underpinnings of SUD takes place against the backdrop of the COVID-19 pandemic which exposed and amplified gross systemic and structural inequities in the US healthcare system [7] - a previously well-known fact but mostly ignored. Since 2019, a racial shift has also been observed in drug related overdose mortality, a phenomenon which has become a rallying point that further called for an urgent need to address disparities in SUD treatment [8-10]. The ongoing opioid epidemic, in its fourth wave iteration, has had its deadliest impact yet in minoritized

communities [11], with evidenced racial disparity specifically in the rise in Black population's deaths by drug overdose rapidly outpacing that of White populations. For example, Black versus White populations' drug related mortality rates increased from 7 and 6.3 per 100,000 in 1999 to 49.5 and 34.6 per 100,000 in 2022 respectively, reflecting a 1.4. increase in death rate [10].

The fourth wave (**Chapter 2 Commentary and Figure 2.1**) of the opioid overdose crisis is characterized by the rise in the combined use of high potency synthetic opioids (HPSO, e.g., fentanyl), other synthetic substances (e.g., xylazine) and psychostimulants (e.g., cocaine and methamphetamine). The fatality of polysubstance combination, in addition to structural inequities are suggested to be the main drivers of the racial disparities in mortality. HPSOs are between 500 – 10,000 times more potent than other opioids [12, 13] and have unpredictable pharmacodynamic and pharmacokinetic potentials when combined with other drugs [13].

In addition, the racial shift in overdose mortality has been shown to be related to disparities in the availability and access to life saving, evidence-based treatments for opioid use disorder (OUD), particularly buprenorphine [14] and naloxone, the overdose reversal antidote whose mechanism of action is as an opioid antagonist [15], and other harm reduction interventions (see Chapter 4 for a more in depth discussion) [16]. Social determinants of health (SDOH) are overarching upstream and downstream (see Chapter 2) factors that drive health outcomes among people with SUD. SDOH encompass the social and environmental contexts in which people are born, live, grow, and age, and continue to be defined and refined in the academic literature.

The five domains of SDOH currently recognized include: economic stability, education access and quality, healthcare access and quality, neighborhood and built

environment, and social and community context. These factors play a very important role in the development, course and trajectory of SUD processes [4]. A related construct, “structural vulnerability”, has also gained traction. It is described by Burgois and colleagues (2017) as an individual's or a population group’s condition of being at risk of negative health outcomes through their interface with socioeconomic, political and cultural/normative hierarchies [17]. Patients with SUD are structurally vulnerable when their positionality and location in societal structural and power hierarchies constrain their abilities to access addiction treatment or pursue healthy lifestyles [17, 18].

Relatedly, beyond social determinants as currently recognized and operationalized, the concept of “metastructural determinants” is considered in this thesis as an emerging concept, not to replace traditional understanding of SDOH but to capture further upstream determinants beyond social determinants. In this conceptualization, metastructural determinants exist within a 3-tiered framework that includes social and structural determinants (see **Chapter 3, Figure 3.4**). Metastructural factors include the impact of globalization [19], global warming (and climate change) [20], political systems [21], wars and human displacements [22], immigration [23]. (Please see Chapter 5)

Biomarkers (biological markers) are objective, reproducible biological indicators of an individual’s clinical state that can be utilized to diagnose, prognosticate, monitor progression of disease, assess treatment effectiveness, and identify at-risk individuals [24]. The National Institutes of Health Biomarkers Definitions Working Group defined biomarkers as “characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic

responses to a therapeutic intervention" [25]. The concept of social biomarkers or "sociomarkers" was introduced by Eun Kyong Shin and colleagues (2018) in their study of asthma, as measurable indicators of social conditions in which a patient is embedded and is exposed to, as analogous to biomarkers indicating the severity or presence of disease states [26].

In this thesis, I explore and expand the hypothesis that SDOH are stable, measurable, reproducible variables and biomarkers of structural vulnerability among people with SUD. This framework has the potential to help addiction clinicians appropriately identify vulnerability, i.e., those who are more likely to have worse health outcomes, assist in risk stratification and provide a clinically meaningful strategy for health equity, SUD prevention, and treatment.

Addiction is often described and discussed within a stigmatizing social milieu of moral failure that focuses on risk behaviors and suggests a "subtle assumption that the genesis of vulnerability and suffering is the individual and their individual choices"[27]. The body of literature presented in this thesis extends previous approaches to understanding structural vulnerability by expressing SDOH as meaningful biomarkers particularly among ethnic minoritized people with SUD.

This approach introduces a translational framework that synthesizes the candidate's research to create real-world impact, by showing benefits in clinical, community, economic, and policy domains. By framing social determinants as biomarkers of structural vulnerability, this thesis bridges existing gaps in translational addiction medicine. Beyond harnessing the candidate's body of work, this thesis engages a paradigm that integrates the social sciences into addiction science research and practice.

1.4 Substance use and substance use disorders: Developmental etiology and the addiction cycle

The spectrum from substance use to substance use disorders, and severe forms of addiction, has been the subject of much research enumerating various risk factors along the addiction continuum [28]. In addition to the neurobiological mechanism of SUD etiology (**Figure 1.2**), social factors including SDOH, adverse childhood experiences (ACES), adult trauma, structural racism and social deprivation are gaining increased recognition as determinants of SUD [29].

From a developmental perspective, experiences of trauma such as childhood trauma, maternal stress [30] and racism-based stress [31] are among factors that have been hypothesized to result in increased risk of substance use via early life changes in brain structure. A recent study utilizing the Adolescent Brain and Cognitive Development (ABCD) dataset, showed that children from higher-income families have larger and thicker frontal cortices and higher cognitive test scores compared with children from lower-income families [32].

Further, this same study found associations between demographic, socioeconomic factors, brain morphometrics, and cognition in two independent subsamples of 3,892 children [32]. The current modern biological understanding of addiction views it as a “brain disease”, contrary to the prevailing negative, stigma-perpetuating moral failure model, which is still persistent across many communities, and forms the basis of some care models [33]. The brain disease model provides a more comprehensive

understanding of addiction with the potential to reduce moral judgement and improve public health–oriented approaches to prevention and treatment [33].

A heuristic of the neurobiological perspective of addiction course [34-36] was described by George Koob (1992, 1997). The so-called addiction cycle involves three stages (**Figure 1.2**), each with specific brain circuitry and neuroadaptations. The addiction cycle includes binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages corresponding with respective neuroadaptations to increased incentive salience (the process and motivation for seeking rewards driven by learned associations about the reward cue), decreased brain reward and increased stress, and compromised executive function respectively. Further, each of these stages occur in three respective neurocircuits each corresponding to basal ganglia, extended amygdala, and prefrontal cortex [37] (**Figure 1.2**).

The description of specific neurocircuitry related to the above stages of addiction has revolutionized the field of addiction science and formed the basis for further “molecular, genetic, and neuropharmacological neuroadaptations” [38]. Individuals have been noted to transition through a continuum from controlled drug use to SUD and severe addiction following repetitive cycles of intoxication, withdrawal (including negative mood states) and craving [38].

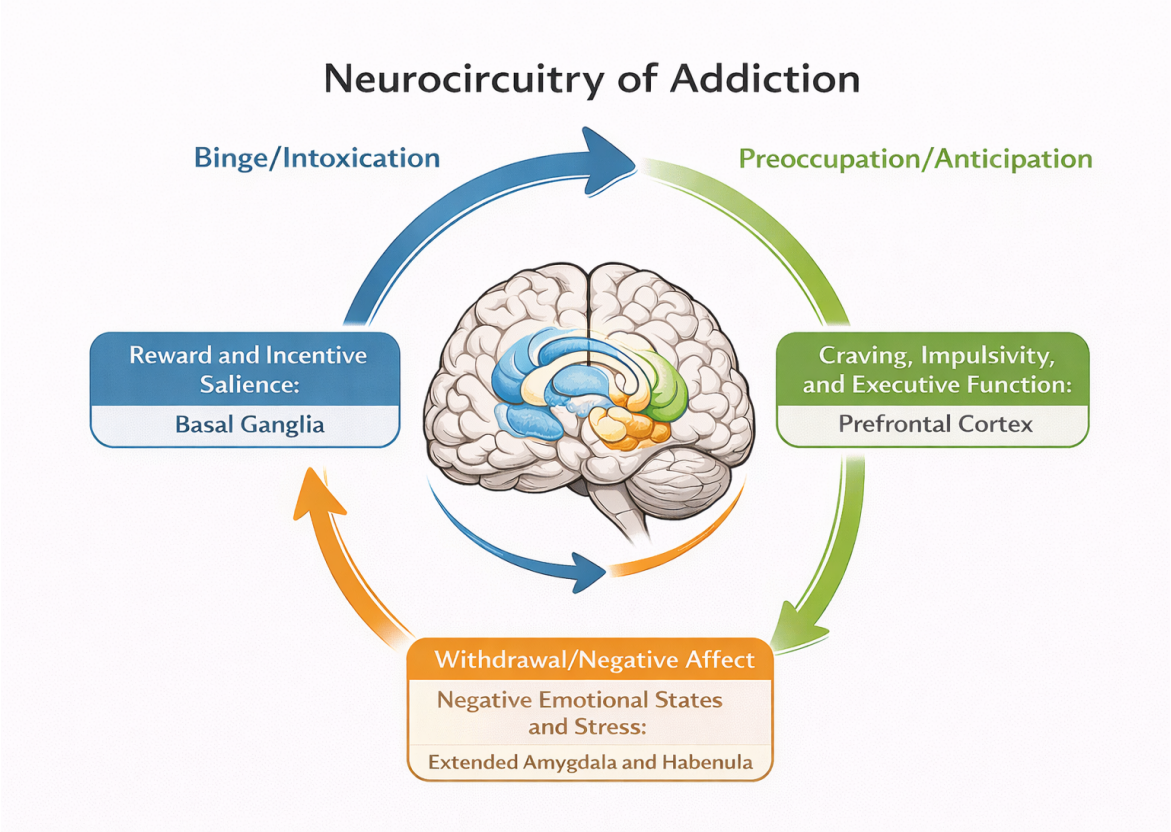


Figure 1.2 The Addiction Cycle: Neurocircuitry of addiction showing binge/intoxication (reward and incentive salience: basal ganglia), withdrawal/negative affect (negative emotional states and stress): extended amygdala and habenula), and preoccupation/anticipation (craving, impulsivity, and executive function) [39]

In the 'binge/intoxication' stage of the addiction cycle, substance use activates brain reward regions (basal ganglia including the nucleus accumbens- NAc) by large increases in dopamine and opioid peptides thus pairing the reward with the inciting stimuli. As individuals become repeatedly exposed to the reward, dopamine cells stop firing in response to the reward and instead fire to the cues of the reward (in an anticipatory response to the conditioned stimuli). Thus, environmental stimuli (people, places and things), may elicit conditioned, rapid releases of dopamine that trigger drug craving and may motivate drug seeking, drug use, and drug binges [33]. Unlike the

pattern of controlled dopamine surges from non-drug rewards like food and sex, where dopamine cells stop firing after repeated consumption, addictive drugs do not follow habituation or natural satiation and continue to directly increase dopamine levels. Repetitive, non-decremental stimulation of dopamine transmission by drugs in the NAc abnormally strengthens stimulus–drug associations [40].

The next stage in the addiction cycle is the 'withdrawal and negative affect' where addiction presents a reward deficit - a major characteristic being the shift from impulsive drug use (positive reinforcement) to compulsive use (negative reinforcement). The latter transition plays a major role in continuing substance use with patients with SUD reporting no longer using drugs for euphoria but to keep from getting sick. Thus, at this stage, people with SUD use drugs to avoid the stress inducing negative emotional state of withdrawal. Neuroadaptations in the brain of an individual with SUD result in an attenuated release of dopamine thus rendering the brain's reward system much less sensitive to stimulation by both drug-related and non–drug-related rewards [41-43]. The neurobiological regions involved in this stage include the extended amygdala comprising the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST).

Finally, the last stage of the addiction cycle, the 'preoccupation/anticipation' stage is the craving stage mediated by the prefrontal cortex. Chronic, intermittent drug use results in the downregulation of dopamine signaling reducing the individual's sensitivity to pleasure, impairing executive processes, self-regulation, self-efficacy and decision making [33]. While Koob's addiction cycle underscores the biological vulnerability for the predisposing, precipitating, and perpetuating factors for addiction, a comprehensive

understanding of addiction cannot be made without taking account of the prevailing psychosocial context.

1.5 Racist structure of drug use policies: A brief historical context

The **"**war on drugs" in the US [44, 45] highlights a racist historical policy-level discrimination of minoritized populations with SUD. President Richard Nixon named drugs as "enemy number 1" and declared the "war on drugs" in 1971, but the admission of the true intent of this so-called war on drugs showed unmistakable race-based underpinnings. In a public admission during a 1994 interview, John Ehrlichman, President Nixon's White House counsel, puts this starkly:

> *"The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did,"*

This statement leaves no doubt about the intentions and targets of the US administration's policies on drugs [46] and sets the stage for race-based discrimination and disparities evidenced in disparate health outcomes decades later. Based on this statement, it is clear that the "war on drugs" had little to do with protecting the health of the populace or even stemming the flow of drugs, but more with a desire to criminalize minoritized communities and marginalize the voting power of communities considered "political enemies" [45]. Before the Nixon era, the Harrison's Narcotic Tax Act of 1914 laid the foundation for the "war on drugs". Initially the law was designed to regulate the

import, non-medical sale, distribution and use of opium and cocaine, which were widespread, over the counter, and unregulated but later became the pillar for the “social-control” of non-Whites [47]. It is of note that the intent of this law was similar to the United Kingdom's “dangerous drugs laws” passed around the same time. However, the application of the law criminalized addiction in a way that the UK law never did, by allowing law enforcement agencies unfettered discretion to prosecute physicians who treated addiction with morphine because opioid addiction was argued to not be a medical condition but rather a moral failure (as discussed above) [44, 47]. The war on drugs led to mandatory sentencing, criminalization, and mass incarceration.

The Harrison Narcotics Tax Act created a basis for prohibition and drug-related panic that lasted into the 1960s and formed the basis for the Marihuana Tax Act of 1937, which criminalized and placed a tax on the sale of cannabis [38]. The Marihuana Tax Act was the federal government's response to political pressure from enforcement agencies and other groups who feared the use and spread of cannabis by "Mexicans" [48]. Further federal legislation for drug control led to the Controlled Substances Act (CSA) of 1970 which classified drugs into five schedules based on their potential for dependence (namely schedules I through V, with schedule V being the least likely to result in addiction).

The 1986 Anti-Drug Abuse Act established equivalent prison sentences for possession of 5 grams crack cocaine and 500 grams powder cocaine. This policy preferentially targeted Black individuals who ostensibly were more likely to use crack cocaine compared to White individuals who were more likely to use powder cocaine. Despite this being the same drug (crack cocaine versus powder cocaine), the law, which established a 1:100 differential punishment meted to Black Americans, was

overtly discriminatory and unfair, outrageously leading to an increase in Black incarcerations from 50,000 in 1980 to 400,000 in 1997 [49]. The U.S Congress passed the Fair Sentencing Act (FSA) in 2010 which amended the Controlled Substances Act and reduced the statutory penalties for crack cocaine offenses to produce an 18-to-1 crack cocaine-to-powder cocaine drug quantity ratio and eliminated the mandatory minimum sentence for simple possession of crack cocaine.

1.6 Structural vulnerability within the health equity framework

The disparities in the treatment of SUD reflect historical systemic exclusion of racial and ethnic minoritized people from access to evidence-based addiction treatments. In parallel, treatment access is limited by poor-built environment, residential segregation, and income inequality. These factors, in addition to other social determinants such as limited access to quality education, social and community context (relationships with family, friends and community members), predispose historically minoritized people with SUD to structural vulnerability [50, 51].

Structural vulnerability is a social science construct that describes the positionality and perceived positionality of individuals on a continuum of socially imposed race-based normative hierarchies. The state of being structurally vulnerable increases the risk of negative health outcomes. Public health attention to structural vulnerability involves interrogation of these factors within a health equity framework that addresses racial and sociopolitical structures as the source of vulnerability, suffering, and inequalities [51].

African-Americans are 6-10 times more likely to be incarcerated for drug offenses compared to White individuals even though the latter are no more likely to use drugs [52]. Some scholars have argued that the disproportionately higher likelihood of interaction with the criminal justice system has also resulted in a higher likelihood of SUD treatment utilization among Black African Americans. However, when the data were adjusted for criminal history and socioeconomic status, they show that the racial divide in the use of addiction services widened significantly in favor of White populations [53-55].

In addition, the ongoing epidemic of drug overdose deaths shows a racialization of medication for opioid use disorder (MOUD), particularly buprenorphine (see Chapter 2). Buprenorphine, a first line treatment for opioid use disorder (OUD), is more likely to be prescribed in White, middle class, more educated communities while methadone (another first line MOUD but with much more stringent restriction such as the need for daily dosing at federally regulated treatment programs and associated societal stigma) is more likely to be available in Black, Latinx and poorer neighborhoods [56, 57]. Although there has been an increase in the uptake of buprenorphine as MOUD prescriptions continue to rise, it has risen far less in areas where Black and Latinx people live [14, 57] and Black people with OUD are far less likely to be prescribed this life saving medication.

The reasons hypothesized for this disparity include structural factors such as systemic racism, intentional race-based marketing of buprenorphine, provider implicit bias [15, 58] as well as the limited availability of buprenorphine providers and restricted buprenorphine dispensing in these communities [59]. The strategic pharmaceutical medicalization of buprenorphine to separate it from the stigmatized methadone ended up contributing to the racialization of the medication. Buprenorphine is currently prescribed from physician's offices like other medications, whereas methadone can only be obtained from specialized clinics under very strict federal regulations [60].

Furthermore, there is a consistent denigrating popular media imagery of urban Black and Latinx "heroin" users compared to the softer, more considerate presentations of suburban White "prescription" opioid users [61]. In fact, it was not until the drug overdose epidemic reached White suburban neighborhoods that the "brain disease" model of addiction received societal acceptance, and the country consequently

witnessed a much-needed public outrage for the escalating opioid mortality and increased funding for substance use disorders diagnosis and treatment; a contrast to the punitive “war on drugs” of the 1970s and the crack cocaine epidemic of the 1980s [62].

1.7 Peer Reviewed Publications

Together, these papers establish the empirical basis for this PhD by Publication and advance a unifying question: Do social determinants of health function as measurable, reliable biomarkers of structural vulnerability in racially and ethnically minoritized populations with substance use disorders? Although SUD is a global phenomenon, the context of this thesis is the United States of America where the Ph.D. candidate is an addiction physician and researcher and where all the papers have been published. This body of work falls under the discipline of Translational Addiction Science. The citations are numbered in the order that they appear in the thesis rather than by the year of publication or any other criteria (**Table 1.1**). Chapter 2 presents the first set of six publications which address racial inequities and disparities in access to evidence-based treatments for SUD and in drug overdose mortality.

Table 1.1: Selected peer reviewed publications for thesis, titles, author position and percent contribution

WORK	TITLE	AUTHORSHIP	% CONTRIBUTION
1	Addressing Racial and Ethnic Inequities in Opioid Overdose Mortality: Strategies for Equitable Interventions and Structural Change https://link.springer.com/article/10.1007/s11920-024-01556-7	Second of Two	45
2	The Impact of High-Potency Synthetic Opioids on Pharmacotherapies for Opioid Use Disorder: A Scoping Review https://journals.lww.com/journaladdictionmedicine/abstract/2024/09000/the_impact_of_high_potency_synthetic_opioids_on.8.aspx	First (co-first author) of Seven	50
3	Association of Distress Due to Systemic Racism and Racial Disparities with Psychopathology and Suicidal Ideation Among US Veterans During the COVID-19 Pandemic https://www.psychiatrist.com/jcp/systemic-racism-and-distress-in-veterans-covid-19/	First of Five	50
4	Persistent distress related to systemic racism among Black veterans in the United States https://www.sciencedirect.com/science/article/abs/pii/S0165032724012643	Second of Five	45
5	Diagnostic remission of substance use disorders: Racial differences and correlates of remission in a nationally representative sample https://www.sciencedirect.com/science/article/abs/pii/S0740547221003858	Second of Five	45
6	Treatment of substance use disorders among black and white adults: rates, correlates, and racial discrimination https://www.tandfonline.com/doi/full/10.1080/10550887.2021.1997038	Second of Six	45
7	Psychiatric and Substance Use Disorders and Related Service Use in the Diverse Black Sub-Populations in the United States https://link.springer.com/article/10.1007/s40615-021-01163-9	First of Five	50
8	Systemic Racism as a Determinant of Health Inequities for People with Substance Use Disorder https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2814162	First of three	70
9	Access challenges to opioid use disorder treatment among individuals experiencing homelessness: Voices from the streets https://www.sciencedirect.com/science/article/pii/S2949875923002679	Fourth of Seven	30
10	Rates and correlates of dual diagnosis among adults with psychiatric and substance use disorders in a nationally representative U.S sample https://www.sciencedirect.com/science/article/abs/pii/S0165178122003158	First of Five	50
11	What Would Equitable Harm Reduction Look Like? https://journalofethics.ama-assn.org/article/what-would-equitable-harm-reduction-look/2024-07	First of Five	60

12	Building outreach and diversity in the field of addictions https://onlinelibrary.wiley.com/doi/full/10.1111/ajad.13097	Second of Two	70

Chapter 2 : Inequities and disparities in the field of addictions

2.1 Publications: Titles and Contributor Roles

Publication 1: Addressing Racial and Ethnic Inequities in Opioid Overdose Mortality: Strategies for Equitable Interventions and Structural Change

Contribution to the publication: Conceptualization, Investigation; Data Curation; Writing – Original Draft; Writing- review and editing, Visualization, Project Administration.

Publication 2: The Impact of High-Potency Synthetic Opioids on Pharmacotherapies for Opioid Use Disorder: A Scoping Review.

Contribution to the publication: Conceptualization, Data curation, Formal analysis, Methodology, Data Curation; Writing – Original Draft; Writing- review and editing, Visualization; Supervision, Project Administration.

Publication 3: Association of Distress Due to Systemic Racism and Racial Disparities with Psychopathology and Suicidal Ideation Among US Veterans During the COVID-19 Pandemic.

Contribution to the publication: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Original Draft; Visualization; Project Administration; Supervision.

Publication 4: Persistent distress related to systemic racism among Black veterans in the United States.

Contribution to the publication: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Original Draft; Visualization; Project Administration; Supervision.

Publication 5: Diagnostic remission of substance use disorders: Racial differences and correlates of remission in a nationally representative sample.

Contribution to the publication: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Review and editing; Visualization; Project Administration.

Publication 6: Treatment of substance use disorders among Black and white adults: rates, correlates, and racial discrimination.

Contribution to the publication: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Review and editing; Visualization; Project Administration.

2.2. Chapter 2 Commentary

The set of publications in this section addresses racial inequities in access to evidence-based treatments for SUD, and in drug overdose mortality. The trajectory of the opioid mortality in the US since 1999 shows unique trends or waves in terms of the peaks in mortality. Each of the identified waves **(Figure 2.1)** represents the dominance of specific drugs as well as racial shifts in mortality rates. Starting in the 1990s, the first wave of opioid overdose deaths was characterized by the rise in non-medical use of prescription opioids. During this wave, the use of hydrocodone and oxycodone rose to unprecedented levels with the opioid pain prescription-related overdose death rate nearly quadrupling [63, 64].

As noted by Kolodny et al. (2015), there was a 900% increase in individuals seeking treatment for addiction to prescription opioid medications in the period between 1997 to 2011, reflecting a strong correlation between opioid sales, overdose deaths, and treatment seeking for opioid addiction around this time frame [65]. Specific supply and demand factors responsible for this wave of opioid overdose mortality include the initial push by the pharmaceutical industry, and healthcare system (including professional medical organizations), to recognize pain as a distinct fifth vital sign, making pain measurement and documentation mandatory for every clinical encounter. This practice established pain-based incentives for hospital systems and physician practices. Thus, this was an iatrogenic wave from unfettered opioid pain prescriptions [66-69].

There was also the aggressive yet misleading pharmaceutical marketing of extended-release formulations of opioid pain medications as a “technological revolution”, that precluded the known addictive potentials of opioids [70]. Further, other

literature has also cited an aging population with increased pain-related somatic symptomatology as a possible factor, highlighting the role of opioids as a necessary panacea for trauma, disadvantage, social isolation, hopelessness and psychological distress especially among the aging population [71].

Unexpectedly, this wave presented an inadvertent outcome of mortality concentrated among White, upper middle-class Americans, who were seen by prescribers as less prone to drug dependence or drug diversion (transfer from prescribed medical use to a range of non-medical, illegal and illicit purposes including selling for profit or giving to others to whom it was not prescribed) [72, 73]. The consequence of higher mortality rates in White communities also reflect racial disparities in the diagnosis and optimal treatment of pain among minoritized Americans particularly Black/African Americans [74].

The second wave of opioid-related overdose mortality began around 2010 with the surge in heroin use. At this time, opioid related deaths had already become a major public health crisis. Owing to public outcry, the public health response was to control opioid prescribing by physicians and enforce a mechanistic refinement of the extended-release opioid pain medications to create tamper-proof formulations which are less likely to be converted to non-prescribed use [70]. For example, extended-release medications started to be manufactured in a way that made them less likely to be crushed for inhalation, dissolved for intravenous injection or otherwise physically or chemically altered compared to standard immediate release formulations. These changes resulted in a limited supply and higher costs of prescription opioid medications, but the unexpected consequence was that heroin, an illicit opioid, became much more appealing and a necessary choice for individuals who at this time were already

dependent on prescription opioids [75]. Heroin therefore became the drug of the second wave of opioid overdose mortality.

The third wave of the opioid-related overdose epidemic began around 2013 with the rise in contamination of community drug supplies by high potency synthetic opioids (HPSO, fentanyl and fentanyl analogs) [76]. Specifically, the third wave revealed a change in the patterns of drug use from heroin to high potency synthetic opioids (HPSO) particularly fentanyl (further details on fentanyl and fentanyl analogs are presented below in **section 2.2.2 and Figure 2.2**). The emergence of HPSO compounds sent major shock waves throughout community drug markets as fentanyl quickly replaced other forms of opioids due mainly to its incredible potency, intense rewarding effects, extremely cheap cost and ease of production. In addition, fentanyl's lethality and unprecedented overdose risk has been worsened by the contamination of products (such as cocaine and methamphetamine) for use by individuals with relatively poor tolerance to opioids as they may be unaware of the composition of the drugs they use [77].

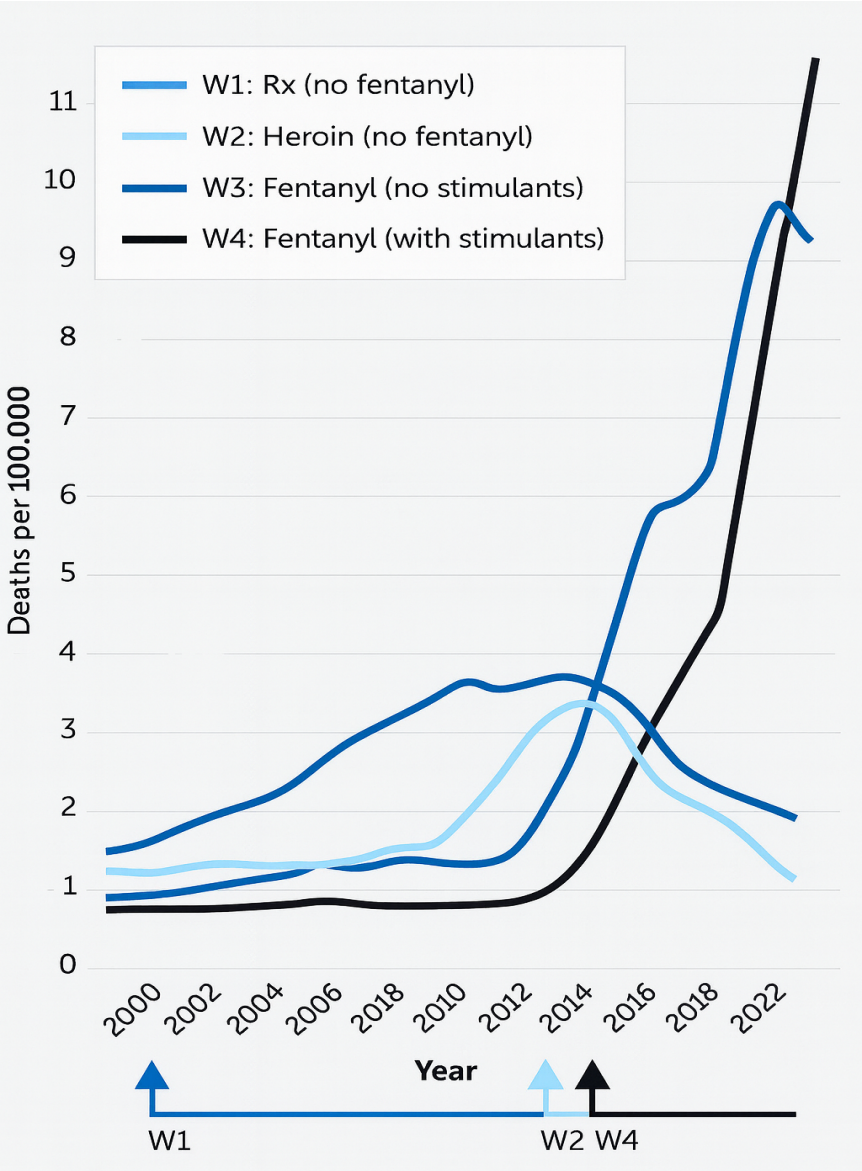


Figure 2.1: A simplified representation of the four waves of the United States overdose mortality crisis.

W- waves; W1-prescription opioids; W2-heroin opioids; W3-fentanyl and fentanyl analogs; W4- fentanyl and stimulants.

Courtey: Friedman et. al, 2024 [10]

The fourth and currently ongoing wave of the opioid overdose epidemic began around 2021 and is characterized by the co-use of stimulants (cocaine and methamphetamine) and HPSO (fentanyl and related analogs). Although the cocaine-fentanyl co-use dates back to the 1970s, this current wave is mostly dominated by methamphetamine-fentanyl co-use [70] in some regions of the US. This has led to the rapid and marked escalation of mortality initially due to the poor tolerance in primary stimulant users who use contaminated drug supplies, but also due to major structural and systemic issues (**see Chapter 3**).

Most of the available fentanyl used in the initial period of this wave was due to contamination and unintentional use. However, in the succeeding years and at the time of writing this thesis, most people with opioid use disorder (OUD) are intentional fentanyl users with more severe addiction patterns, increased overdose risk, higher burden of social challenges [78, 79], and medical comorbidities such as infectious diseases [70, 80, 81] and chronic wounds/ulcers, especially when used in combination with other synthetic drugs such as xylazine [82-84].

Xylazine (street name “tranq”, is a methyl benzene (1,3-dimethylbenzene), which is substituted by a 5,6-dihydro-4H-1,3-thiazin-2-ylnitrilo group at position 2 (**Figure 2.2**). It is also a clonidine analog, which acts as an agonist at α2 adrenoceptors. Xylazine has no Food and Drug Administration (FDA) approved indications in humans, it is a non-opioid large animal tranquilizer (*anestesia de caballo*), emetic and sedative agent, with analgesic and muscle relaxant properties [85] .

Notwithstanding its non-approval for human use, xylazine has emerged as a major component of this wave. The routes of xylazine administration are via injection (84.5%), inhalation (14%) and more than 40% in a mixture with “speedball” (combination with

cocaine) [85]. Human xylazine use was first reported in Puerto Rico among people who inject drugs (PWID) in the 2010s, but current data show that xylazine-related mortality has continued to increase across the northeastern states [86]. An ecological clustering of xylazine and fentanyl has also been recognized [85, 86]. The use of xylazine in fentanyl drug supplies is in part explained by the fact that xylazine can prolong the euphoric effects of fentanyl (i.e., “xylazine gives fentanyl legs”)[86]. Even more concerning is that overdose deaths linked to the co-use of xylazine and fentanyl frequently involved other substances, including cocaine, heroin, benzodiazepines, alcohol, gabapentin, methadone, and prescription opioids [86]. The historical basis and trends of opioid overdose mortality, set the stage for understanding and addressing inequities in overdose mortality and evidence-based treatments.

2.2.1 Addressing Racial and Ethnic Inequities in Opioid Overdose Mortality: Strategies for Equitable Interventions and Structural Change [12] (Publication 1)

Publication 1 is a solicited expert opinion and recognition of the candidate's expertise as an addiction health equity clinician-researcher. This was a review of extant literature that synthesized up to date data on the worsening racial and ethnic inequities in OUD treatment, opioid overdose mortality. It presented strategies for intervention based on an equity framework while advocating for structural change. In the context of the escalating opioid crisis, as of 2021, more Americans had died from drug overdoses than from both vehicle accidents and firearms combined (drug overdose deaths: 106,699; motor vehicle deaths: 42,939 and firearm deaths: 48,830) [87, 88].

Publication 1 provided a contextual understanding of the inequitable burden of OUD and proposed specific strategies that may be deployed to address these inequities. These included expanding and implementing cultural adaptation of evidence-based interventions, integrating social determinants frameworks into addiction treatment, implementing an anti-racism praxis in addiction research, diversifying the addiction workforce, and integrating structural competency into medical education and practice.

As described above (section 2.1), the US is in the fourth wave of the opioid related overdose crisis characterized by co-use of stimulants, fentanyl and other synthetic compounds. As at the time of writing, there is a recognized racial shift in overdose patterns [9, 10, 89-92] with deaths among White Americans continuing a downward trend compared to rates among other racial groups which have continued to rise

unabated **(Table 2.1).**The highest overdose mortality rates are observed among Black Americans 55-64 years of age and Native Americans 25-44 years of age [10, 93].

Table 2.1: Trend of drug-related overdose mortality rates (per 100,000 population) by specific years [10]

Year	Mortality / 100,000 population		
	Black	**White**	**Native American**
1999	7.0	6.3	5.8
2010	7.9	15.9	16.4
2022	49.5	34.6	62.9

A critical focus of this paper was the disparities in access to medication for opioid use disorder (MOUD) treatment. Convergent data showed that minoritized people with OUD are less likely to be prescribed buprenorphine, a first line treatment for OUD with advantages over methadone (another first line treatment for OUD), due to the structures around administration and federal regulatory oversight. There remains a significant stigma around methadone despite it being possibly the most federally regulated medication in the US [94].

The stigmatization of methadone reflects a community misconception as a “drug that merely replaces another drug”, and a historical identification as a “tool for crime control”. These stigmatizing sentiments reflect the attitude at the FDA at the time of its approval for opioid use disorder (OUD) [95] and the consequent strict federal regulations around methadone prescription and dispensing. Methadone for OUD remains one of the most regulated medications in the US, as it is still only available in opioid treatment programs (OTP) and patients with OUD must meet strict criteria to obtain take-home bottles. Buprenorphine, on the other hand has been “medicalized” since its FDA approval and is available by prescription from physicians’ offices without the strict regulations placed on methadone. This may explain why methadone remains highly stigmatized and regarded as a tool of “social control” in some Black communities [96, 97].

This hypothesis is supported by Lagisetty and colleagues’ (2019) study which, using data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from 2004-2015, showed distinct disparities in buprenorphine prescriptions by race/ethnicity and payment [14]. The study found that buprenorphine treatment was concentrated among White individuals, those with private

insurance and those who can pay cash for services (self-pay). By contrast, Black individuals with OUD had significantly lower odds of receiving buprenorphine at each clinic visit, even after adjusting for payment method, sex and age (aOR, 0.23; 95% CI, 0.13-0.44) [14].

This trend has been consistent with existing literature. In a recent study of Medicare data claims, Barnett and colleagues' (2023) results showed racial disparities in buprenorphine receipt in the 180 days after index events; for example, only 12.7% of Black individuals received buprenorphine post-event compared to 18.7% of Hispanic and 23.3% of White individuals respectively. In the same study, naloxone prescriptions patterns were also disparate showing that only 14.4% Black individuals received naloxone prescriptions compared to 20.7% Hispanic and 22.9% White individuals respectively). Of note is that the frequency of ambulatory clinic visits was comparable across racial groups (mean number of visits, 6.6, 6.7 and 7.6 days for Black, Hispanic and White individuals respectively) [15]. The results of this study provided further insight into the inequity of access to care, uncovering the premise that even when access to care was consistent across racial/ethnic groups, inequities in access to evidence-based treatment persisted.

The reason for persistent inequities even when populations have similar ostensible access to healthcare may be explained by Phelan and Link's Theory of Fundamental causes [98] which posits that in unequal societies, new treatments and technologies further widen inequities as privileged populations invariably benefit more than socially disadvantaged groups [10, 98]. This case was made in Publication 1 and described by the author in another publication [16]. This theory is further discussed in Chapter 4 in Publication 11, describing social determinants of health (SDOH)-neutral

harm reduction services as perpetuating inequities, leading to the proposition that integrating SDOH frameworks into available harm reduction programing might be a possible way to improve health equity.

Publication 1 also highlighted the importance of cultural adaptation of evidence-based interventions within an equity-based framework as another strategy to address inequities. Cultural adaptation is the systematic modification of evidence-based interventions in terms of language, culture, and context that is compatible with a population's or group's cultural patterns, cultural meanings, and values [99]. Studies show that existing evidence-based interventions may have limited efficacy when not appropriately tailored to specific populations and that cultural adaptation may improve clinical outcomes [100-103].

An example of a cultural adaptation of addiction treatment tailored to Black and Latinx communities, is the IMANI program in New Haven, Connecticut which, using the salience of religion and spirituality evidence-based SUD treatment, is culturally adapted to these communities. The adaptation resulted in improved treatment outcomes and improved quality of life, with a significant increase in both citizenship scores and wellness within the occupational, intellectual, financial, and personal responsibility dimensions [104, 105].

Publication 1 also discussed structural competency as a tool to inform addiction education. Metzl and Hansen's (2014) seminal work on structural competency in medical education emphasized a "structural" focus on health outcomes at the population level [106]. While traditional education of healthcare providers has often emphasized biological determinants of disease processes, social causes have been neglected [106]. Structural competency represents a shift in medical education from traditional

pedagogical approaches to a focus on the multilevel social, structural, and cultural factors that shape patient presentations [106]. It emphasizes the importance of addressing both individual and population-level health outcomes.

Finally, Publication 1 articulated that structural change must center antiracism in the conceptualization, execution, dissemination and translation of addiction research [107]. Employing the antiracist lens in the early stages of developing research questions is critical while interrogating the needs of communities and seeking to ethically engage populations [107]. The theoretical framework of antiracism is based on the understanding of racism as a modifiable construct, while noting that antiracism is not (a finite) an outcome but a process, a set of practices that must be incorporated into research and clinical practice. This operationalization moves addiction research from just documenting racial inequities to a set of practical and clinical imperatives and actions.

A useful pedagogical model of antiracism for addiction science research must include identifying and measuring racism, addressing racialized power dynamics that exclude centering the margins, and acknowledging the social construction of knowledge [108]. Came and Griffith (2018) outlined five core components of an antiracism praxis to include: reflexive relational praxis, structural power analysis, socio-political education, monitoring and evaluation and systems change approaches [109].

Other aspects of structural change presented in Publication 1 are discussed in more detail in other areas of this thesis including social determinants in harm reduction programing (Publication 11) and improving diversity in the addiction workforce (Publication 12).

2.2.2 High Potency Synthetic Opioids (HPSO) and pharmacotherapies for opioid use disorder (Publication 2) [13]

While Publication 2 does not directly address inequities in addiction treatment, it sets the stage for an in-depth introduction and discussion of the current wave of the opioid overdose epidemic, by describing nuanced but critical issues around the changing landscape of opioids use, opioid related mortality, polysubstance use and OUD treatment. To the best of the candidate's knowledge, Publication 2 is the first systematic synthesis of observational evidence regarding the impact of high potency synthetic opioids (HPSO) on clinical outcomes for individuals with OUD. As described before (section 2.1), the fourth wave of opioid overdose mortality is driven by the co-use of psychostimulants (e.g., cocaine) and HPSO (fentanyl and fentanyl analogs, **Figure 2.2**).

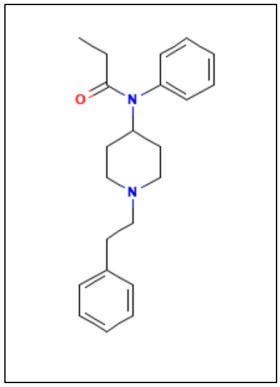
Medications for opioid use disorder (MOUD) including methadone, naltrexone and buprenorphine were all approved by the United States Food and Drug Administration (FDA) for OUD, long before the emergence of HPSO in community drug markets, in 1972, 1984 and 2002 respectively. With community supplies being recently overtaken by fentanyl and fentanyl analogs, anecdotal, clinical evidence and emerging literature have shown that traditional MOUDs may retain their effectiveness in the treatment of these emergent synthetic opioids that can be up to 10,000 times more potent than morphine, albeit at higher medication doses [110].

Fentanyl is a synthetic opioid synthesized in the 1960s from the meperidine molecule with better bioavailability (a measure of the rate and fraction of the initial dose of a drug that successfully reaches the site of action), lipophilicity (a measure of a drug's

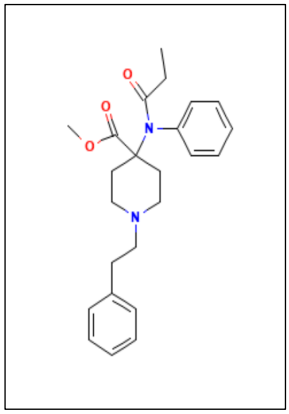
affinity or tendency to dissolve in lipids, fats, and other non-polar solvents) and improved potency than earlier opioids [111]. Fentanyl was approved as an intravenous short-term anesthetic in 1968, categorized as a Schedule II substance by the United States Controlled Substances Act.

Although fentanyl is made through a relatively simple process, its analogs, which are even much more potent, are made by simple tweaks to the parent fentanyl compound [112]. For example, carfentanil can be made by attaching a small C-O-C tail to the original fentanyl compound thus creating a chemical 10,000 times more potent than morphine when the original fentanyl is only 100 times more potent (**Figure 2.2**) [113]. The ease and cost effectiveness of producing synthetic opioids in relatively commonplace, unsophisticated conditions amounts to only $3,500 for 1 kg of fentanyl compared to $65,000 for 1 kg of heroin is one reason that accounts for its persistence as the new community drug [114].

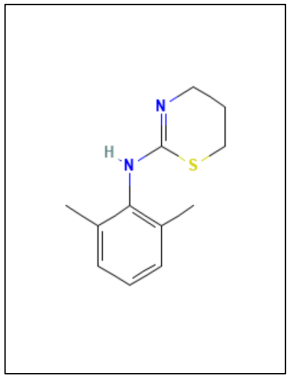
Since its approval for medical use in the 1960s, fentanyl has made occasional uptick emergence in community drug supplies, known as *China White* in the 1980s as a combination with heroin, and later as *drop-dead* and *lethal injection* in the early 2000s [115]; but not until 2013 did it really take off as the major culprit for drug related deaths in the US. According to the latest reports, fentanyl is responsible for about 70% of all drug-related mortality [116]. In addition to fentanyl, other synthetic opioids, such as nitazenes, and the veterinary sedative, alpha 2 agonist, xylazine (which supposedly prolongs the effect of fentanyl) have increased the harms associated with fentanyl [8] including festering ulcers and amputations.



A. Fentanyl



B. Carfentanil



C. Xylazine

Figure 2.2: Chemical structures of A. fentanyl; B. carfentanil with attached C-O-C tail to the original fentanyl compound; and C. xylazine

Publication 2 was conceptualized through the candidate's clinical experience as a community Addiction Psychiatrist during the COVID-19 pandemic on the front line of addiction treatment during a particularly troubling period of escalating overdose deaths, and the intersection of social determinants and substance use disorders (SUD). The study was designed to investigate the effectiveness of known MOUDs (buprenorphine and methadone) given the changing climate of the ultrapotent fentanyl and fentanyl analogs.

The study addressed this question systematically using the scoping review methodology in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta Analysis Extension for Scoping Reviews) [117]. The study protocol identified 9,150 records from various databases (MEDLINE, EMBASE, PsycINFO, Web of Science, CINAHL, and Cochrane), from which only 34 publications met the final selection criteria. The results showed a remarkable paucity of data on the effectiveness of known MOUDs in the context of fentanyl, as the literature reviewed was mostly observational. Nevertheless, Publication 2 represents a critical addition to the literature that clarifies the utility of available MOUDs in the era of fentanyl, and discusses methodological, mechanistic, and clinical implications as well as extensive recommendations for future research areas.

One important contribution of Publication 2 to the literature is the examination of methods for the initiation of buprenorphine in patients with OUD exposed to fentanyl. Buprenorphine, like methadone and naltrexone, is a medication approved by the United States FDA for the treatment of OUD. Buprenorphine is a partial opioid agonist whereas methadone is a full opioid agonist, and naltrexone an opioid antagonist. However,

buprenorphine has an advantage over methadone in that it does not carry the stigma and strict federal regulations imposed on methadone. Based on the complex pharmacology of buprenorphine as a partial agonist at mu-opioid receptors (MOR), it is clinically required that before starting a patient on buprenorphine, they must present current symptoms of mild to moderate opioid withdrawal (Clinical Opiate Withdrawal Scale, COWS of at least 5 but usually 8). However, this requirement poses a significant barrier to treatment access, particularly for individuals exposed to fentanyl. Owing to fentanyl's delayed excretion patterns and prolonged presence in the body, these individuals often take much longer than a few days to reach the necessary withdrawal state to be prescribed buprenorphine. As a result, they face an increased risk of treatment dropout and precipitated withdrawal (see below).

In addition, despite being a partial agonist, buprenorphine has a very high affinity for the mu-opioid receptor, compared to other opioids including fentanyl, thus exposure to buprenorphine in the presence of a full agonist opioid results in the immediate displacement of the latter and an opioid withdrawal state ensues. In other words, an individual taking any full agonist opioid (such as heroin, oxycodone or fentanyl) may likely experience a withdrawal state if exposed to a partial agonist such as buprenorphine - a phenomenon referred to as precipitated withdrawal. The likelihood of precipitated withdrawal is well known among opioid users and creates an aversion to initiating buprenorphine treatment [118].

In response to this challenge in treatment initiation, Publication 2 presents evidence that buprenorphine and other MOUDs remain first-line medications in the treatment of people with OUD even when exposed to fentanyl. The study highlighted an innovative method of buprenorphine initiation, Low Dose Initiation (LDI or buprenorphine

microdosing), a method that avoids the precipitation of opioid withdrawal in those who may have recently used fentanyl, precluding the clinical need to wait for the individual to present with mild to moderate symptoms of opioid withdrawal, which may involve an extended wait period in those exposed to fentanyl. As shown in **Table 2.2***,* LDI is emerging as a recognized buprenorphine induction protocol, however, there is currently no clear clinical consensus or guideline for it.

Publication 2 outlined three methodologies that address LDI in people exposed to fentanyl including: 1.) Standard LDI [119-122], 2.) Rapid LDI [123] and 3.) Ultra-rapid LDI [124]. Buprenorphine micro-induction (LDI) utilizes the novel pharmacology of buprenorphine including its partial agonism at the mu-opioid receptor (MOR), receptor dose dependent activity, affinity and slow dissociation from the MOR. Mechanistically, LDI involves a gradual escalation of small doses of buprenorphine, in the presence of full agonist opioid until reaching a full dose of buprenorphine within about 5-7 days. Research shows that the gradual escalation keeps concentration below the threshold required to displace the full opioid agonists that would precipitate any withdrawal. Therefore, the individual would not go through withdrawal in the process. In Standard LDI protocol, buprenorphine doses are escalated in multiples of 0.5 mg until a stable maintenance dose is reached and the full agonist opioid discontinued [118, 121]. Both the rapid/ultra rapid methods are variations of the standard LDI with a more rapid escalation till reaching therapeutic doses (see **Table 2.2**).

The results of Publication 2 showed that fentanyl exposure remained high among people with OUD on active methadone treatment, up to 80% (range: 38-80%). However, the literature on the impact of fentanyl positivity on treatment entry suggests minimal to no impact on long term retention [125-127]. There appears to be a consensus though,

that higher maintenance doses of buprenorphine and methadone increase treatment retention and other clinical outcomes [128].

Of particular interest in the burgeoning literature is the protective capacity of MOUD. For example, one longitudinal follow-up study from a single methadone maintenance program, showed the safety and protective capacity of methadone against opioid overdose and mortality even among individuals who continue to be exposed to fentanyl [129, 130]. The same holds true for buprenorphine with convergent literature showing its life saving properties in people with OUD [125, 131]. This is further demonstrated in preclinical studies showing that in the presence of buprenorphine, fentanyl is unable to activate enough MOR receptors to result in overdose [132], and when compared to no exposure to treatment, being treated with methadone or buprenorphine reduced the relative risk of overdose mortality by 38% and 34% respectively [133].

Finally, Publication 2 showed a significant gap in human experimental data on the impact of high potency synthetic opioids on critical parameters related to treating OUD such as cravings, withdrawal symptoms, and pain management. This publication also discussed the methodological, clinical and mechanistic implications to guide future observational and experimental research [13].

Table 2.2: *Low-dose* Buprenorphine induction protocols in patients with HPSO-OUD*

Study reference	Protocol Description	Duration of induction (days)	COWS on induction	Type of protocol
Brar et al, 2020 [119]	D1 - 0.5mg x1; D2 -0.5 BID; D3 - 1 BID; D4 - 2 BID; D5 - 3 BID; D6 - 4 BID; D7 -12mg x1; D8 variable.	8	NA	Standard
Antoine et al, 2021 [120]	Patient 1 Bup 2 mg at time 0 and additional 2 mg at 100, 220 and 368 minutes Patient 2: Bup 2 mg at time 0 and additional 2 mg at 85, 160 and 190 minutes	NA	13	Standard
Kaliamurthy et al, 2022 [121]	D1- 0.5 mg daily; D2- 0.5 mg Bid; D3-1mg BID; D4- 2mg BID 2mg TID; D5- 4mg BID; D6- 8mg BID D7- 16 mg daily	7-10	0	Standard
Shearer et al 2022 [122]	2 mg Bup induced PW in all 3 patients	Incomplete	13, 19 and 14 respectively	Standard
Suen L et al, 2022 [123]	D1-0.5 mg Bup q6 hours (total dose 2 mg) D2-1 mg Bup every 6 hours (total dose 4 mg) D3-2 mg Bup every 6 hours (total dose 8 mg) D4-12 mg Bup	3	NA	Rapid
Azar et al, 2023 [124]	Patient 1- Bup 0.5 -1 mg q3h, then given 12 mg at hour 24 for cumulative 18.5 mg within 24 hours. Over next 24hr, received total 32 mg. Discharged on Bup 20 mg. Patient 2: Bup 0.5 q1h and 4mg at hour 5 for total 7.75 mg within 6 hours. Over next 24hr, received total 32 mg, on day 3 received total 16 mg, discharged on 12 mg BID.	1	3 and 7 respectively	Ultra-Rapid

HPSO- High potency synthetic opioids; OUD- opioid use disorder; COWS- clinical opiate withdrawal scale; D-day; Bup- Buprenorphine; q-every (e.g. q2h-every 2 hours); BID- twice daily.
*Table 3 is not in original publication

2.2.3 COVID-19 and the syndemic of inequities (Publication 3) [134]

The syndemics model was introduced in the 1990s by medical anthropologist, Merrill Singer, who applied the construct to describe the intersection of substance use, violence, and Acquired Immune Deficiency syndrome (AIDS) which at the time, had just become prevalent in the city of Hartford, Connecticut [135]. Syndemics describe the intersection of two or more disease states that interact with each other, in a way that mutually and negatively affects the trajectory of each component disease, exacerbating inequities, social determinants and exponentially enhancing the vulnerability of impacted individuals [136]. Put differently, it is the co-occurrence of two or more disease states in a population in which there exists an interface (biological or behavioral), that mutually exacerbates the negative health effects of the diseases [137].

The COVID-19 pandemic was a watershed moment for health equity researchers as the period underscored a *syndemic of inequities* in minoritized communities. The period presented a “naturalistic experiment” that tasked healthcare systems like never before in modern times and exposed a weakness that had long been noted by equity researchers- the unequal healthcare system in the US. At the time of Publication 3, there were no known studies that examined the prevalence and mental health impact of distress resulting from the intersection of systemic racism and the COVID-19 pandemic [134]. Publication 3 utilized a national representative dataset of US veterans, National Health and Resilience in Veterans Study (NHRVS) to examine: 1) The prevalence of perceived systemic racism and racial disparities in COVID-19 related outcomes and 2) The association of racism-related stress with internalizing and externalizing psychopathology (including alcohol and drug use disorders) and suicidal ideation. Over

4,000 military veterans completed an initial survey (T0) and later 3,078 veterans (75.6%) completed the questionnaire at 12 months follow up (T1). Specifically, the following 2 questions were asked to assess distress related to systemic racism and COVID-19 health disparities:

1. *To what extent have you felt emotionally affected or distressed by systemic racism highlighted by recent events across the country?*
2. *To what extent have you felt emotionally affected or distressed by the racial disparities in COVID-19–related health outcomes?*"

Both items were rated on a 5-point scale from "*not at all*" (1) to "*extremely*" (5). A score of 3 ("moderately") or above was operationalized as a positive endorsement for both items. The reported burden of distress was highest among Black veterans with 73.5% feeling distressed about systemic racism and 60.2% reporting racial disparities in COVID-19 related health outcomes **(Figure 2.3)** compared to other racial/ethnic groups.

Further, multivariable logistic regression analyses revealed that distress related to systemic racism was independently associated with SUD (positive screens for alcohol or drug use disorder, OR 1.17, 95% CI 1.03-1.33) and suicidal ideation (OR 1,29, 95% CI 1.07-1.55). Publication 3 demonstrated a clinical need for a more robust assessment of emotional distress related to systemic racism and racial disparities of health outcomes, especially the addiction related burden of such disparities. The next featured publication (Publication 4) extended these results by establishing a longitudinal relationship between systemic racism and persistent emotional distress.

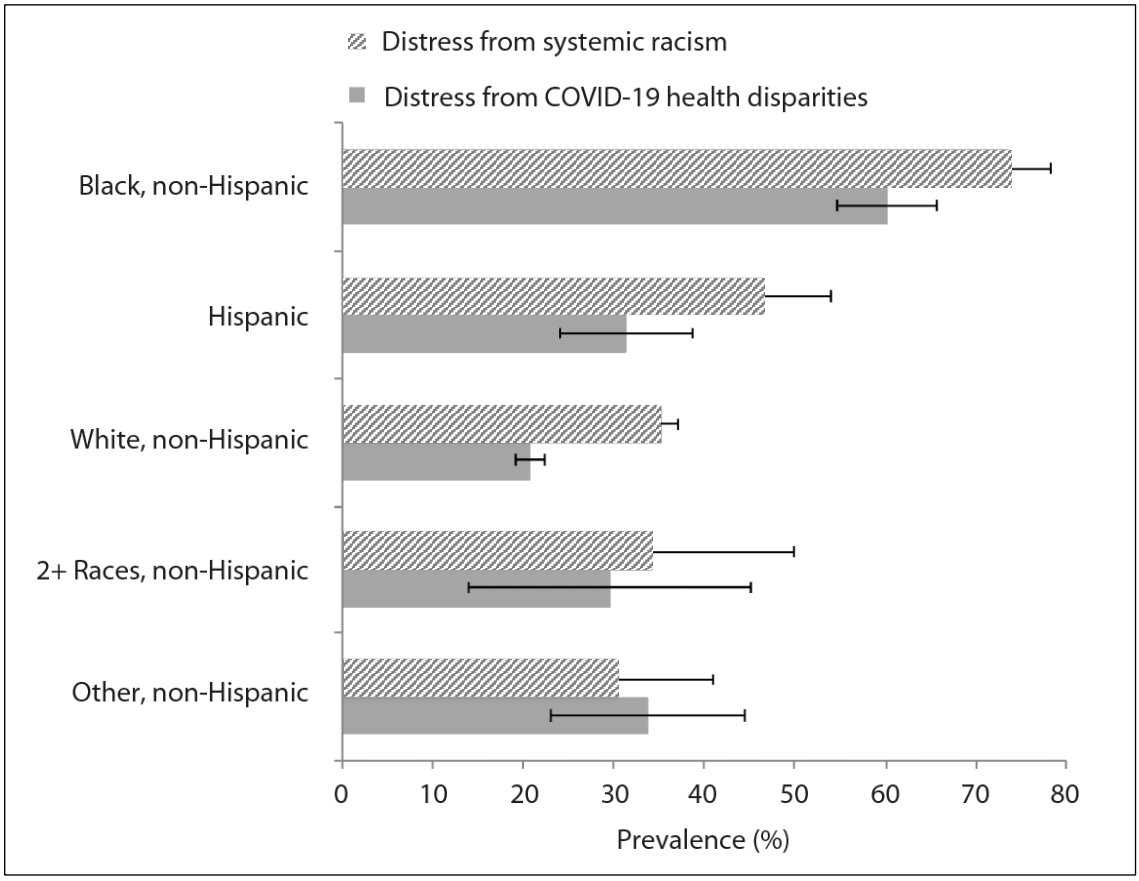


Figure 2.3: Prevalence of distress related to systemic racism and COVID-19 health disparities across racial/ethnic groups (Jegede et al, 2022) [134]

2.2.4 Systemic racism is related to persistent distress and SUD (Publication 4) [138]

Race-based stress is gaining prominence as a determinant of health among minoritized people with SUD. This is a recurrent theme across the publications presented in this thesis and the foundation for both Publication 3 and Publication 4. In the United States, Black people have been shown to experience unique stressors [31, 139]. In fact, a laboratory-based study showed that personalized imageries of race-based stressors increase alcohol cravings among this population [140]. The impact of race-based distress (particularly around the COVID-19 pandemic) associated with SUD has been reported in previous literature [141, 142].

This evidence points to the importance of acknowledging that race-based stressors impact the effectiveness of evidence-based treatments specifically tailored towards minoritized populations with SUD. Publication 4 extended the results from Publication 3 by providing a longitudinal examination of persistent race-based emotional distress. To the best of the candidate's knowledge at the time of writing Publication 4, it was the first study to provide evidence of this relationship using a longitudinal design rather than the usual cross-sectional study designs from previous literature [143]. While Publication 3, using a cross-sectional design, provided a snap-shot observation of race-based distress, Publication 4 provided more in-depth evidence of the persistence of the findings from Publication 3.

A total of 2,361 US veterans participated in the 2-year study as part of the NHRVS. The study was divided into two phases. Phase 1 took place during the COVID-19 surge (Fall 2020), before the availability of COVID vaccines and phase 2 was conducted at the

2-year mark (Summer 2022) when most adults in the US were already vaccinated, and social distancing rules were no longer mandated. A single item question was examined on a 5-point Likert scale from “Not at all” (1) to “Extremely” (5).

> *To what extent have you felt emotionally affected or distressed by systemic racism highlighted by recent events across the country?*”.

Responses of “Moderately,” “Quite a bit,” or “Extremely” were indicative of a positive endorsement of racism-related distress. Distress was operationalized using four levels including *Persistent, Increasing, Decreasing and None* based on the differential participant response across the two timepoints as described in **Figure 2.4** [138]. Consistent with Publication 3, Black veterans were 2-3 times more likely to report persistent distress compared to Hispanic and White participants (61.2%, 29.1% and 20.3% respectively).

Further, relative to those with no experience of racism, the participants with *increasing distress* were more likely Black, female, older, and to report more lifetime traumatic events. Relatedly, those with *persistent distress* were older, more likely to be female, Black and Hispanic, reported more lifetime trauma, and were more likely to screen positive for SUD. Of all the possible interactions statistically tested, only race/ethnicity had a significant interaction with SUD ($p<0.05$).

Compared to people with no SUD, Black and White people with SUD were more likely to report *persistent* race-related distress [98.2% v 73.4% for Black individuals and 30.3% v 23.7% for White individuals respectively].

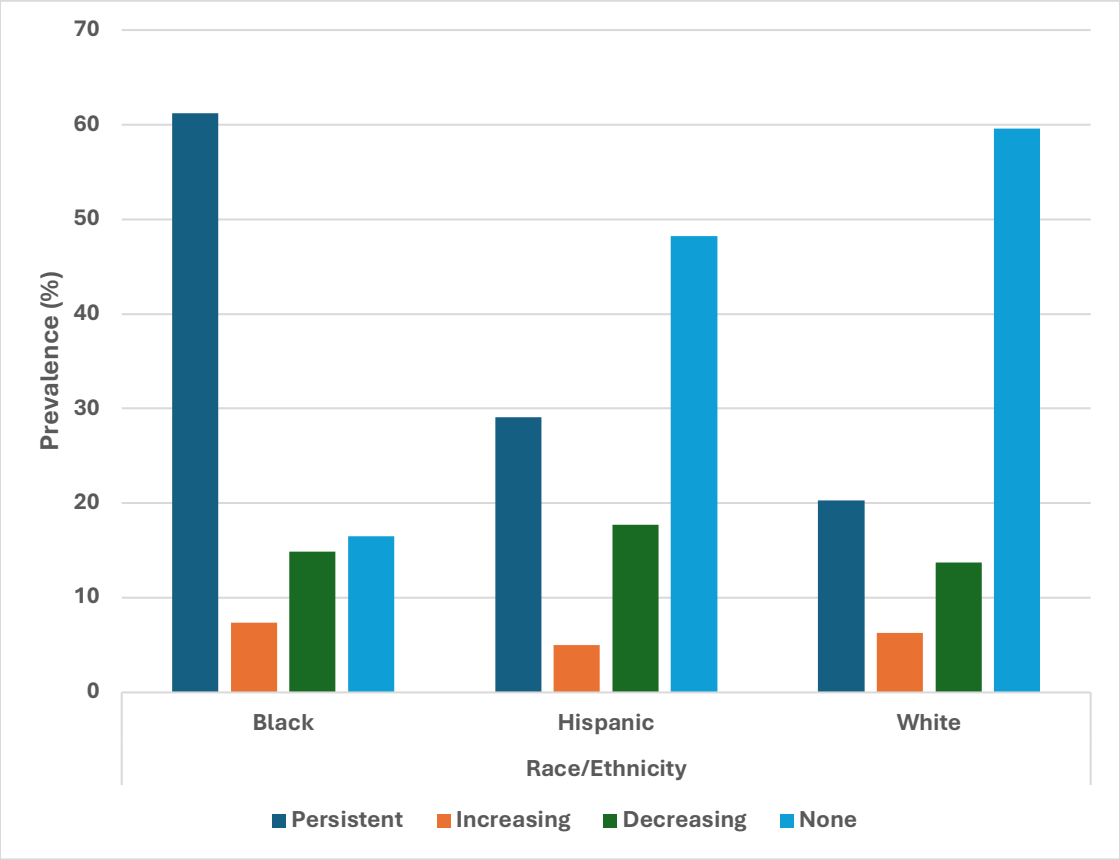


Figure 2.4: Prevalence of 4-level 2-year longitudinal racism-related distress across races (Whealin et al, 2024) [138]

2.2.5 Racial disparities in SUD diagnostic remission (Publication 5) [144]

In Publication 5, as a developing researcher, the candidate learned to handle large datasets and complex statistical analysis. This was the first study to examine diagnostic remission from SUD using the third wave of the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC III). Publication 5 extended prior literature that examined, in a variety of contexts, racial/ethnic disparities in access to evidence-based addiction treatments, and treatment completion [145-147].

Prior research showed mixed results: in some studies, Black and Hispanic individuals had higher remission rates (lower diagnostic persistence) [148, 149] while others suggested similar rates across racial groups after controlling for sociodemographic characteristics [150, 151]. For example, of respondents who reported that they thought they *had problems with substances*, there were no significant racial/ethnic group differences among those who *felt that they were in recovery* (as subjectively defined by respondents), according to the latest report from the National Survey of Substance Use and Health (NSDUH) [152].

Further, of people aged 12 and older in the United States, only 19.1% *felt that they needed SUD treatment in the past year* (American Indian or Alaska Native, 30.6%; Multiracial people 26.2%; White 19.9%; Black 19.7%; Hispanic 17.5%; Asian people 10.5%) [3]. According to the same report, of those who *needed SUD treatment* in the past year, there were no significant differences by race/ethnicity (ranging from 18.9% among Black people to 25.3% among Hispanic people) [3].

A meta-analysis of available evidence also suggested that individuals with SUDs achieved remission at a rate between 35.0% to 54.4%, occurring after a mean follow-up

period of 17 years [153]. Another large review of treatment outcomes suggested similar rates of remission [154] but failed to address racial/ethnic disparities. Publication 5 thus fills a crucial gap by examining racial disparities in diagnostic remission i.e. no longer meeting criteria for SUD in the past year, using a large nationwide dataset, NESARC III.

The NESARC III was sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a nationally representative cross-sectional survey of non-institutionalized civilian adults aged 18 or older, conducted from April 2012 through to June 2013 and analyzed from February through to March 2015. The study selected respondents through a multi-stage probability sampling with African American, Asian, and Hispanic individuals oversampled. In-person structured interviews excluded individuals who were institutionalized (e.g., in nursing homes, prisons, hospitals, or shelters). The original sample of NESARC-III respondents included 36,309 US adults with a household response rate of 72%; person-level response rate of 84%; and overall response rate of 60.1% [155].

Publication 5 showed that 30.1% (10,916 individuals) of the entire NESARC III sample met the criteria for a lifetime SUD. Of these, 46.9% met the criteria for remission (i.e. no longer met criteria for SUD in the past year) corresponding to 52.2% White individuals but only 34% and 38.5% of Black and Hispanic individuals respectively. In both unadjusted and adjusted regression analyses, Black and Hispanic individuals compared to White individuals were less likely to remit (unadjusted OR 0.42, 95% CI 0.36-0.48 and 0.51, 95% CI 0.45-0.58 respectively and adjusted 0.49 95% CI 0.41-0.57 and 0.68 95% CI 0.59-0.78 respectively).

Even more interesting, but perhaps not surprising, were social factors being recognized as potential confounders in the adjusted analysis. Stratifying the analysis

based on remission status showed that factors associated with remission included: employment status, income, homelessness, presence of legal issues, experience of lifetime discrimination, marital status, and veteran status. The most important factors in the adjusted regression analyses (based on effect sizes) that predicted remission included *less* likelihood of- being Black, being Hispanic, being of another race/ethnicity, having past year trouble with the police, having a lifetime opioid use disorder, and being married or cohabiting. Publication 5 showed significant and robust findings that suggest that minoritized individuals were less likely to remit from SUD, including from both alcohol use disorder (AUD) and drug use disorder (DUD). While the reason for this disparity is unclear from the results, based on other literature discussed in this thesis and the clinical experience of the candidate in his clinical role, unmeasured upstream structural factors (including structural racism and various forms of discrimination) likely played a significant role.

Unlike prior studies of diagnostic remission, Publication 5 was the first one, using a nationally representative sample, to address racial discrimination, which was associated with a decreased likelihood of diagnostic remission even after controlling for various confounders. In other words, lower levels of self-reported racial discrimination were independently associated with higher remission rates. Further research is needed to investigate this association.

2.2.6 Disparities in the rates and correlates of SUD service utilization (Publication 6) [156]

Literature on racial disparities in addiction services has expanded over the past few years, especially in the wake of the COVID-19 pandemic as discussed earlier. Publication 6 expatiated on disparities in SUD treatment using a large (pre-pandemic) national database. As a contributor to this work, it is significant to show that Publication 6 formed the springboard for many subsequent scholarships including book chapters, (post-pandemic) academic publications, presentations and lectures [157, 158].

While the focus of Publication 6 and related literature is on SUD treatment utilization in general, it is instructive to note that racial/ethnic disparities become more evident when examined on a more granular scale that involves specific substance disorders (such as opioid, alcohol, stimulant or hallucinogens) or in research designs that address specific evidence-based treatments (such as MOUD, psychotherapies or contingency management) or treatment models such as harm reduction programing or integrated co-occurring disorder treatment. Racial disparities have been well documented in the utilization of MOUDs as discussed in section 2.2.1; yet studies about racial disparities in SUD treatment service utilization have yielded mixed results with some studies showing no clear disparities and other showing that the racial burden shifted in either racial direction depending on the study being examined [159].

Access to addiction treatments within the US healthcare system involves complex sociopolitical mechanisms including federal and local policies and regulations, the operation and organization of which are influenced by individuals (stigma, health

insurance coverage), provider level factors (bias, stigma), built environmental context (urbanicity and geographical access to treatment facilities), and the operation of community systems [160].

A study of the impact of SUD treatment facilities closure on emergency room (ER) visits among nearby residents of the state of New Jersey found that drug-related ER visits increased by 7.4% after a facility closure and decreased by 6.5% after the ER facility opening [161]. This study showed that the disparate impact of SUD treatment access, mediated by race, insurance status and age, was much larger for Black residents and those on Medicaid (a joint federal and state health insurance program for low-income individuals) compared to other racial groups, but smaller for middle aged compared to younger and older people [161]. In another study with adults receiving publicly funded outpatient SUD treatment showed that Black and Native American individuals were less likely to initiate or engage in treatment compared to non-Hispanic White individuals [162].

The primary objective of Publication 6 was to identify potential factors that mediate racial disparities in the utilization of SUD treatment by comparing the receipt of services among Black and White individuals with past year SUD, and then comparing treatment recipients to non-recipients according to sociodemographic, behavioral and diagnostic characteristics [156]. Data for this study were obtained from a restricted version of NESARC III. In analyzing the specific measures of interest (i.e. receipt of services), responses to the question of whether the respondent had received any services related to SUD were examined as well as a further measure of treatment receipt of any outpatient or residential treatments (excluding crisis intervention or ER services and inpatient hospitalization as these do not offer definitive treatments).

Results showed that among the entire NESARC sample, 29.9% and 70.1% of Black and White respondents respectively met the criteria for past year alcohol use disorder or drug use disorder. Overall, results showed a gross dismal receipt of SUD treatments among all respondents, at around 10%. There were, however, no significant differences between Black (26.1%) and White (28.6%) individuals who had ever sought any kind of help (including hospitalization, ER visit, or ongoing treatment, p=0.09) or received outpatient or any residential treatment that could lead to potentially durable clinical improvement beyond crisis intervention (10.1% versus 11.3% for Black and White individuals, p = 0.24).

In Bivariate analysis, results showed that Black treatment recipients were more likely to report abusive discrimination and other life adversities (**Table 2.3**) including past year or lifetime homelessness, lifetime suicide attempts, incarceration prior to age 15 years old, past year trouble with the police, and violent behavior. Black treatment recipients (compared with those who did not receive any treatments) were also more likely to have past year co-occurring disorders (mental health disorders and substance use disorders) (see Chapter 3 for more discussion on co-occurring disorders). This pattern of associations was observed in the White cohort as well, as illustrated in **Table 2.3**.

In another set of bivariate correlation analyses, experiences of discrimination was analyzed. The experiences of discrimination variable was constructed using the six discrimination questions contained within the AUDADIS-5 modeled after the Experiences of Discrimination Scale, which has been consistently shown to have good validity and reliability for measuring experiences of racial discrimination [163]. The variables were based on Bommersbach and colleagues' (2023) factor analysis that

suggested a three-factor solution addressing health system discrimination, public or job discrimination, and abusive, in-person discrimination [164].

Black individuals who received treatment for SUD were more likely to report past year discrimination compared to White individuals who received treatment (1.84 $\pm$ 0.77 versus 1.34 $\pm$ 0.55; Cohen's d=0.89). The pattern remained the same among those who did not receive treatment (1.68 $\pm$ 0.69 versus 1.2 $\pm$ 0.39; Cohen's d=0.85). These substantial differences were observed for all subscales including health system discrimination, public or job discrimination, and abusive in-person discrimination. Nevertheless, as noted above, among both Black and White populations, individuals who received treatment reported greater experiences of past-year racial discrimination than those who did not (Treatment versus No Treatment, Cohen's d= 0.25 and 0.12 for White and Black populations respectively).

In multivariable analyses, the strongest associations with receiving treatment among Black respondents were earning >$60,000 per year (OR=0.10, negative effect), having a parent with a drinking problem (OR=2.11) and having a co-occurring disorder [i.e. having both past year psychiatric and substance use disorders, (OR=2.01)]. Among White respondents, the strongest associations with treatment receipt were lower mental health quality of life (OR=0.97), past year SUD multimorbidity (OR=1.84), past year psychiatric multimorbidity (OR=1.74), past year trouble with the police (OR=2.12) and violent behavior (OR=1.12). Four variables were significantly differentially associated with treatment receipt among Black and White individuals - three of which (unemployment, low income, and criminal justice involvement) were more associated with treatment among White individuals, whereas parental problematic alcohol use was more strongly associated with receiving treatment among Black individuals.

Although this is an interesting finding among the White population, the racial difference was specifically attributable to those who did not receive treatment. In other words, compared to Black individuals, White individuals who did not receive any SUD treatment have far less unemployment and past year police trouble. Most individuals with past-year SUD (about approximately 90% in Publication 6), did not receive any addiction outpatient or residential treatment.

Regardless of race, however, people who did receive treatment were significantly more likely to be involved with the criminal justice system but Black individuals who did not receive treatment were far more likely to be involved with the police compared to White individuals (8.5% vs 3.7% respectively). This is not surprising as many studies have suggested that the criminal justice system has become a pathway for SUD treatment among Black individuals in the US [165, 166] and up to 34% of all SUD treatment referrals in 2011 came from the criminal justice system [167].

In summary, Publication 6 sought to identify correlates of SUD treatment receipt that differed across racial groups, to describe actionable areas that might facilitate service use by addressing the distinct needs and circumstances of Black and White individuals.

Table 2.3: Behavioral characteristics of Black and White individuals with current year SUDs, comparison by treatment status

	BLACK		RR/Cohen's d	WHITE		RR/Cohen's d
	Treatment (n = 133; 10.1%)	No Treatment (n = 1179; 89.9%)		Treatment (n = 349; 11.3%)	No Treatment (n = 2727; 88.7%)	
Homelessness						
Lifetime	21.2%	12.0%	1.77*	19.6%	8.4%	2.35*
Past Year	12.4%	7.1%	1.74*	10.2%	2.7%	3.75*
Suicide Attempt						
Lifetime	17.4%	9.0%	1.93*	22.5%	8.6%	2.62*
Incarceration						
Before 15 years old	19.8%	12.4%	1.59*	18.6%	7.6%	2.43*
After 15 years old	44.1%	32.2%	1.37*	39.4%	20.2%	1.95*
Police Trouble	13.0%	8.5%	1.52*	13.2%	3.7%	3.56*
Violent Behavior	1.98 ± 1.74	1.27 ± 1.54	0.45^	1.77 ± 1.72	1.07 ± 1.36	0.5^
Multiple SUD	39.7%	18.2%	2.18*	31.1%	11.6%	2.69*
Co-occurring disorders	50.9%	28.2%	1.81*	49.8%	28.4%	1.75*

SUD= substance use disorder; psych = psychiatric.
*Relative risk (RR) > 1.50 or < 0.67.
^Cohen's d, treatment vs. no treatment >0.20.
^^Cohen's d, treatment vs. no treatment <-0.20.

Source: Bommersbach, T. J., Jegede, O., Na, P. J., Stefanovics, E. A., Rhee, T. G., & Rosenheck, R. A. (2022). Treatment of substance use disorders among black and white adults: rates, correlates, and racial discrimination. Journal of addictive diseases, 40(3), 345-356.

2.3 Conclusion:

Chapter 2 presents a foundational and up to date understanding of inequities in the field of addiction in the current context of multidimensional challenges posed by fentanyl domination in community drug supplies. Inequities and correlates of inequities in addiction treatment were presented in varied contexts including: 1.) Racial inequities in evidence-based SUD treatments (including access), 2.) Inequities in treatment receipt (rate and correlates), 3.) Inequities in systemic racism and discrimination-based distress, and persistent distress, and 4.) disparities and inequities? in SUD diagnostic remission. Overall, the inequities in SUD treatment remain a treatment gap that will only respond to structural interventions within a complex, multidimensional healthcare system as described in the next chapters.

Chapter 3 : Developing a new paradigm: Social determinants as biomarkers of structural vulnerability

3.1 Publications: Titles and Contributor Roles

Publication 7: Psychiatric and substance use disorders and related service use in the diverse Black sub-populations in the United States.

Contribution to the work: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Original Draft; Visualization; Project Administration; Supervision.

Publication 8: Systemic racism as a determinant of health inequities for people with substance use disorder.

Contribution to the work: Conceptualization; Literature Search; Data Curation; Writing – Original Draft; Visualization; Project Administration.

Publication 9: Access challenges to opioid use disorder treatment among individuals experiencing homelessness: voices from the streets

Contribution to the work: Methodology; Formal Analysis; Writing – Review & Editing; Supervision.

3.2 Chapter 3 Commentary:

The set of three publications in this chapter advances the concepts introduced in Chapter 2 by presenting detailed observations of racial heterogeneity among sub-populations of Black African-Americans as related to diagnosis of SUD, related mental health disorders and SUD treatment service utilization (Publication 7 [168]); systemic racism is presented as a fundamental cause of health inequities among minoritized populations with SUD (Publication 8 [4]). Finally, the section ends with a qualitative study of access challenges to SUD treatment (with a focus on opioid use disorder) among people experiencing homelessness (as a social determinant) in a major American metropolitan city (Publication 9 [169]).

3.2.1 Diverse Black sub-populations and differing experiences of disparities (Publication 7) [168]

Publication 7 is a deep exploratory analysis of inequities in the Black population with SUD, co-occurring disorders and mental illness. This research deconstructed the Black population into its component sub-populations while identifying diagnostic and related service use variables. This publication uses a sociological disaggregation approach to explore differences at the population level by categorizing the Black population based on immigrant status, nativity and perceived social identity. Using this approach, immigration is treated as a social determinant of health and a known risk factor for SUD, through the acculturative stress, trauma, discrimination, and lack of access to care pathways.

The Black population in the U.S was categorized into 4 groups: African-born, Caribbean-born, US-born with at least one immigrant parent and US-born with no immigrant parents (both parents born in the U.S) [23]. Publication 7 extends the results from earlier studies of Black populations with SUD and those on the healthy immigrant effect or *immigrant paradox* - a concept that has been applied to explain the course of many heath conditions [170-172]. From the addiction perspective, the healthy immigrant effect posits that recent immigrants are less likely to be at risk for SUD compared to native-born Americans.

Krim Lacey et al's (2017) study on the differences in substance use across Black ethnic populations examined the prevalence rates across three geographic regions (U.S, Jamaica, and Guyana) and showed higher rates among Black individuals in the US compared to those in the Caribbeans. Further, the study showed that SUD differed

across cohorts by nativity and length of time in the U.S, also reflecting high rates of substance use among those who were born in the US, compared to foreign-born participants. Results from this study point to the impact of acculturative stress and exposure to social determinants as possible explanations for this difference [173].

Further, Broman et al. (2008), using data from the National Survey of American Life, examined the prevalence of SUD among U.S-born Black African-Americans and Caribbean-born Black Americans with reports consistent with the immigrant paradox namely that first generation Caribbean-born Black Americans were less likely than second generation (U.S-born) Caribbean Black Americans to meet criteria for SUD, but the latter were more likely than US-born African-Americans to meet criteria for SUD [174].

The analytic sample for Publication 7 was selected from the NESARC III data to include respondents who self-reported their race as Black (N=7734, representing a total population of 27,630,580) and identified their nation of birth as either Africa (2.82%), the Caribbeans (4.23%), the US- with one immigrant parent (6.54%) or the US- with no immigrant parents (86.4%). Data included sociodemographic variables, behavioral variables, health-related quality of life, social support (using the Interpersonal Support Evaluation List [175]), discrimination variables, psychiatric, SUD and service use variables. Interpersonal Support Evaluation List (ISEL-12) was used to measure social support [175].

The ISEL-12 is a 12-item questionnaire rated on a 4-point severity scale (range 0–4) with higher scores indicating greater social support. Social contact was measured by self-reported total numbers of family, friends, and other acquaintances with whom participants had meaningful contact in the past two weeks.

In terms of behavioral characteristics, results from the bivariate analysis comparing each sub-population category [African-born (Group 1), Caribbean-born (Group 2) and US-born with at least one immigrant parent (Group 3)] to US-born with no immigrant parents (Group 4)] are shown in **Table 3.1**.

Table 3.1: Behavioral characteristics by Black sub-population categories

	(1) African-born (n=218;2.82%)	(2) Caribbean-born (n=327;4.23%)	(3) U.S- born with at least one immigrant parent (n=441; 5.75%)	(4) U.S-born with no immigrant parent (n=6683;86.41%)	(1) vs. (4)	(2) vs. (4)	(3) vs. (4)
History of incarceration (%)					RR or *d*	RR or *d*	RR or *d*
Before 15	0.00	1.41	6.50	5.97	NA	**0.24**†	0.97
After 15	3.73	6.37	10.83	15.88	**0.23**†	**0.40**†	0.68
PY trouble with police (%)	1.17	0.88	2.02	2.74	**0.43**†	**0.32***	0.74
PY homelessness (%)	0.33	1.44	6.75	2.88	**0.11**†	**0.50**†	**2.34**†
Parental history (%)							
Alcohol use	8.95	14.78	16.67	20.74	**0.43**†	0.71	0.80
Drug use	0.30	1.84	8.18	8.13	**0.04**†	**0.23**†	1.01
Incarceration	1.82	2.19	10.69	12.15	**0.15**†	**0.18**†	0.88
Psychiatric hospitalization	1.51	1.90	3.44	5.44	**0.28**†	**0.35**†	**0.63**†
Suicide attempt	0.35	0.00	0.83	2.25	**0.16**†	NA	**0.37**†
Death by suicide	0.35	0.33	0.38	0.63	**0.55**†	**0.52**†	**0.60**†
Adverse childhood experiences							
Neglect, mean (SD)	12.32 (5.12)	12.46 (5.03)	12.67 (5.40)	12.54 (5.20)	-0.04	-0.02	0.02
Sexual abuse, mean (SD)	4.31 (1.50)	4.54 (1.74)	4.51 (1.89)	4.60 (2.19)	-0.14	-0.04	-0.05
Repeated trauma (%)	11.34	13.17	11.59	12.72	0.89	1.03	0.91
Witnessed trauma (%)	34.36	44.37	43.02	48.09	0.71	0.92	0.89
Any trauma (%)	35.74	38.27	42.93	47.17	0.76	0.81	0.91
Discrimination							
Any discrimination (%)	50.20	33.41	41.66	42.80	1.17	0.78	0.97
PY Discrimination, mean (SD)	1.58 (0.70)	1.43 (0.58)	1.51 (0.63)	1.52 (0.64)	0.10	-0.13	-0.02
Health System Discrimination	1.40 (0.76)	1.25 (0.53)	1.28 (0.63)	1.30 (0.62)	0.16	-0.07	-0.03
Public/Job Discrimination	1.82 (0.94)	1.55 (0.73)	1.72 (0.87)	1.72 (0.87)	0.12	-0.02	0.00
Abusive Discrimination	1.41 (0.66)	1.29 (0.57)	1.35 (0.55)	1.33 (0.55)	0.15	-0.08	0.04
Social Support (ISEL), mean (SD)	2.96 (0.46)	2.95 (0.50)	2.93 (0.50)	2.98 (0.49)	-0.06	-0.07	-0.10
Health-related Quality of Life							
Mental component summary: SF-12, mean (SD)	53.32 (8.02)	51.61 (9.93)	49.94 (9.75)	49.91 (10.59)	**0.33**¶	0.16	0.00

	(1) African-born (n=218;2.82%)	(2) Caribbean-born (n=327;4.23%)	(3) U.S- born with at least one immigrant parent (n=441; 5.75%)	(4) U.S-born with no immigrant parent (n=6683;86.41%)	(1) vs. (4)	(2) vs. (4)	(3) vs. (4)
Physical component summary, SF-12, mean (SD)	53.81 (6.49)	50.56 (9.46)	49.55 (10.70)	48.23 (10.97)	**0.52¶**	**0.22¶**	0.12
Quality Adjusted Life Years (EQ-5D), mean (SD)	0.94 (0.08)	0.90 (0.11)	0.89 (0.12)	0.88 (0.13)	**0.55¶**	**0.24¶**	0.09

† RR>1.5 or <0.67 and refers to ¶ Cohen's *d*>0.2 or <-0.2, *d*=Cohen's *d*, RR=Risk ratio, SD=standard deviation, SUD=Substance use disorder, ISEL= Interpersonal Support and Evaluation List

The main results show that:

1. African-born (Group 1) and Caribbean-born (Group 2) Black individuals were *less likely* to report having been *incarcerated after the age of 15* compared to U.S-born with no immigrant parents (Group 4) [RR= 0.23 (Group 1 vs. 4) and 0.40 Group 2 vs. 4)]; or to have experienced past year trouble with the police compared to U.S-born (Group 4) [(RR= 0.43 (Group 1 vs. 4) and 0.32 Group 2 vs. 4)]. However, no significant differences were found between Group 3 (U.S-born with at least one immigrant parent) and Group 4 (U.S-born with no immigrant parents) in terms of history of incarceration before and after the age of 15 years old or past year trouble with the police (RR, 0.97, 0.98 and 0.74). Please see **Table 3.1**.

2. In terms of homelessness, African-born (Group 1) and Caribbean-born (Group 2) Americans were *less likely* to report that they had been homeless in the past year compared to Group 4 (U.S-born; RR= 0.11 and 0.50 respectively) but unexpectedly, U.S-born with at least an immigrant parent (Group 3) were significantly *more likely* to report having been homeless in the past year compared to U.S-born with no immigrant parent (Group 4) (6.75% versus 2.88%; RR = 2.34). Thus, compared to those born in

the U.S to no immigrant parents (Group 4), those born to the U.S with at least one immigrant parent (Group 3) were 134% more likely to experience homelessness.

3. Parental alcohol and drug use, parental incarceration, parental psychiatric hospitalization, parental suicide attempt and parental death by suicide were all significantly less frequent among Group 1 and Group 2 compared to the U.S-born with no immigrant parent (Group 4).

4. Interestingly, there were no statistically significant differences between each of the three groups (Groups 1, 2 and 3) and Group 4 on the indicators of Adverse Childhood Experiences (including family neglect, sexual abuse) or on other indicators of trauma: repeated trauma, having witnessed trauma to others, or having experienced any trauma.

5. There were no significant differences across all groups in any measures of racial discrimination experience: *any* discrimination, past year discrimination, health system discrimination, public/job discrimination and abusive discrimination.

6. African-born, Caribbean-born and U.S-born to immigrant parents Americans (Groups 1-3) scored higher on all indices of quality of life (QOL) including a mental component summary, physical component summary and adjusted quality of life year compared to Group 4. Of note, however, is that no significant differences were observed between US-born with an immigrant parent (Group 3) and U.S-born with no immigrant parents (Group 4) across these same measures.

In terms of diagnostic characteristics, African-born participants (Group 1) were *less likely* than U.S-born with no immigrant parent (Group 4) to have either *any* lifetime single psychiatric diagnosis (15.53% vs. 27.81%, RR=0.56) or more than one psychiatric diagnosis (5.28% vs. 11.53%, RR=0.46). Compared with U.S-born with no

immigrant parent (Group 4), this pattern was consistent for past year alcohol use, lifetime single drug use and lifetime polydrug use disorders for African-born (Group 1) (RR=0.51, 0.48 and 0.11 respectively) and for Caribbean-born participants (Group 2) (RR= 0.35, 0.33 and 0.37 respectively).

Particularly interestingly, however, is that the U.S-born Americans (Groups 3 and 4) showed diagnostic similarities in terms of alcohol and drug use, as no significant differences were found in alcohol or single drug use and polydrug disorders (RR = 0.91, 1.03 and 1.13) except for cocaine use disorder (0.16% vs. 0.74%; RR = 0.22) where Group 4 had a higher likelihood of reporting cocaine use disorder.

Medical comorbidities also followed the same pattern as reported with other characteristics, African-born individuals (Group 1) had significantly fewer medical comorbidities and less chronic pain compared to the U.S-born with no immigrant parent (Group 4) (Cohen's $d = -0.31$ and RR = − 0.38, respectively). The burden of medical comorbidities was not significantly different between the US-born groups, Groups 3 and Group 4 (RR= -0.18), nor chronic pain (20% vs. 23%, RR=0.87).

Finally regarding service use, bivariate analyses showed that African-born and Caribbean-born individuals (Groups 1 and 2) were less likely to report lifetime use of any mental health treatment than U.S-born with no immigrant parents (Group 4) [(Group 1: 5.98%, Group 2: 12.18% versus Group 4: 21.18, RR = 0.28 (Group 1 versus Group 4) and 0.57 (Group 2 versus Group 4)] and past year substance use treatment services [Group 1: 0.77%, Group 2: 0.39% versus Group 4: 2.37%, RR= 0.33 (Group 1 versus Group 4) and 0.17 Group 2 versus Group 4)].

Conversely, there were no significant differences in lifetime or past year mental health or SUD treatment service use between U.S-born with an immigrant parent

(Group 3) and U.S-born with no immigrant parents (Group 4). It is of note however, that individuals in Group 3 (1.52%) were less likely to have sought substance use treatment in the past year despite knowing that they needed treatment compared to Group 4 (2.33%) (RR = 0.65).

Publication 7, therefore, highlights the heterogeneity of the Black population in the US across a range of behavioral, diagnostic and service use variables. The results show that African-born and Caribbean-born Black individuals experienced a significantly lower burden of mental, medical and SUD than US-born Black individuals. Consistent with earlier literature, Publication 7 strengthens the notion of the *healthy immigrant effect* [176, 177].

Interestingly, despite the known high incidence of acculturative stress and its likely deleterious impact on health [178] that often accompany the process of immigration, the study shows comparable levels of discrimination across the disaggregated groups, ACES and social support. However, this study unexpectedly showed a likely erosion of the protective healthy immigrant effect as this did not appear to apply to Black individuals born in the US with at least one immigrant parent (Group 3). This group did not differ from U.S-born with no immigrant parent (Group 4) on most behavioral characteristics, including history of incarceration, past year trouble with the police, all components of health related QOL, psychiatric, substance use diagnoses, medical comorbidities, chronic pain and even SUD service use indices.

The research team was surprised by the finding that U.S-born with one immigrant parent (Group 3) had a higher likelihood of past year homelessness when compared with U.S-born with no immigrant parent (Group 4). This needs further corroborating with future research. However, it may reflect the intersection of multiple, unrecognized or

underreported cultural vulnerabilities. Group 3 (U.S-born with one immigrant parent) may face diminished access to intergenerational safety nets, and weaker ties to established community immigrant support systems, a notion that is the subject of ongoing investigation by the candidate.

Other issues to be considered may include cultural identity stresses, and the social stigma associated with both racialization and immigrant backgrounds. Black people with immigrant parents likely represent a distinct and understudied subgroup whose housing instability may be shaped by complex sociocultural dynamics not adequately captured by traditional racial or immigrant-status categories alone. It is worth emphasizing that policy on immigrants should consider that immigrants and their progenies often lose the healthy immigrant effect, with longer time of acculturation into the dominant culture leveling the risk of psychiatric, SUD and medical conditions [176].

Publication 7 concludes that the Black African American population is a complex group, and that the understanding of the nuanced characteristics of the constituent subpopulations can be clinically meaningful.

3.2.3 Systemic racism is a determinant of substance use (Publication 8) [4]

Publication 8 was an expert opinion viewpoint that captured the essence of the addiction science field at a critical moment in the United States. Precisely, it addressed the need to understand social and cultural contexts of escalating drug overdose mortality in the wake of the COVID-19 pandemic. This publication marked the period in the candidate's development as a researcher that defined his evolution and national recognition as a scholar in addiction science and health equity research. It is worthy to note that two book chapters, first authored by the Ph.D. candidate, followed Publication 8 and expanded the key ideas presented here [157, 158].

The overarching objective of Publication 8 was twofold; 1.) To present the need for the medical field to have clear definitions of inequality and inequity by showing the implications of this distinction on health policy **(Figure 3.1)** and 2.) To identify and describe systemic racism as a social determinant of SUD and the root cause of inequities in SUD treatment drawing upon Link and Phelan's Theory of Fundamental Causes [179].

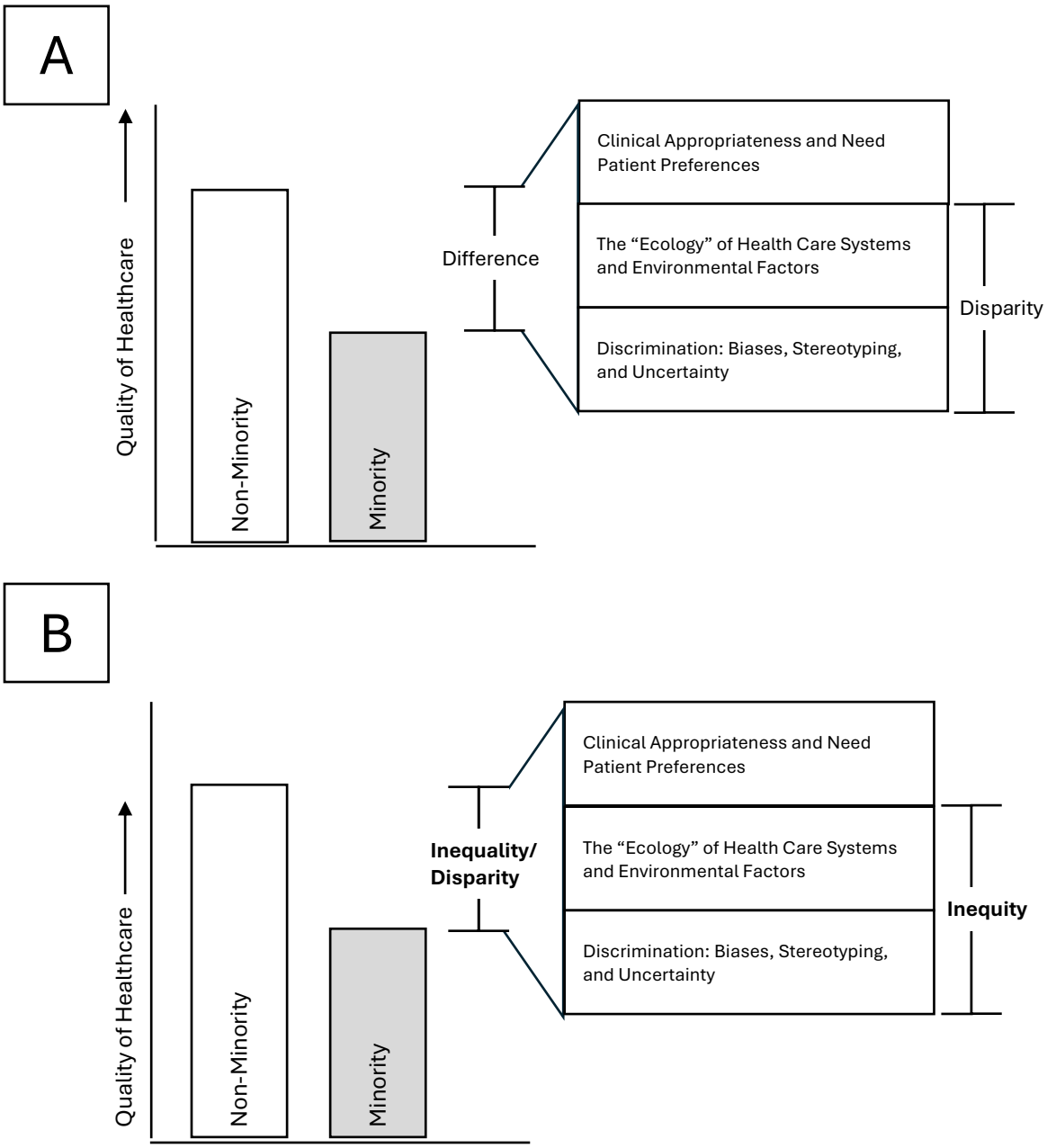


Figure 3.1: An updated conceptualization of the definitions of inequality/disparity and inequity. [A] is the traditional definition of disparity and inequality referring to any measurable differences in health and [B] is the updated definition as presented in this thesis as processes or differences that are specifically due to avoidable factors. Modified from: Nelson et al, 2022 [180]

Chapter 2 presented a review of the racial inequities in addiction to include inequities in drug-related mortality, inequities in SUD treatment and treatment access as well as racism-related, persistent distress. Convergent evidence supports the worsening impact of inequities on mental health as in other healthcare fields. The terms disparity, inequality and inequity have a long tortuous political and academic history and have been used interchangeably in the literature and clinical practice [181-183]. However, it is essential to note the differences in terminology and its attendant clinical and policy implications.

Any difference in the quality of care provided to minoritized populations compared to any non-minoritized group is known as a disparity or inequality (**Figure 3.1**). Health equity however extends this definition to include social justice, referring to any difference in health outcomes that reflects social disadvantage (social determinants of health i.e. poverty, discrimination, and their consequences - unemployment, poor access to quality education, built environment, lack of safe housing, and access to quality healthcare) [184, 185]. Social disadvantage, from the addiction perspective, includes the positionality or perceived positionality of people who use drugs within society's power hierarchies and perceived powerlessness related to their substance use and other factors including race/ethnicity and socioeconomic status. While health inequality or health disparity refers to measurable differences in health, health inequity refers to specific processes or differences that are due to avoidable factors. Put together, health equity is an ethical concept, grounded in the principles of distributive justice based on social justice and fairness [181].

However, it must be noted that there is no consensus on these definitions in the literature. As shown in **Figure 3.1**, the unmodified panel A portrays the description of

disparity from the seminal 2003 publication by the Institute of Medicine (IOM) (now known as National Academy of Medicine), *Unequal Treatments*, which defines disparity as any difference in healthcare quality not due to differences in the needs or preferences of the patient [180]. This is in contradistinction to the definition provided by the Agency for Healthcare Quality and Research (AHRQ), where any difference between populations is regarded as disparity, notwithstanding the underlying needs of the populations [186]. Regardless of these nuanced definitional differences, health equity involves elimination of health disparities/inequalities based on the principles of justice and fairness [187].

The central message of Publication 8 is that systemic racism is a social determinant of SUD and the fundamental cause of inequities in SUD treatment. The publication drew upon Link and Phelan's Theory of Fundamental Causes (1995), which posits that individual risk factors are not enough to explain the course of diseases, and suggests that attention must also be paid to social factors (socioeconomic status (SES) and social support) as "fundamental causes" [179]. The association between SES and disease is, however, ubiquitous and based on changes in perceived risks and protective factors which influence the SES-disease association, the impact of which is dynamic and subject to variations in ecological, temporal and spatial factors [188].

Publication 8 presented an extension of the Fundamental Cause Theory to explain inequities in addiction, arguing that systemic racism in the US is etiological to the course and trajectory of SUD. Pathways from racism to SUD are, however, unlikely to be as simple as the theory may suggest but rather may result from complex interrelated and mutually exacerbating biopsychosocial processes.

Elucidating how social factors impact biological processes and the development of SUD (a phenomenon known as “getting under the skin” [189]) can potentially transform not only the understanding of the cause and trajectory of SUD but also its prevention and treatment [190]. Biomarkers of stress (cortisol), cellular aging (telomere length) [191], and epigenetics (how environmental and social contexts affect heritable gene expression) [192, 193] have gained recognition in the field of addiction science over the past decade as pathways that link SDOH (including systemic racism) to SUD and other chronic diseases [194].

Further, evidence shows strong associations between social adversity, ACES, adult trauma as well as uncontrollable and unpredictable stressful events and the risk of addiction [195-200]. A recent, small proof-of-concept study showed that racial discrimination and microaggressions resulted in significant instantaneous and temporal increases in physiologic stress responses among subjects [201]. In this study, participants showed that previous day’s racial discrimination was significantly associated with the next day’s elevated cortisol level at wakening ($\beta = 0.81$, partial $r = 0.74$, $p<0.01$) and diurnal slope ($\beta = -0.85$, partial $r = -0.73$, $p<0.01$) suggesting that more discrimination was linked to a flatter/slower decline in cortisol across the day. Further, they reported that microaggressions were significantly associated with flattening of the diurnal cortisol slope in the same day [201]. Stress and stress-related pathways have been consistently used to illustrate the biological impact of social stressors including systemic racism [202-204]. Publication 8 notes the impact of stressful perturbations on the body’s homeostatic mechanisms.

Homeostasis (from the Greek words *homeo* meaning “similar” and *stasis* meaning “stand” or “state”) refers to the body’s ability to maintain its internal stability

(**Figure 3.2**). As the body maintains stability across perturbations, the ability to adapt to maintain such equilibrium and preserve homeostasis is referred to as allostasis. Allostasis is controlled by the hypothalamic-pituitary-adrenal (HPA) system activated in response to stress with cardiovascular, metabolic, and autonomic nervous system changes. Persistent, repetitive, cumulative stress causes an allostatic load whose impact on physiologic systems results in a variety of measurable pathologies manifesting as cellular, cognitive, and physiological deleterious weathering (wear and tear) [205-207] . This framework of stress response, allostasis and allostatic load, has been utilized to explain the epigenetic impact of racism and ACES over the life course. **Figure 3.2** illustrates the pathways from systemic racism to the development of chronic diseases via transient and chronic exposures to systemic racism-related stress.

One of the consequences of the legacy of systemic racism is racial segregation which has led to housing instability and homelessness, maintained by discriminatory policies such as the historical “redlining” in which minoritized communities were marked for disinvestment [208, 209].

The next publication, Publication 9 is a qualitative evaluation of the impact of homelessness on access to evidence-based treatment for opioid use disorder.

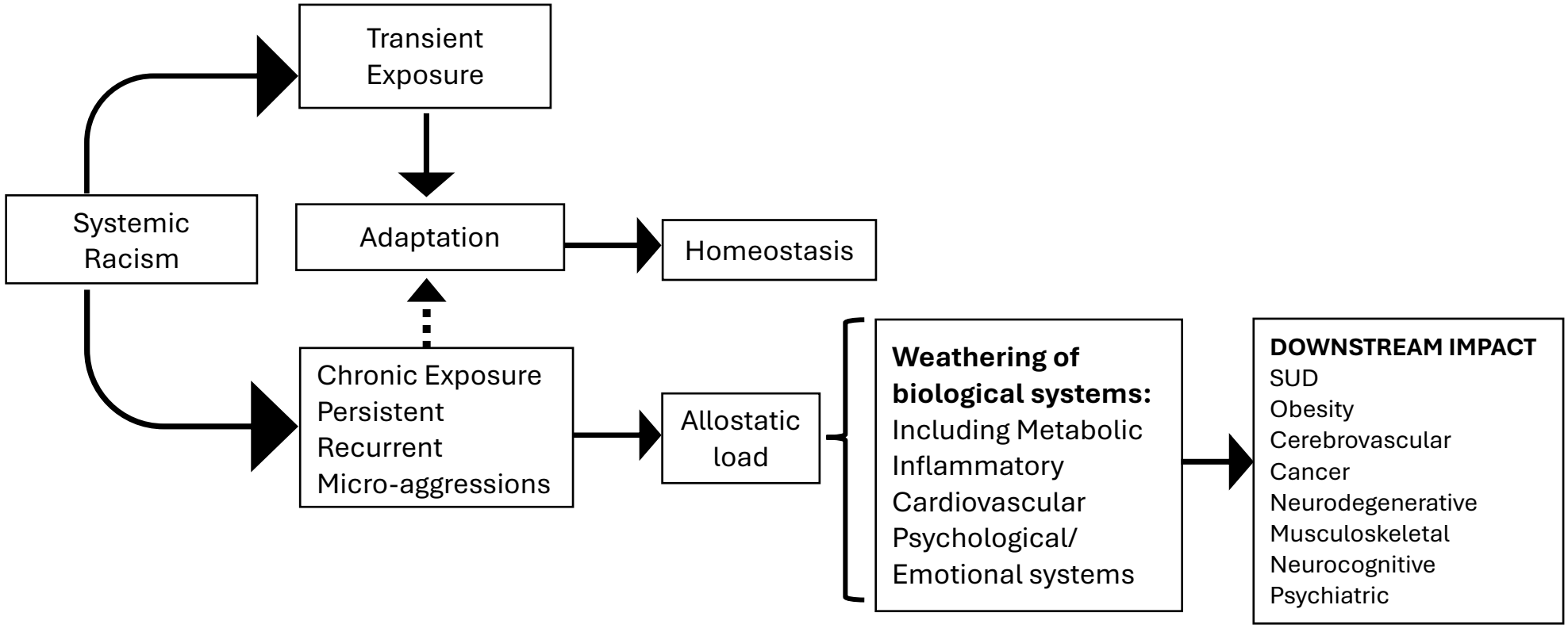


Figure 3.2: A heuristic representation of the chronic diseases downstream impact and stress pathways of systemic racism.

Note that dotted arrows suggest that “adaptation” is not the usual pathway for chronic exposure to stress.

3.3.2 Homelessness as a social determinant of access to SUD treatment (Publication 9) [169]

Publication 9 is a qualitative study that addressed inequities in addiction treatment among people with opioid use disorder experiencing homelessness. Homelessness is at the extreme end of the housing instability spectrum [210]. Evidence shows a bidirectional association between homelessness and SUD including the recognition of homelessness as a risk factor for drug related overdose [211, 212]. Unfortunately, despite the pervasiveness of homelessness, its relationship with SUD and related risks, remains an understudied subject with a paucity of data.

Publication 9 adds to the existing literature by exploring the experiences of people with OUD who are homeless regarding their access to MOUD and other SUD treatment using a qualitative field survey and semi-structured interviews. A field interview guide was developed after a literature review of MOUD patient experiences [213-216] and expert guidance of the research team including the Ph.D. candidate. Participants were recruited and interviewed around an area of the city of Boston that was known for high density injectable drug use, housing instability and opioid overdose mortality. Of 91 adult individuals (18-65 years old) who were approached for the study, 33 agreed to participate but only 28 met the inclusion criteria and were included in the study.

Historically racialized and minoritized individuals were oversampled for inclusion (African Americans and Latinx people). Other inclusion criteria included a history of homelessness and OUD in the past year. Interviews were conducted in-person, audio recorded, deidentified and transcribed verbatim. Thematic analysis of data included an

initial deductive approach to organize data based on the Penchansky and Thomas's five dimensions of treatment access: availability, accessibility, accommodation, affordability, and acceptability (**Figure 3.3**) [217].

The transcripts were coded to recognize thematic patterns related to the above treatment access domains. Codes were consistently reviewed by the research team but the themes for this study were created based on only four of the five Penchansky and Thomas's dimensions as "affordability" was deemed not relevant (**Figure 3.3**) after a review of the interview transcripts.

Next, an inductive approach entailed reviewing and open coding the organized segments from the transcripts using *Dedoose*, a qualitative analytic software (SocioCultural Research Consultants, LLC, Los Angeles, CA). Specific patterns and emerging themes associated with respondents' beliefs, attitudes, and experiences related to the availability, accessibility, accommodation, and acceptability of MOUD and substance use treatments were determined. Constant comparison techniques were used to compare each transcript with previously coded text to ascertain whether new text segments conveyed similar versus novel concepts.

Availability refers to the relationship between the volume and type of existing services available to respond to the patients' needs [217]. In this study, the domain reflected the themes of inaccessible outpatient and inpatient SUD treatment services, including withdrawal management (detox), as manifested by non-available inpatient beds (especially for female patients), fear of COVID infection and long wait times.

> *"Every place is full. You want to go get help? Every place is full. You got to sit there and wait, wait all day. When you're sick, you don't want to wait all day. You want to go. When you make a decision, you want to go."*
> *(Participant 67, 43-year-old, Female, Hispanic).*

> *"I've had difficulty getting into a detox. There are no beds. There are more beds for males than for females. It's been this way since I've been going to detox, for 20 years."*
> *(Participant 68, 45-year-old, Female, White).*

Accessibility relates to the relationship between the geographical location of service supply and patients' location reflecting means of transportation, travel time, distance and cost. In this study, 8 out of the 28 participants reported facing significant challenges with transportation or living too far from a clinic with OUD treatment services.

> *"The methadone clinic was too far away. It was a long distance that I had to travel, and it was hard to get there. They offered resources but it was a real big process to go through, and it was hard."*
> *(Participant 87, 38-year-old, Male, Black)*

Accommodation refers to the organization of health systems and resources to accept patients' needs. This includes systemic issues such as hours of operation, mode of appointment scheduling: walk-in, schedule only, open access, and availability of telehealth versus hybrid services. In this study, two themes reflected the accommodation domain- 1.) Cumbersome substance use treatment schedule, especially the federal opioid treatment guidelines that mandate strict methadone dosing schedules (including daily clinic attendance, observed dosing, mandatory urine screening, and documentation requirements etc.); 2.) Unique challenges of lost or stolen medications posed for people experiencing homelessness. The healthcare system (insurance) and providers may not be accommodating about medication refills for lost or stolen medications for OUD, which may lead to treatment discontinuation.

> *Well, the messed-up part is having to come in every day. I tried to do take-home methadone, but the bottles got stolen from me. When I tried to explain what happened at the clinic, they didn't want to hear it. So now I have to go in every day instead of twice a month. That take-home is an incentive, because you don't have to come in every*

day. Every day I get here before 11 o'clock and get out around one o'clock. So, it can be somewhat of a bitch doing that, coming in. (Participant 17, 64-year-old, Male, Black).

Finally, Acceptability concerns the relationship between patients' reaction to provider attributes including sex, age, ethnicity, religious affiliation, and neighborhood of facility etc. Of note is that based on the inductive codes, acceptability of MOUD and other SUD treatments were coded under this theme. Acceptability expresses the extent to which the client is comfortable with the "more immutable characteristics of the provider", and the reciprocity of such relationships [218]. In this study, data relating to acceptability of MOUD were coded under four themes. The first theme related to fear and encompassed perceived fear of adverse effects of MOUD (including precipitated withdrawal), fear of being around those in treatment, fear of MOUD after hearing about people who overdosed while taking them, fear of methadone after hearing about specific adverse effects such as stunted growth, teeth rotting, weakening of bones, and sexual dysfunction.

Acceptability theme 1:
"I took a Suboxone film, and I got the immediate withdrawal one time. I had a vicious detox that happened right after, and it gave me trauma, so I am unable to use the stuff. I can't smell it. I can't be around it. Or I vomit from the trauma. I took it too soon after I used." (Participant 40, 36-year-old, Male, White)

The second *Acceptability* theme centered on patients' belief that taking MOUDs replaces one addiction for another.

Acceptability theme 2:
"Suboxone, that stuff is addictive too. People get addicted to Suboxone. It's supposed to stop your addiction or you getting high from dope, but people have addictions. It's just another addiction." (Participant 7, 32-year-old, Female, Black)

The third *Acceptability* theme focused on community disapproval about taking MOUD, perception that taking MOUD was at odds with personal religious beliefs and stigma from their families and the community:

> *Acceptability theme 3:*
> *"I'm Muslim. It's strongly forbidden even to smoke cigarettes. So to do the drug thing, that's even more so. It isn't that they're strongly against anything, like medications to take for opioid disorder. But anything that's going to cause you to get a habit, in exchange for another habit, that's forbidden."*
> *(Participant 17, 64-year-old, Male, Black)*

The final theme conveys the negative experiences concerning neglect and discrimination at treatment clinics. Participants expressed the feeling that they were differentially treated based on race and/or gender as regards to being connected to treatment resources, receiving medication doses in methadone clinics, and admitted to medically supervised withdrawal management.

> *Acceptability theme 4:*
> *"There's racism every day. When you're Black or Hispanic, they don't want to treat you. They give you the run-around. Go over here, go over here, but if you're white you get more treatment than anybody. It aggravates me. When you walk into a detox or a treatment facility and you say, "I need help for this addiction" and they'd be like, "we don't have those services here." But if you're white and you're right behind me, everybody be like, "Come on in, we can help you." The color of my skin dictates everything: job employment, resources in detox, any help that I want. They think all Black people, or Hispanic people are addicts. We're no different than the next person."*
> *(Participant 89, 37-year-old, Male, Black).*

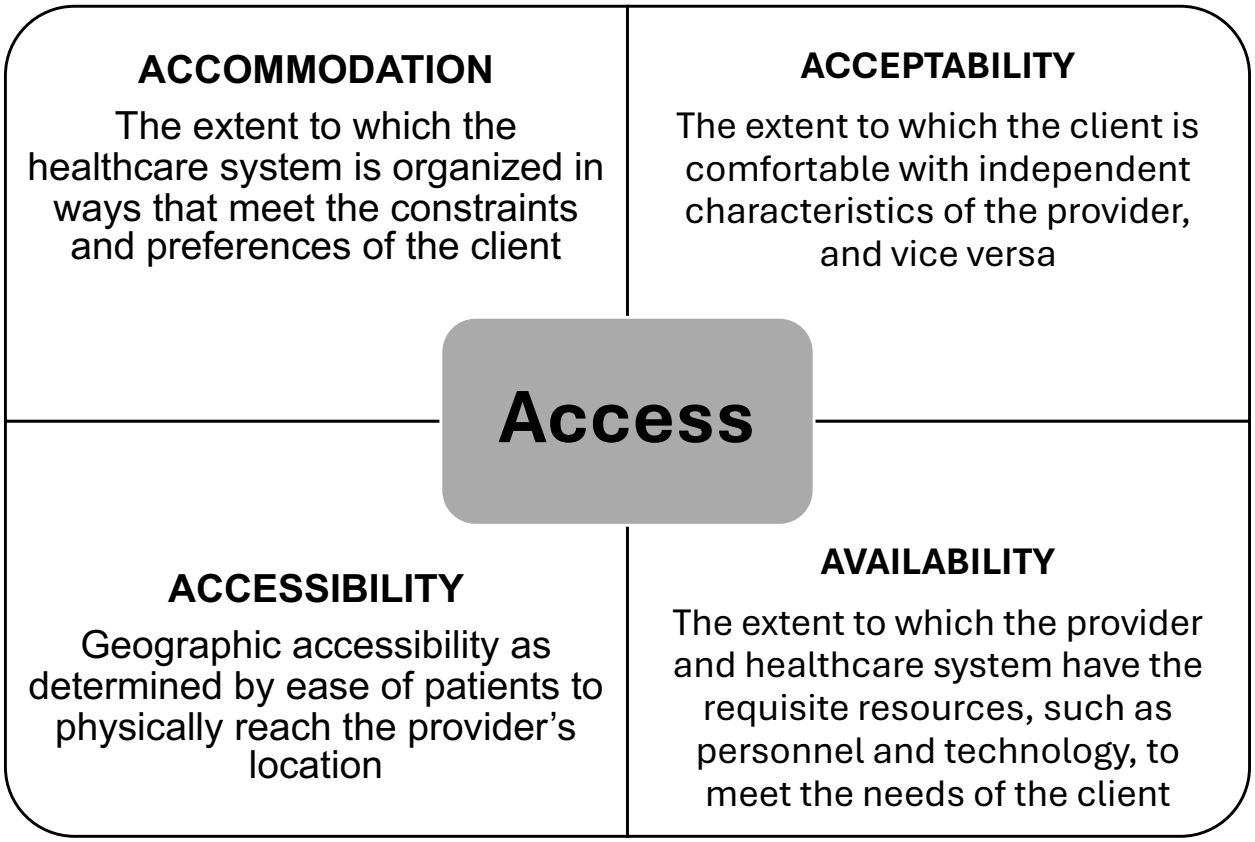


Figure 3.3: Interconnectedness of the 4-dimensional access points based on thematic analysis reported in Publication 9.

3.3 Conclusion:

As illustrated in Figure 3.4, Chapter 3 conceptualizes a paradigm that positions systemic racism as a fundamental cause of inequities in substance use disorder treatment - producing structural vulnerability and adverse health outcomes, particularly among minoritized populations. The interaction between social determinants of health and structural vulnerability is complex and can be understood through the representation of social determinants as markers of structural exposure and risk. This integrative understanding offers a novel lens for prevention and intervention, highlighting how addressing structural inequities is essential to improving addiction treatment outcomes and advancing health equity.

Chapter 4 : Implications for translational addiction science within a complexity framework

4.1 Publications: Titles and Contributor Roles

Publication 10: Rates and correlates of dual diagnosis among adults with psychiatric and substance use disorders in a nationally representative US sample [219]

Contribution to the work: Conceptualization; Methodology; Investigation; Formal analysis; Data Curation; Writing – Original Draft; Visualization; Project Administration; Supervision.

Publication 11: What Would Equitable Harm Reduction Look Like? [16]

Contribution to the work: Conceptualization; Literature Search; Data Curation; Writing – Original Draft; Visualization; Project Administration.

Publication 12: Building Outreach and Diversity in the Field of Addictions [220]

Contribution to the work: Conceptualization; Literature Search; Data Curation; Writing – Original Draft; Visualization; Project Administration.

4.2 Chapter 4 Commentary

This chapter brings together Chapters 1 and 2, focusing specifically on the practical applications of the candidate's body of work in clinical addiction science using the framework of complexity. The concept of complexity forms the foundation for translating addiction research into actionable processes that can benefit patients with SUD. It bridges the understanding of SUD as disorders with complex biopsychosocial etiology and treatment outcomes which are impacted by proximal and distal social determinants. As complex disorders, SUDs are better managed within dynamic systems that can self-interrogate, evolve, integrate care management [221], use collaborative care models [222], as well as other comprehensive treatment strategies that address biopsychosocial factors.

Complex systems, as defined by Öngür and Paulus (2024), are "a network of interacting components, the collective behavior of which exhibits properties that are not easily predictable from the individual components alone," and "are characterized by non-linearity, feedback loops, emergence, and multi-level interactions" [223]. Thus, from an intervention perspective, managing SUD must involve embracing complex systems that can integrate traditionally siloed treatment components and care models.

The core principle of complexity further shows that the integration of these component systems is by no means a simple linear process but one that is dynamic, interactive on multiple levels with a potential for self-correction by built-in feedback loops. As stated, although SUDs are complex disorders in themselves, another layer of additive multidimensionality is presented in co-occurring disorders (COD) which combine psychiatric and substance use disorders [219]. The challenges of co-occurring disorders include the heterogeneity of diagnostic characteristics, risk factors, as well as

the challenge of integrating otherwise parallel or sequential siloed treatment systems and designing preventative strategies [224-226].

Traditional approaches and frameworks that address co-occurring disorders ignore the dynamic nature of these interactions, and instead assume and propagate a linear cause and effect relationship that is often reductionistic [223, 224]. Therefore, the paradigm of complexity presents a robust, comprehensive and integrated approach to understanding the interplay between SUD and psychiatric disorders [226]. For example, in the U.S, care models such as Improving Addiction Care Team (IMPACT) [227] and Care Management Models (CMM) [228] have demonstrated the benefits of integrated care. IMPACT is a care model for medically complex hospitalized patients with SUD, which consists of an inpatient addiction medicine consultation service, rapid-access pathways to SUD treatment on discharge, and a medically enhanced residential care model that integrates general medical treatments and residential addiction care [227]. CMM focuses on integrating medication management (such as antibiotic infusions), case management, care coordination, supportive counseling, thus engaging patients with complex SUD who are high utilizers of services [229]. These models have been shown to be effective in reducing hospital readmissions and improving treatment adherence [230, 231].

Further, it is important to highlight that complexity in addiction science has extended beyond the interplay between SUD and psychiatric illness in the past year, to include contextual and structural environments in which they exist, interactions of multiple SUD (polysubstance use) and the increased risk of other medical comorbidities. Thus, SUDs present fluid, dynamic, and multidirectional relationships with multiple modifying biopsychosocial factors.

Translational addiction science must therefore embrace the complexity framework to understand and address the multiplicity of factors that interact within the frame of an individual with SUD and the structure within which they seek treatment. The incorporation of complex systems into healthcare has important policy implications with a potential to reduce racial disparities through self-correcting mechanisms, which detect and adjust for emerging programmatic and structural imbalances without needing constant external intervention.

These systems are constructed to continuously monitor outcomes, identify inequities and trigger interventions (e.g. policy changes, resource reallocation, clinical decision support prompts). For mental health systems to be equity-based, they must address stigma and incorporate open access, low barriers models, cultural humility, multidisciplinary, and harm reduction approaches that address SDOH as discussed in this chapter (**see section 4.2.2 below**).

It is of note that in the U.S. State of Connecticut, the complexity and significance of co-occurring disorders is recognized throughout the state healthcare system. Testament to this, the candidate serves as the co-occurring disorders consultant to the State Department of Mental Health and Addiction Services (DMHAS), and in this capacity, provides biweekly consultation and training for mental health clinicians across the state Local Mental Health Authorities (LMHAs) that offer a wide range of therapeutic programs and crisis intervention services for individuals with co-occurring disorders. A practical example of an evolved mental health system will include integrated mental, primary care, and addiction services for individuals with co-occurring disorders. Such systems must recognize that co-location of these services is necessary but not sufficient to address comorbidity which will require adaptive, networked and relational systems

[232, 233]. A complexity-informed dual-diagnosis system might include co-location of mental health and addiction clinic with integrated electronic medical records, multidisciplinary case conferences incorporating patient and community voices, regular reflective analysis of systemic patterns and workflows, constructive provider outcome dashboards, community partnerships and social services (housing and employment agencies).

Chapter 4 is focused on the translational aspect of the candidate's research in addiction science as follows: 1.) Publication 10 discusses the rates and correlates of co-occurring disorders (dual diagnosis). Based on this work, dual diagnosis is represented as a proxy for complexity in the field of addiction science; 2.) Publication 11 extends the theme of complexity by highlighting emerging racial disparities in harm reduction programs and argues for the urgent need to integrate SDOH into harm reduction programing to reduce inequities in its offering. Finally, 3.) Publication 12 discusses the limited state of workforce diversity in the field of addiction science and offers strategies to build outreach and diversity.

4.2.1 Dual diagnosis challenges mental health systems (Publication 10) [219]

As discussed in Chapter 3 (**section 3.1**), psychiatric disorders add a burden of co-morbidity to SUD as both disorders have a shared etiology, a shared vulnerability and mutually exacerbating clinical course, but unfortunately have siloed treatments. There is a high prevalence of past year and lifetime psychiatric and SUD co-morbidity. For example, according to the National Comorbidity Survey (NCS), individuals with any lifetime DSM-III-R psychiatric disorder were 2.4 times more likely to have any lifetime SUD compared to those with no psychiatric disorders.

About half (51.4%) of participants in the NCS who reported a lifetime alcohol or SUD, also met the criteria for at least one lifetime psychiatric disorder, and 50.9% of those with a lifetime psychiatric disorder also had a history of SUD [234, 235]. Data from the 2019 National Survey on Drug Use and Health (NSDUH) showed that 9.5 million U.S adults (15.5% of those with either past year SUD or any mental illness) were dually diagnosed.

However more recent NSDUH data, published in 2023, showed that 21% had past year serious mental illness (SMI, defined as a diagnosable mental, behavioral, or emotional disorder that substantially interferes with a person's life and ability to function, typically including DSM-5 diagnoses like bipolar disorder, major depressive disorder, and schizophrenia) or SUD and among the 14.6 million adults who had a SMI, nearly half (6.8 million people) also had an SUD [3].

Publication 10 examines the complexity of co-occurring disorders, and its distinct public health and psychosocial challenges that will require a mental health system with complexity scaffolding to address. Such scaffolding will include adaptive, networked and relational systems as discussed in section 4.2 above.

Previous studies based on clinical samples have shown that compared with those with either primary psychiatric disorders or SUD, individuals with co-occurring disorders tend to have a higher burden and severity of symptoms, poorer treatment outcomes, greater risks of homelessness, greater involvement with law enforcement and more frequent utilization of inpatient and emergency department services [236-238].

However, prior nationally representative epidemiologic studies on co-occurring disorders have only primarily examined the prevalence of co-occurring psychiatric and SUD [239-243] and not their associated socio-behavioral correlates. In addition, data on the clinical severity and life adjustment challenges of dual diagnoses, have been mainly based on convenient clinical samples [238, 244, 245]. As a result, information on the socio-behavioral adversities associated with dual diagnoses is limited.

Publication 10 fills this gap by presenting the scope of socio-behavioral complexity of co-occurring disorders [219]. Using a nationally representative sample, Publication 10: 1.) Presented estimated proportions of dually diagnosed adults in the population with either any psychiatric disorder or SUD, with both diagnostic groups considered separately and combined. 2.) Examined the sociodemographic, behavioral, diagnostic, and service use characteristics of dually diagnosed adults compared with those of adults with psychiatric disorders or SUD only.

Publication 10 used the NESARC III dataset, to explore *sociodemographic characteristics* (age, sex, race, marital status, annual income, education, employment,

urban residence, primary health insurance coverage, and veteran status), past year and lifetime psychiatric diagnosis and SUD (based on the AUDADIS-5 [246], which were constructed on criteria from the DSM-5), and dual diagnosis constructed as a dichotomous variable representing the presence of any past year psychiatric diagnosis and any past year SUD.

Behavioral variables included history of incarceration, involvement with the criminal justice system, violent behavior, past year homelessness, parental history (of substance use, incarceration, psychiatric hospitalization, suicide attempt or death by suicide), adverse childhood experiences, social contacts, religious services, and health-related quality of life (HRQOL).

HRQOL was assessed using the Short Form 12 (SF-12), a 12-item standardized questionnaire with algorithm-based scores ranging from 0 to 100 for both a mental health component score (MCS) and a physical health component score (PCS), with higher scores indicating better mental and physical HRQOL [247]. Both were standardized to the US population with a mean of 50 (standard deviation of 10, range 0–100).

Homelessness was assessed by three dichotomous variables reflecting self-reported lifetime homelessness, past-year homelessness, and homeless experience before the age of 15 years old. *Social Support* was measured by the Interpersonal Support Evaluation List (ISEL-12) as described in section 3.2.1 [175]. The e*xperiences of discrimination* variables were constructed as described in Section 2.2.6 (page 67).

For *psychiatric and SUD service use*, first, a lifetime treatment for primary psychiatric disorders was identified. Then, a global dichotomous variable was created to indicate whether respondents had ever received any care for any substance use-related

problem. A second dichotomous measure was created to indicate receipt of SUD treatment that could potentially be of definitive value, including services received from family services agency, outpatient clinic such as outreach day or partial patient programs, private physician, psychiatrist, psychologist, social worker, rehabilitation programs, or other professional or another agency or professional in the past year. Crisis intervention, emergency room services, or inpatient hospitalization programs were not included in this second measure as they offer time-limited services and not ongoing, potentially long-term treatment. Self-help groups and help from clergy were also not included as *definitive* treatments for SUD as they are located outside professional SUD treatment programing; however, they were examined separately.

Results from Publication 10 are as showed in **Table 4.1**.

The main results showed that:

1. 2,176 U.S adults had a dual diagnosis (estimated to represent 13.5 million adults) corresponding to 25.8% of those with any psychiatric disorder (n = 8272, estimated to represent a total of 52.2 million adults). Individuals with dual diagnosis were further estimated to represent 36.5% of those with any SUD (n = 5,774, representing 36.8 million adults). Combining these figures, results show that adults with dual diagnosis are estimated to represent 17.8% of all adults with either psychiatric or SUD (n = 11,870 representing 75.6 million adults) [219].
2. Across the three groups (dual diagnosis, psychiatric disorders-only and SUD only-group), the dual diagnosis group were younger (35.8±13.6) and more likely to be male (47.6%). The dual diagnosis group were also more likely to have *never married* compared to those in the psychiatric disorders-only group (41.7% versus 20.3%; RR=2.05), to be disabled compared to the SUD only-group (9.7%

versus 3.3%; RR=2.97) and more likely than the SUD only-group to have an income <$20,000 (36.5% versus 23.7%; RR=1.54).

3. Individuals with dual diagnosis also had more burden of life adversities across all measured behavioral variables. Compared to the other groups, they were more likely to report (i) a history of incarceration both before and after the age of 15 years old, (ii) past year trouble with police, (iii) violent behavior, and (iv) past year homelessness as well as (v) parental characteristics such as alcohol use, drug use, incarceration, psychiatric hospitalization, suicide attempt and death by suicide. Compared to the SUD-only group, individuals with dual diagnosis reported worse adverse childhood experiences including childhood neglect, sexual abuse and repeated trauma.
4. Compared to both the psychiatric disorders-only and the SUD-only groups, those with dual diagnosis, were more likely to report past-year racial discrimination, and to have less social support than the SUD-only group. Individuals in the dual diagnosis group also had a significantly poorer mental HRQOL than the other two groups, and poorer physical HRQOL than those from the SUD-only group.
5. In terms of clinical characteristics, both single and multiple lifetime psychiatric diagnoses were far more likely to be reported among those dually diagnosed than among those with past year SUD-only. Of note is that the dual diagnosis group, compared to the psychiatric disorders-only group, was significantly more likely to meet the criteria for bipolar I disorder in the past year (12.2% versus 5.1%, RR=2.40). Relatedly, lifetime SUDs were more likely to be reported among those with dual diagnosis compared to those with psychiatric disorders-only. The dual diagnosis group also reported significantly higher proportions than the SUD-

only group with past-year opioid, cannabis, cocaine, and sedative use disorders as well as with more than one SUD. In addition, compared to the SUD-only group, the dual diagnoses group had a higher number of medical comorbidities (Cohen's d = 0.36) and more chronic pain (29.9% versus 15.0%; RR=1.99).

6. Regarding service use, as expected, the dual diagnosis group reported greater likelihood of receiving both *any mental health* and *psychiatric treatment* than the SUD-only group but interestingly, they were also more likely than the SUD-only group to receive all types of SUD treatment services.
7. Multivariable logistic regression models identified variables that were independent correlates of being dually diagnosed among those with psychiatric disorders, showing statistically significant positive correlations with younger age, lifetime violent behavior, poor mental HRQOL, male gender, with better physical health-related quality of life, meeting diagnostic criteria for bipolar disorder, past year police trouble, past year homelessness, having never been married, and being widowed. When service use variables were added to these factors, in the psychiatric disorders-only group substantial effects were found for past-year SUD treatment (outpatient or residential treatment) and any kind of assistance for SUD, including hospitalization and emergency department use.
8. Among those with any past year SUD, multivariable logistic regression analysis of dual diagnosis revealed the following statistically significant positive correlates: poor mental HRQOL, witnessing trauma in childhood, more than one lifetime SUD diagnosis, childhood sex abuse, parental suicide attempt, parental drug use, number of current medical problems, being retired, exposure to repeated traumas, child neglect, less social support, being in the lowest income category

(<$20,000), insurance coverage by Medicaid and having a parent who completed suicide. When service use variables were added to the model, those dually diagnosed were more likely to have received lifetime psychiatric treatment, participated in self-help and to have received past-year alcohol treatment than other groups.

In summary, Publication 10 showed that among U.S adults, about a quarter (25.8%) of those with any past-year psychiatric disorder met diagnostic criteria for dual diagnosis (both past year psychiatric and SUD), 36.5% of those with any past-year SUD, and 17.8% of those with either past year psychiatric disorder or SUD met criteria for dual diagnosis.

This study strengthened the hypothesis articulated in this thesis that dual diagnosis represents psychiatric complexity in terms of its associated biological (diagnostic), social, and behavioral-related adversities.

Publication 10 also showed that adults with dual diagnosis were more likely to experience multimorbidity, i.e., to have more than one lifetime psychiatric diagnosis or SUD than both single diagnosis groups. This extensive burden among these individuals underscores why healthcare systems must accommodate the needed complexity by developing systems and sub-systems to address these problems. Some ways to embrace this complexity include:

a) Avoid reductionistic siloed treatment models and move towards integration of mental, addiction and medical treatments, not only through co-location of services but also embracing other aspects of systems complexity such as functional

networked integration that includes electronic record systems that talk to each other and cross-trained clinicians (see section 4.2).

b) Use layered, adaptive and multilevel interventions that simultaneously address more than one aspect of the socioecological framework, including intrapersonal and interpersonal, organizational, community and policy.

c) Identify and address barriers to treatment integration including the expansion and cultural adaptation of evidence-based treatments.

d) Encourage a cross-sector collaboration and multidisciplinary approach to treatment including support systems such as family members, peers support, and community resources.

e) Incentivize equity-based payment/reimbursement models within complex systems including workforce diversification.

f) Address mental health and addiction stigma by incorporating social determinants of health into current models of care, and

g) Expand the training and education of healthcare workers by building learning networks where clinicians can continuously generate and adapt knowledge, identify complexity, and prioritize and practice cultural humility.

Table 4.1: Selected behavioral and clinical characteristics of patients with dual diagnosis, psychiatric diagnosis-only and SUD-only

	(1) Dual Diagnosis (n=2,176; 18.33%)	(2) Psychiatric disorders-only (n=6,096; 51.36%)	(3) SUD-only (n=3,598; 30.31%)	Group (1) vs. Group (2)	Group (1) vs. Group (3)
Variables				RR(†) or *d* (¶)	RR(†) or *d*(¶)
Adverse childhood experiences					
Neglect, mean (SD)	15.86 (7.41)	14.60 (7.03)	12.72 (4.85)	0.19	0.48¶
Sexual abuse, mean (SD)	5.31 (3.02)	5.07 (2.77)	4.32 (1.39)	0.09	0.40¶
Repeated trauma (%)	21.46	20.93	11.69	1.03	1.83†
Witnessed trauma (%)	72.43	65.42	53.94	1.11	1.34
Any trauma (%)	72.06	67.55	50.95	1.07	1.41
Discrimination					
Any discrimination (%)	34.96	24.56	23.43	1.42	1.49
PY Discrimination, mean (SD)	1.41 (0.59)	1.28 (0.50)	1.25 (0.46)	0.25¶	0.32¶
Health System Discrimination	1.26 (0.62)	1.20 (0.54)	1.14 (0.45)	0.12	0.23¶
Public/Job Discrimination	1.51 (0.76)	1.37 (0.68)	1.35 (0.64)	0.20¶	0.24¶
Abusive Discrimination	1.42 (0.65)	1.25 (0.52)	1.26 (0.51)	0.31¶	0.30¶
Social Support (ISEL), mean (SD)	2.82 (0.56)	2.88 (0.54)	3.03 (0.44)	-0.12	-0.41¶
Health-related Quality of Life					
Mental component summary: SF-12, mean (SD)	41.65 (11.59)	44.96 (11.60)	50.45 (8.64)	-0.31¶	-0.82¶
Physical component summary, SF-12, mean (SD)	49.69 (11.08)	46.52 (12.35)	51.94 (8.63)	0.29¶	-0.20
Quality Adjusted Life Years (EQ-5D), mean (SD)	0.83 (0.12)	0.82 (0.14)	0.91 (0.09)	0.05	-0.06
Clinical Characteristics					
Lifetime Psychiatric diagnosis (%)					
Single diagnosis	38.99	45.75	12.79	0.85	3.05†
>1 diagnosis	60.49	53.31	4.21	1.13	14.36†
PY Psychiatric diagnoses (%)					
MDD	57.03	49.89	NA	1.14	NA
Generalized Anxiety	24.32	23.69	NA	1.03	NA
Bipolar I disorder	12.22	5.09	NA	2.40†	NA
PTSD	25.66	19.31	NA	1.33	NA
Single diagnosis	53.13	64.10	NA	0.83	NA
>1 diagnoses	46.07	34.74	NA	1.33	NA
Lifetime SUD diagnosis (%)					
Single diagnosis	58.10	22.48	77.69	2.58†	0.75
>1 diagnoses	41.87	8.11	22.25	5.16†	1.88†

† RR>1.5 or <0.67 and refers to ¶ Cohen's *d*>0.2 or <-0.2, *d*=Cohen's *d*, RR=Risk ratio, SD=standard deviation, MDD= Major depressive disorder; PTSD= post-traumatic stress disorder; SUD=Substance use disorder, ISEL= Interpersonal Support and Evaluation List

4.2.2 Addressing inequitable complex SUD treatment using the harm reduction model (Publication 11) [248]

Traditional healthcare systems and education providers have predominantly focused on reductionistic biological disease causation and treatment models of SUD while ignoring social causation [249]. Thus, there is an urgent need to explore alternative models that center complexity and equity within the addiction field. Publication 11 is an invited narrative review that focuses on the emerging concern for inequity regarding harm reduction programing. This paper argues that to be truly equitable, harm reduction programs must focus on the social determinants of health **(Figure 4.1).** Harm reduction optimizes individuals' safety by reducing the harmful effects of minoritization and stigmatization. It is indeed a recognized method to achieve equity, but like many programs, without proper oversight, it can become inequitable.

Harm reduction affirms people with SUD by centering their voices, elevating their autonomy while interrogating policies that impact people with lived experience. Harm reduction seeks to eliminate judgmental and coercive language, services, and mandates. Harm reduction programs involve distribution of naloxone, improving access to medication treatments for SUD, and expanding Good Samaritan laws, safe consumption sites, and clean needle exchange. Harm reduction has been in the news since the escalation of the opioid overdose crisis as traditional interventions are limited and inequitable [248, 250] .

The harm reduction philosophy is however not new; it started as grassroots, bottom-up, community-based movement championed by people with lived experience during the HIV/AIDS era of the 1980s. Indeed, the modern harm reduction movement, as a

formalized public health approach, is traced back to the United Kingdom in the early 1980s, especially the Mersey Model, which originated in Liverpool and included providing the community with methadone, sometimes heroin, clean needles, condoms, and safe sex education. It is known, however, that parallel harm reduction efforts were also taking root in the Netherlands, Australia, and activist networks in North America [251].

The central assumptions of harm reduction as described by Alan Marlatt (1996) [252] include the following: 1.) Harm reduction is a public health alternative to the moral, criminal and disease models of drug use and addiction; 2.) Harm reduction recognizes abstinence as an ideal outcome but accepts alternatives that reduce harm; 3.) Harm reduction has emerged primarily as a “bottom-up” approach based on addiction advocacy, rather than a “top-down" policy; and 4.) Harm reduction promotes low-threshold/easy access to services, representing a fast, simple, non-judgmental, and flexible means of accessing care as an alternative to traditional high-threshold approaches.

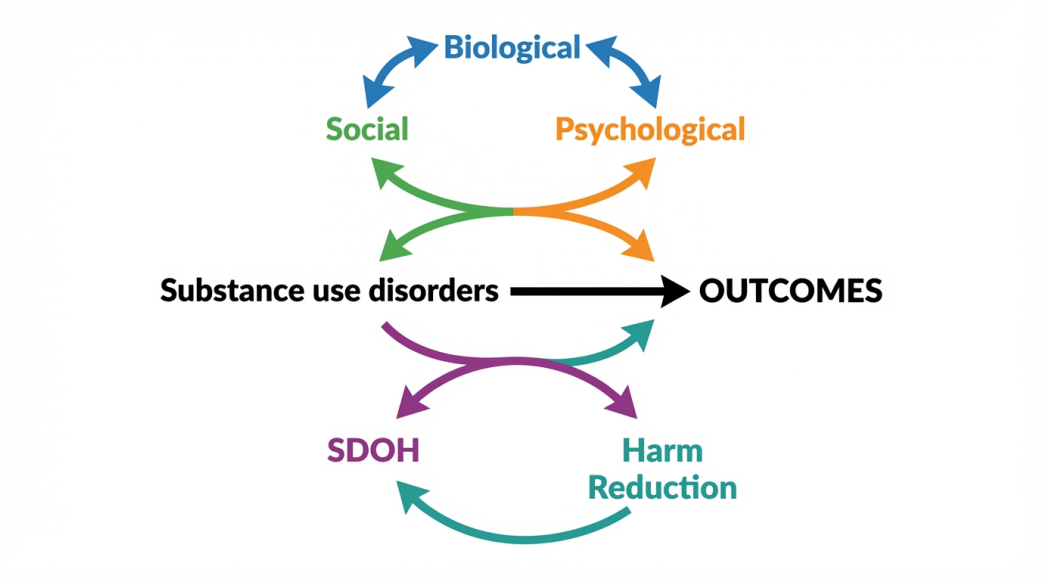


Figure 4.1: Interaction of social determinants of health and harm reduction within an interrelated framework, and a biopsychosocial model of substance use disorder. [16]

SDOH-social determinant of health

The history of harm reduction in the U.S has been inextricably linked with the Black Panther and Young Lords movement. Huey P. Newton and Bobby Seale founded the Black Panther Party in 1966. They established several programs for minoritized communities, including food banks (Free Breakfast for Children initiative), free medical clinics (including sickle cell anemia tests), free legal advice seminars, clothing banks, and housing cooperatives [253]. Based on these programs and its focus on social justice and health equity, the movement demonstrated the essential principles of harm reduction.

Alongside the Black Panthers, the Young Lords, in 1970, revived the Lincoln Hospital in the Bronx, at a time when the hospital was neglected, mired in unsanitary conditions, understaffed and located in the neighborhood consisting of people mostly affected by social and economic inequalities and drug mortality above the national average [254]. These organizations (The Black Panthers and the Young Lords) established drug detoxification and acupuncture programs for people with SUD in that community, thus addressing the needs of the community in a culturally sensitive and appropriate way.

Modern harm reduction programing in the United States includes supplies and services. Harm reduction supplies comprise overdose reversal medication (naloxone), drug test kits (fentanyl and xylazine test strips), safe sex kits (condoms), sharps disposal and medication disposal kit, wound care supplies (particularly for xylazine related wounds) and syringe services programs (SSP). SSPs are community-based prevention programs that provide a range of services including testing, counseling and sterile injection supplies. Over the past three decades, SSPs have been shown to be safe and effective in reducing drug overdose deaths, cost-saving, not associated with

increasing illegal drug use or crime and to reduce the spread of viral hepatitis, HIV, and other infections [255, 256].

Publication 11 pointed out the key equity foundations of harm reduction including the following [248]: 1.) Reducing the stigma of substance use by providing an alternative to the moral failure and disease model approaches to substance use treatment; 2.) Respecting the human rights and personhood of people with SUD; 3.) Elevating and affirming the autonomy of people with SUD and their right to be included in their own treatment by providing a choice for safer use, managed use, or abstinence; and 4.) Adopting a community-oriented approach by ensuring the overall safety of the community.

However, emerging literature shows evidence of inequity in harm reduction services. A qualitative study of harm reduction programing shows the prevalence of structural and institutional racism in services suggesting that race-neutral harm reduction policies and practices fail to address the intersectional nature of the drug crisis [257].

Further, Publication 11 highlighted studies of the adoption of Good Samaritan laws (which confers criminal immunity to individuals who offer assistance during an overdose event), as inadvertently exacerbating preexisting racialized inequities. This is because public education campaigns have failed to offer minoritized communities with SUD the same level of awareness of these laws compared to privileged populations, thus fostering misinformation about the legal protection these laws offer and resulting in a lack of willingness among minoritized individuals to offer assistance [258].

Inequities have also been reported regarding naloxone training and distribution. A study on Medicare claims from 2016 to 2019 showed that within 180 days of an opioid

overdose event, only 14.4% of Black Americans with OUD were prescribed naloxone compared to 22.9% of their White peers [15]. Data among people who use illicit opioids in New York City also showed quantified racial/ethnic disparities in the naloxone care cascade (assessing progressive steps of successful naloxone distribution, including naloxone awareness, obtainability, availability, training, and possession) [259, 260]. Khan and colleagues (2023) also showed that Black participants with SUD compared to White participants, had disproportionately low odds of naloxone training (OR 0.40, 95% CI 0.22–0.72) [259].

In summary, harm reduction programing is a complex, dynamic set of practices poised to continue to evolve as a major intervention regarding the care for people with SUD within a complex healthcare system. Publication 11 is a reminder that, as communities continue to struggle with the toll of drug overdose mortality, well-meaning harm reduction practices and programs must center the assessment of social and structural dynamics (i.e. SDOH) to ensure protection for racially minoritized people with SUD [261].

4.2.3 Building outreach and diversity in addiction science (Publication 12) [220]

Publication 12 is an invited manuscript for the Special 35th Anniversary Edition of the American Journal on Addictions, marking a milestone of organized addiction sciences in the U.S by the American Academy of Addiction Psychiatry (AAAP) [262]. AAAP is a national professional body of board-certified Addiction Psychiatrists in the U.S, established in 1985 with a mission to foster evidence-based prevention, treatment and recovery approaches, particularly for people with SUD and co-occurring disorders. The AAAP and American Society of Addiction Medicine (ASAM) are the major professional bodies of addiction physicians in the U.S. While the addiction psychiatry specialty is only open to board certified psychiatrists, addiction medicine is open to physicians in other medical fields such as internal medicine, pediatrics, family medicine, obstetrics and gynecology as well as psychiatry [263].

This publication is a response to the state of addiction practice in terms of the dismal representation of minoritized physicians in the field. Unfortunately, this trend persists at the time of writing this thesis [264-266]. In 2018, according to the handbook of the American Council of Graduate Medical Education (ACGME) [267] - a body that sets training standards for postgraduate specialty and subspecialty medical education in the United States – Black African-Americans made up only 3.61% of subspecialty trainees in Addiction Psychiatry and 0% in Addiction Medicine compared to 55.4% and 59% of White trainees respectively **(Table 4.2).** Specifically in Addiction psychiatry, according to personal communication by the Ph.D. candidate with the AAAP, based on information provided by 1,599 out of 1,800 AAAP members, African Americans and Native

Americans make up only 6.9% and 0.25% of practicing addiction psychiatrists compared to 62% of people who identify as White **(Table 4.3).**

In addition to the obvious lack of racial/ethnic diversity and representation in the addiction field, and in the wake of the escalating opioid crisis and COVID-19 pandemic, the American Journal on Addictions recognized the urgent need to build diversity, equity and inclusion in the addiction workforce, thus the invitation to contribute this manuscript to the anniversary edition.

Publication 12 highlighted the changing ethno-demographic population of an emerging minoritized majority in the country and discussed the urgency for a diverse workforce to meet the needs of the evolving population of people with SUD, specifically given the deepening opioid crisis.

Table 4.2: Race/ethnicity profile of current addiction psychiatry and addiction medicine subspecialty trainees in 2018 (Source: ACGME data resource book)

Ethnicity	Addiction Psychiatry (N, %)	Addiction Medicine (N, %)
White non-Hispanic	46 (55.4)	23 (59.0)
Asian/Pacific Islander	18 (21.7)	4 (10.26)
Hispanic/Latino	4 (4.81)	4 (10.26)
Black/African American	3 (3.61)	0 (0)
Native American	1 (1.20)	0 (0)
Other	7 (8.43)	2 (5.12)
Unknown	4 (4.81)	6 (15.38)

Table 4.3: Race/ethnicity profile of practicing addiction psychiatrists as of January 2020 (personal communication with AAAP)

Ethnicity	Addiction Psychiatry (N, %)
White non-Hispanic	992 (62.0)
Asian/Pacific Islander	285 (16.1)
Hispanic/Latino	102 (6.4)
Black/African American	110 (6.9)
Native American	4 (0.25)
Other	130 (8.1)

Extant literature shows a decreased initiation, engagement and retention of Black, Latinx, and Native American populations in the treatment for SUD, despite increasing rates of drug overdose mortality [145, 160, 268-271]. In this context, improving diversity efforts in the workforce is crucial to understand the systemic and systematic exclusion of racial/ethnic minorized populations from the existing evidence-based treatment options, and highlight how to improve culturally affirming addiction treatment [270].

As reported in Chapter 1, even with access to care (in the form of proximity to treatment centers or availability of health insurance), minoritized communities continue to be structurally excluded from evidence-based treatments, thus bringing up the larger question of why this population is not being adequately served by the existing addiction treatment system. One possible reason, Publication 12 affirms, is the lack of racial congruency between the addiction workforce and the communities they serve.

Given racial/ethnic disparities in treatment outcomes and lack of provider diversity, it stands to reason that racial concordance (defined as shared racial identity between patient and provider) may be a possible solution to bridge the gap. In other words, improving the proportion of minoritized providers who possess culturally congruent characteristics may likely improve provider/patient communication, decrease race-based stereotyping, and thereby improve treatment outcomes.

Indeed, increasing representation among minoritized healthcare providers was a major recommendation of the Institute of Medicine report on disparities in healthcare in 2003 [272]. However, research on the subject has only yielded mixed results, with some studies showing that racial concordance may increase patient satisfaction, informed decision-making, treatment seeking behaviors and trust [273-276] while others show

that racial concordance may not be required for improved treatment outcomes [277, 278]. Put together, it is reasonable to conclude that concordance has a positive effect among “those who prefer concordance” and that the mixed results in literature reflect patient choice rather than an actual effect of racial concordance [279].

Publication 12 highlighted further the disparity in the landscape in research funding, whereby racial/ethnic minoritized scientists have been vastly underrepresented in the National Institute of Health (NIH) funding. In a cross-sectional study, the number of principal investigators (PI) holding three or more research project grants increased 3-fold between 1991 and 2020, but female and Black PIs were significantly underrepresented, even after adjusting for career stage and degree [280].

Addiction funding for research from the National Institute on Drug Abuse (NIDA) also showed a similar pattern of disparity, now known as the *Ginther gap* (after Donna Ginther of the University of Kansas) as Black PIs were 8% less likely than White PIs to be awarded NIDA funding [281, 282]. The implications of these disproportionate funding portfolios are significant, with potentially far-reaching consequences since researchers from racial and ethnic underrepresented backgrounds are more likely to pursue and conduct research that directly impacts their communities.

It is instructive that the research questions and methodologies (community interventions, cultural adaptation, health disparities) proposed by Black researchers receive less competitive scores from reviewers and are less likely to be funded [283]. Publication 12 recognizes that diversity, equity and inclusion efforts, while critically important and necessary, alone will not suffice to change this narrative. However, they remain one of the pillars for structural change.

4.3 Conclusion

Chapter 4 concludes this thesis by presenting the salience of complexity in addiction science and the implications for meaningful clinical translation. SUD and mental health treatment systems and sub-systems must evolve to manage the complexity of co-occurring psychiatric and SUD, by integrating otherwise siloed treatment frameworks and models, centering SDOH within those frameworks and improving outreach and diversity in the addiction workforce.

This needs to occur despite the changing political reality in the U.S and around the world at the time of writing this thesis (2025). Such changes includes the elimination of diversity, equity and inclusion from academic discourse, intellectual infrastructures and institutions as well as the federal defunding of various mechanisms that address these necessary pillars of equity. From a translational perspective, attention to diversity is pivotal to begin to reverse and redress the impact of structural neglect among minoritized communities with SUD.

The next chapter (Chapter 5) provides a succinct discussion of the entire thesis, summarizes highlights, important contributions of the candidate's research and future directions in translational addiction science.

Chapter 5 : Discussion and Conclusions

This *Ph.D. by Publication* thesis advances the conceptualization of social determinants of health as clinically meaningful indicators of structural vulnerability - a social science construct that captures the heightened risk of adverse health outcomes experienced by individuals or populations based on their social location or perceived positionality within societal mutually reinforcing hierarchies of power, socioeconomic disadvantage, and political dynamics [17, 18]. Three overarching themes are developed throughout the thesis:

First, inequities in drug overdose mortality are increasing for minoritized communities, driven in the U.S by high potency synthetic opioids (fentanyl and fentanyl analogs) and the co-use of synthetic opioids and stimulants (cocaine and methamphetamine). In addition to these changes in drug use patterns, the observed mortality is compounded by structural factors fueling differential access to addiction treatment, and racism-related distress and psychopathology. Together, these factors underlie the disproportionate burden borne by minoritized populations with SUD.

Second, by disaggregating the Black population into constituent subpopulations based on nativity and immigration status, the thesis demonstrates important heterogeneity in socio-behavioral characteristics across groups. This approach challenges assumptions of homogeneity and importantly, underscores the role of immigration as a determinant of health and substance use.

Third, the concept of complexity is introduced as a useful lens for understanding multimorbidity in the field of addiction science and translating addiction research into clinical care. In the complexity model, substance use disorders and co-occurring disorders in minoritized populations are conceptualized as complex conditions requiring

integrated, multidimensional healthcare systems, sub-systems, diverse workforce and evidence-based interventions (including harm reduction programs) appropriately tailored to engage the needs of the population they serve.

5.1 Translational Implications of thesis

This thesis explores the Ph.D. candidate's corpus of research with the following translational implications:

I. Policy and structural implications

Reframing social determinants of health as biomarkers of structural vulnerability in the field of addiction has important policy implications for responding to the addiction crisis in the U.S and globally. This reframing of SDOH as biomarkers of structural vulnerability challenges the traditional paradigm that otherwise emphasizes personal responsibility. In this reframed model, healthcare access, unemployment, housing instability, and systemic racism are seen as measurable and trackable signals. Thus, SDOH become legitimate targets for prevention, intervention and political investment. This reframing can justify redirecting funding from punitive enforcement approaches toward interventions that directly mitigate social determinants.

Policies could prioritize Housing-First initiatives, transportation support, employment, educational opportunities, and culturally adapted interventions tailored to marginalized communities. By embedding SDOH into the biomarker-framework, resource allocation would be better aligned to the needs for minoritized populations, with evidence showing

that addressing upstream determinants improves addiction outcomes, especially when combined with medical approaches [284, 285].

Equity-focused policy initiatives, including efforts to destigmatize mental illness, SUD and MOUDs (especially methadone) are required to address the disparities in addiction treatment. In the United States, currently less than 10% of people with SUD receive any evidence-based treatments including medications for addiction [152]. Stigma against methadone remains very pervasive. More than 90% of patients on methadone report experiencing blame or shame, and about 70% report feeling the need to conceal their treatment status [286]. Minoritized people on methadone have been described as having a *trifecta of stigmas* (of being Black, having an opioid use disorder and being on methadone) leading to poor self-esteem, psychological distress, social isolation, reluctance to initiate treatment, poor treatment retention and poor quality of life [287].

In the United States, new steps are being taken in the right direction in the wake of the COVID-19 pandemic, including a new Substance Abuse and Mental Health Services Administration (SAMHSA) rule known as Final Rule (42 CFR Part 8). This significant update to stringent regulations regarding methadone prescription, has made some of the COVID-19-related flexibilities permanent. These include take-home doses of methadone, the ability of opioid treatment programs (OTP) to screen patients and prescribe medication for OUD via audio-visual telehealth under certain conditions. It also establishes flexibility for practitioner staffing to improve access, especially in underserved areas.

II. Embedding structural vulnerability in addiction science

The conceptualization of social determinants of health as social biomarkers of structural vulnerability provides a unifying framework that bridges implementation science, health equity research, and translational addiction science. By modeling SDOH as latent variables, risk vectors, or weighted social indices, this approach enables the quantification and integration of social and structural forces into predictive and causal models of substance use and recovery. The structural context of minoritized people who use drugs can be encoded within computational architecture, thereby enhancing predictive validity, algorithmic fairness, and contextual precision. Thus, advancing an equity-centered addiction science framework that conceptualizes social and structural adversity as biologically embedded processes that shape adaptation. In doing so, this thesis theorizes a foundation for integrated, culturally responsive, and structurally competent models of addiction care that improve engagement and outcomes among historically marginalized populations.

III. Co-occurring disorders as a model of complexity and clinical translation

The thesis also addresses the implications of complexity for clinical care. Co-occurring disorders (dual diagnoses) reflect a multidimensional complexity. The systemic interdependence of SUD and psychiatric disorders challenges traditional categorical frameworks and necessitates complexity-informed approaches to treatment design, policy, and implementation.

As contextualized, dual diagnosis is a functional model for clinical translation, by illustrating the importance of integrated, cross-disciplinary care models that address both neurobiological and structural dimensions of substance use disorders. Individuals

with both psychiatric and substance use disorders are more likely to experience multimorbidity, social and behavioral adversities, and disproportionate medical diagnostic burdens than those with any single disorder (Chapter 4, Section 4.2.1).

These findings highlight the need for healthcare systems that are not only comprehensive and holistic but reflexive, adaptive, dynamic, and interconnected. Effective SUD treatment must, therefore, account for the interplay of multimorbidity, social forces, embed equity into treatment frameworks, center SDOH in clinical decision-making, and ensure workforce diversity.

Co-occurring disorders are not just diagnostic overlaps but emergent phenomena within complex adaptive networks—highlighting the need for flexible, equity-oriented interventions capable of responding to the dynamic realities of addiction and mental health care. Only through these multidimensional interventional approaches can the addiction field address the structural, social, and clinical complexities that define addiction.

5.2 Future Directions

As discussed in section 5.1, the results of this body of work have important research and policy implications. This work provides a strong rationale for future research on the social mechanisms and pathways that determine the development of substance use disorder. Despite the remarkable increase in SDOH research, there remains a gap in establishing causal pathways of social determinants to the development of SUDs that may be amenable to public health interventions.

Further, this thesis establishes the premise that although SDOH, as currently understood, are consistent and reliable indicators of structural vulnerability, showing the same patterns across different studies and populations but, as noted by Alegria and colleagues (2018) [288], there is an urgent need to develop robust and consistent strategies to collect, evaluate, and analyze the impact of social determinants. Beyond the erstwhile descriptive associations of most SDOH research, future research should employ more sophisticated statistical models to advance and simplify the understanding of the impact of SDOH on health outcomes of minoritized people with SUD. Such approaches may include life course models [289, 290], multilevel and geospatial perspectives that shed light into geographic clustering of specific determinants [291, 292], leveraging big data and machine learning to identify high risk populations and modeling complex systems interactions, for example using systems science methodologies to address SUD [293, 294]. Further, cultural adaptation of traditional, evidence-based interventions may address gaps in implementation research in addiction science.

Finally, building on the concepts this thesis introduces, future research can extend to upstream determinants beyond social determinants of health to include a set of factors

that operate at levels beyond those described in this thesis but conceptualized by the Ph.D. candidate as metastructural determinants of health. This conceptual idea is not proposed as a replacement of known frameworks but as a necessary complement to social and structural determinants - all of which co-exist and are operationalized within a mutually reinforcing tiered structure.

The tiered framework (**Figure 5.1**) acknowledges the limitation of the SDOH framework in describing further upstream elements that control and maintain inequities in addiction science. Metastructural factors situate SUDs within a wide structural and historical context, extending beyond conventional determinants to the forces that shape societies themselves. They encompass global systems, historical forces, and ideological frameworks that shape and sustain inequitable health processes. Specifically, these are factors that include colonialism, capitalistic legacies of globalization, global warming, and human displacement and nativism (**Table 5.1**). Recognition of the interconnectedness of these factors in addiction science is necessary to develop preventative strategies for SUD, developing new equitable technologies for treatments and other interventions.

Table 5.1 Proposed causal mechanisms of metastructural determinants and SUD

Metastructural Determinant	Mechanism Linking to SUD	Example	References
Colonialism	Dispossession, racial hierarchies, intergenerational trauma	Emergent and changing Indigenous substance use patterns post-colonization	[295-297]
Capitalism	Commodification of health, profit-driven drug industries, labor precarity	Opioid epidemic fueled by pharmaceutical capitalism	[71, 298, 299]
Globalization	International/cross-border drug trade, cultural diffusion, neoliberal reforms	Global drug markets, globalized stigma	[300]
Climate Change	Ecological stress, resource scarcity, forced migration	Substance use as coping in climate-displaced populations	[20, 301]
Displacement/Nativism	Migration, loss of social networks, trauma exposure	Refugees and migrants with disrupted access to care	[302, 303]

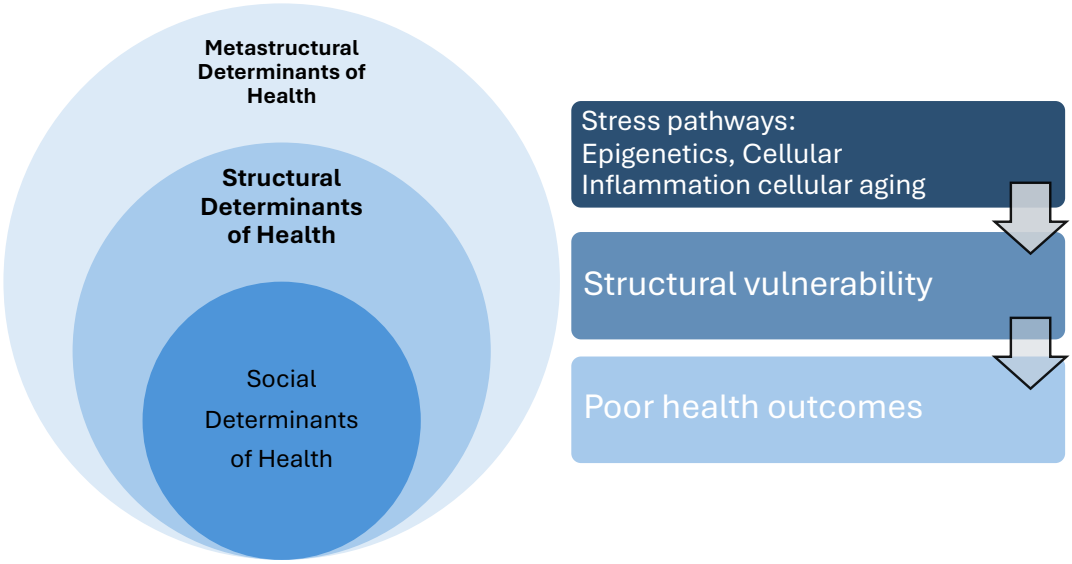


Figure 5.1: A conceptualization of a 3-tiered construction of social determinants resulting from fundamental causes and leading to poor health outcomes via biological and cellular processes and pathways

5.3 Contributions to knowledge

Each of the selected publications that comprise this thesis has made significant contributions to the addiction science literature. For example, to the best of the candidate's knowledge, Publication 2 was the first systematic synthesis of observational evidence regarding the impact of high potency synthetic opioids on clinical outcomes for people with OUD. Publication 3 was the first study to examine the prevalence and mental health impact of distress resulting from the intersection of systemic racism and the COVID-19 pandemic. Publication 4 was the first study to provide evidence of this relationship (determined in Publication 3) using a longitudinal methodology, thus offering more in-depth evidence around the persistence of the findings from Publication 3. Publication 5 was the first study to examine the association of racial discrimination and diagnostic remission from SUD using the third wave of the NESARC III, throwing light into prior research that showed mixed results. The other publications selected for this thesis have also made a significant impact in the field of addiction science and added to existing literature as reported in the respective sections of this thesis. Overall, this thesis makes the case that social determinants of health are biomarkers of structural vulnerability particularly among minoritized people with substance use disorders.

5.4 Thesis Limitations

Despite the strengths of the individual publications included in this thesis, and of combining different publications to establish a coherent portrait of scholarship, this thesis is not without limitations. Individual publication limitations were addressed in each published work and in relevant chapters of this thesis. However, the limitations in the methodological constraint of the retrospective nature of a PhD by Publication is acknowledged as is of generalizability of findings or inferring causation from cross-sectional data not otherwise designed to establish such inference.

Additional thesis-level limitations include a framework-maturity gap. While this thesis reframes social determinants of health as biomarkers of structural vulnerability, further work is required to fully operationalize this construct for clinical and health-systems use. This includes the development of standardized measurement approaches, assessment of cross-cultural reliability, and the establishment of pragmatic implementation pathways. As such, this thesis advances a necessary translational paradigm rather than providing definitive causal proof, which will require prospective designs and implementation-focused evaluation.

Finally, this synthesis integrates peer-reviewed research conducted over different time periods. Some included publications were completed prior to the availability of more recent data or evolving conceptual frameworks, introducing an inherent retrospective constraint. This limitation is partially mitigated by the integrative discussion, which applies updated theoretical framing to the existing empirical evidence.

5.5 Reflections on candidate's academic and research trajectory

Embarking on this *Ph.D. by Publication* has afforded the candidate the opportunity to reflect on his trajectory, development and growth as an academic, researcher, and physician scientist and to ponder on his contributions to the field of addiction science. This Ph.D. thesis is a representation of the candidate's corpus of scholarship with a thematic exploration of peer-reviewed published papers that demonstrate a focused and coherent line of research in translational addiction science.

These contributions are manifest in the areas of addiction pharmacology, health disparities and minority health, co-occurring disorders and health service systems development. The candidate's scholarship centers on studying SUDs as complex neurobiological disorders with underlying psychosocial correlates of etiology, course, prognosis and treatment outcomes. His work seeks to improve the dissemination of evidence-based interventions in historically minoritized, hard-to reach populations. These interventions include the utility of current pharmacotherapies and behavioral treatments in the context of high potency synthetic opioids, improving pharmacologic and behavioral treatments for stimulant use disorder and opioid-stimulant polysubstance co-use.

In the area of addiction pharmacology, his work has described protocols of low dose induction of buprenorphine as an effective alternative means to initiate buprenorphine in the absence of the clinically required mild to moderate opioid withdrawal symptoms as recommended in traditional protocols; this has the potential to improve the uptake of this life saving medication for people with OUD especially those exposed to HPSO.

In addition, the candidate has led work to enunciate the extent of disparities and inequities among historically minoritized people with SUD, highlighting how such

inequities impact health outcomes. Using national data, his research described inequities in the rates and correlates of SUD among Black populations and sub-populations of the United States. Further, his research highlighted inequities in service use, access to care, diagnostic remission, and racial discrimination among minoritized populations, including the impact of structural racism as determinants of inequity in SUD treatment, which reveal a concern for cultural determinism and race-neutral frameworks.

In addition to centering disparities and inequities, the thesis shows the translation of the candidate's research into clinical addiction practice. This thesis underscores the formulation of the candidate's research and clinical questions on social determinants of health as key biomarkers of structural vulnerability among minoritized people with SUD. The Ph.D. candidate's proximity to issues faced by minoritized populations has continued to inform his research questions. For example, he is the recipient of a recent NIH funded K23 5-year grant to develop a novel cultural adaptation of an evidence-based intervention, Contingency Management for African Americans with stimulant use disorder.

The candidate has undergone profound growth during his career and development as an independent addiction physician and scientist. His journey from clinician to researcher and academic leader reflects a deep commitment to advancing knowledge in addiction medicine. This is manifest from his selection as a REACH scholar (*Recognizing and Eliminating Addiction through a Culturally informed Healthcare*), recipient of the National Institute on Drug Abuse (NIDA) Diversity Scholars Network award - and recipient of the NIH K23 career research award (Mentored Patient-Oriented Research Career Development Award).

Over the years, the candidate has successfully published over 50 peer reviewed publications in top-tier journals. He currently serves on the board of the *Journal of Nervous and Mental Disease* and functions as a regular reviewer for several other journals including *Journal of the American Medical Association - Psychiatry*, *British Medical Journal*, *American Journal of Psychiatry*, *Journal of Addiction Medicine*, *American Journal on Addictions*, *Psychiatry Research and Journal of Substance Use and Addiction Treatment.* The candidate's work on addiction disparities research requires a strong foundation in both qualitative and quantitative methodologies as exemplified in the selected publications in this thesis. Over the course of his career, the candidate has expanded his skills in data analysis, implementation science, and health policy research, to be thus positioned as a well-rounded scientist.

In his role as faculty at Yale University School of Medicine, the candidate gives invited presentations and talks on substance use disorders, provides regular teaching as core teaching faculty of the Department of Psychiatry and serves as mentor to trainees at different levels including undergraduate, graduate and advanced trainees in psychiatry and addiction medicine. The candidate's research collaborations also include his role at the Equity Research and Innovations Center (ERIC) at Yale School of Medicine and other collaborations reflected in his body of publications.

5.6 Conclusions

This thesis brings together and extends a critical mass of literature connecting health outcomes to social determinants by extending the biomarker paradigm. The overarching hypothesis supported by the set of peer-reviewed publications synthesized in this thesis validates structural vulnerability as a measurable construct, fostering cross-sector data integration that links health outcomes with housing status, employment, criminal justice, educational attainment, and racism-related distress.

This integration could allow researchers to develop predictive models that identify populations at greatest risk, as well as evaluation of structural interventions with the same scientific rigor applied to pharmacological trials. SDOH can be modeled computationally alongside biological or behavioral data, thus creating a multilevel data architecture that captures the interaction between biology, behavior, and social structure.

This orientation situates addiction science within precision medicine, but with a broader lens that accounts for how social, environmental and structural exposures shape biological expression and treatment trajectories. This understanding not only expands the knowledge of the etiology, course and prognosis of SUD but also highlights new opportunities for innovative intervention and substance use prevention.

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