5-2024

The Implications, Magnitude, and Development of Traumatic Brain Injury for Individuals Undergoing Treatment for Opioid Use Disorder

Hannah G. Mitchell
East Tennessee State University

The Implications, Magnitude, and Development of Traumatic Brain Injury for Individuals Undergoing Treatment for Opioid Use Disorder

---

A dissertation

presented to

the faculty of the Department of Psychology

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Doctor of Philosophy in Psychology, concentration in Clinical Psychology

---

by

Hannah G. Mitchell

August 2024

Meredith K. Ginley, Ph.D., Chair

Robert P. Pack, Ph.D.

Kelly E. Moore, Ph.D.

Gerald A. Deehan, Ph.D.

Keywords: traumatic brain injury, opioid use disorder, psychotherapy, concussion, substance use

ABSTRACT

The Implications, Magnitude, and Development of Traumatic Brain Injury for Individuals Undergoing Treatment for Opioid Use Disorder

by

Hannah G. Mitchell

There is an established bidirectional relation between substance use and traumatic brain injuries (TBIs). Despite the high rate of prescribing opioids for pain management following a TBI and the epidemic of opioid use disorder (OUD) in the United States, scarce research has specifically analyzed the association between TBI and OUD. In a series of three interrelated manuscripts, the present study will first examine the prevalence and features of TBIs among persons seeking treatment for OUD. Next, the present study will evaluate the association between TBI and indicators of risky health behaviors and OUD severity, including the risk of overdose and polysubstance use. The predictive ability of symptoms of posttraumatic stress disorder, anxiety, impulsivity, depression, and chronic pain on odds of having had a TBI will also be calculated. Last, a systematic review will be conducted to provide comprehensive guidelines for effective methods of tailoring OUD treatment to mitigate the effects of TBI on treatment outcomes. Altogether, the findings will aid in the understanding of the development of TBI for persons with OUD, provide insight into common clinical complexities for patients with OUD and TBI, and offer guidance on how best to tailor interventions to increase substance use treatment efficacy for persons with TBI.

ACKNOWLEDGMENTS

I would like to extend my deepest gratitude to the participants of this study. Without their willingness to contribute their time and share their experiences, this dissertation would not have been possible. I also wish to thank the Brain Injury Association of America for generously providing grant funding that supported this research. I would like to express my appreciation to the faculty and staff at Emmaus Medical Center and Overmountain Recovery, who, despite their demanding schedules and responsibilities, kindly volunteered to help with participant recruitment. Similarly, the undergraduate and graduate-level research assistants on this project are deserving of recognition for their consistent work ethic and commitment, especially with the 5:30 AM start time. I am thankful to the supervisors who gave me the knowledge of brain-behavior relations I needed to conduct this research, including Drs. Laura Maphis and Malcolm Spica. I am also indebted to my dissertation committee members, Drs. Kelly Moore, Robert Pack, and Gerald Deehan, whose expertise and guidance strengthened and directed this project. I would like to extend my sincere gratitude to my dissertation chair and academic advisor, Dr. Meredith Ginley, for her unwavering flexibility, patience, and support throughout this dissertation and the entirety of my graduate training. Finally, I owe sincere gratitude to my parents, sisters, friends, and fiancé, whose enthusiasm and encouragement has made the pursuit of this dissertation, and my PhD, drastically more enjoyable. To all those mentioned, I am truly fortunate to have accrued such a wonderful system of personal and professional support, and I hope I have made- and will continue to make- each of you proud.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1. Introduction

Traumatic Brain Injury

A traumatic brain injury (TBI) is defined as a structural injury and/or physiologic disruption of brain function as a result of an external force that results in adverse clinical outcomes. The Center for Disease Control and Prevention (CDC) estimates that 1.5 million persons sustain a TBI annually in the United States (CDC, 2023a). TBI is a significant cause of death and disability in the United States, accounting for 64,362 deaths in 2020 (CDC, 2023a). In 2015, the CDC reported that 13.5 million civilian persons are receiving long-term disability due to impairment following a TBI (CDC, 2016).

However, the true frequency of TBIs is likely much higher than estimated by national statistics (Koval et al., 2020; Rowe et al., 2018). It has been estimated that between 50-90% of patients with a mild TBI are unidentified or undiagnosed (McCrea et al., 2017). Approximations of national TBI prevalence are typically extrapolated from the use of diagnostic codes in electronic health records (EHRs), which research has shown to be unreliable (Powell et al., 2008). In one study, only 56% of patients identified by hospital staff as having a TBI also had a documented TBI in the EHR (Powell et al., 2008). Evaluations of EHR data have suggested that TBIs are more likely to go undocumented when other injuries are present, the TBI is considered mild, or magnetic resonance imaging (MRI) or computed tomography (CT) scans are negative for lesions (Koval et al., 2020). Additionally, the cost of physician visits and potential occupational or recreational restrictions following diagnosis of TBI may result in a reluctance to seek medical care, and thereby contribute to the underdiagnosis of TBI (Ware & Jha, 2015).

Specific subsets of individuals are likely at heightened risk for underdiagnosis. For example, older adults have an elevated risk of misdiagnosis, despite their relatively high rates of

TBI-related hospitalization and death (CDC, 2023a). The presence of comorbid conditions, medication use, and neurological changes associated with typical aging can hinder the accurate diagnosis of TBI among geriatric persons (Albrecht et al., 2016). Additionally, neuropsychological symptoms of TBI may be misattributed to neurodegenerative disorders (e.g., stroke, dementias) or age-related cognitive decline (Peters & Gardner, 2018). Increased efforts are needed for the detection of TBI among persons at the highest risk for underdiagnosis (Coxe-Hyzak et al., 2022).

Evaluation of TBIs

Accurate evaluation of TBIs is essential to ensuring appropriate diagnosis. TBIs are categorized as mild, moderate, or severe. The diagnosis and classification of a TBI is typically based on observational assessments, such as the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974). The GCS assesses patients' responsiveness in terms of eye-opening, verbal, and motor responses to identify coma and determine the severity of TBI (see Figure 1.1).

Figure 1.1

Glasgow Coma Scale

		Score
Eye Opening Response		
	Spontaneous; open with blinking at baseline	4
	To verbal stimuli, command, speech	3
	To pain only (not applied to face)	2
	No response	1
Verbal Response		
	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words	3
	Incomprehensible speech	2
	No response	1
Motor Response		
	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Flexion in response to pain (decorticate posturing)	3
	Extension response in response to pain (decerebrate posturing)	2
	No response	1

The length of posttraumatic amnesia (PTA) is also used to gauge the severity of TBIs and predict long-term cognitive outcomes of TBI (Ponsford et al., 2016; Venkatesan et al., 2021). Estimates of TBI severity based on PTA duration are presented in Figure 1.2. Standardized

measures, such as the Galveston Orientation Amnesia Test, assess patients' orientation to person, place, and time, and memory for events preceding and following the TBI, thereby establishing PTA duration (Levin et al., 1979).

Figure 1.2

TBI Severity Based on PTA Duration

PTA Duration	*TBI Severity*
<5 minutes	Very mild
5-60 minutes	Mild
1-24 hours	Moderate
1-7 days	Severe
1-4 weeks	Very severe
>4 weeks	Extremely severe

The extent of structural damage evident on neuroimages, such as CT or MRI scans, is also used to inform TBI diagnosis and classification (Hawryluk & Manley, 2015). CT scans tend to be preferred during the acute stage of TBI since they are less costly than MRIs, yet sufficiently detect significant signs of trauma, including lesions, contusions, hemorrhaging, and bone fractures (Lezak et al., 2012). During the chronic stage of TBI, MRIs are typically preferred due to their relative accuracy in detecting brainstem lesions and improved ability to predict long-term neuropsychological impairment (Bodanapally et al., 2015). MRI and CT results must be interpreted within the context of observational assessments since they are not sensitive to damage incurred during mild TBIs (mTBIs; Bodanapally et al., 2015).

Between 75-80% of all TBIs are considered mild TBIs (mTBIs) or concussions (Jacotte-Simancas et al., 2021). The American Congress of Rehabilitation Medicine Special Interest Group on TBI relies on both GCS scores and PTA to diagnose mTBI, defining it as the following: a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: a) Any loss of consciousness (LoC), b) Any loss of memory for events immediately before or after the accident, c) Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused) and focal neurologic deficit(s) that may or may not be transient, *but where the severity of the injury does not exceed the following:* 1) LoC of approximately 30 minutes or less, 2) After 30 minutes, an initial GCS of 13-15 and post-traumatic amnesia not greater than 24 hours.

Neuropathology of TBIs

During a closed head injury (CHI) TBI, a blunt force strikes the head but does not penetrate the skull or meninges. The force of the CHI disrupts normal functioning of the brain at the location of impact, damaging the vascular tissue and neurons. The brain can suffer acceleration and deceleration forces that lead to the compression of brain tissue and injury within other brain regions (contrecoup injury; Bagri et al., 2021). Open head injuries, also known as penetrating head injuries, occur when an object pierces the skull and dura mater. The term "acquired brain injury" is occasionally used as an umbrella term that encapsulates a multitude of etiologies of brain damage, including TBI, stroke, and anoxia (Lezak et al., 2012).

TBIs are further separated into focal or diffuse injuries, although most TBIs present with elements of both subtypes (McKee & Daneshvar, 2015). Focal injuries include contusions, subdural and epidural hematomas, and intraparenchymal hemorrhage, whereas diffuse injuries refer to axonal damage, hypoxia, ischemia, and widespread cellular degradation (Lezak et al.,

2012). Focal TBIs tend to be more fatal than diffuse TBIs, regardless of injury severity (Vos, 2011).

Despite variation in points of impact, TBIs tend to produce hallmark neuropathologies, chief among them being traumatic axonal injury (TAI). Primary axotomy is a form of TAI that involves tearing or sheathing of axons and occurs within one hour of injury. Secondary axotomy is a downstream effect of cerebral vessel damage, compromise to the blood-brain barrier, increased cerebral fluid and pressure, and vasogenic edema that can develop from TBI. These neurobiological changes cause axotomies and cell death (Javeed et al., 2021).

The primary outcomes of TBI refer to damage directly inflicted by the impact to the head (e.g., skull fracture, primary axotomy, contusion, hemorrhage, destruction of brain tissue). Secondary or delayed outcomes refer to damage to the brain from a variety of sources, including hemorrhage, hypoxia, ischemia, elevated intracranial pressure, or fever, that occurs within days of incurring the TBI. Clinical monitoring post-TBI is critical for identifying and treating secondary damage. As seen in Figure 1.3, the neurological changes following TBI develop in a cascade for weeks and months post-injury (Wang et al., 2013).

Seizure activity may result from a TBI immediately (within 24 hours post-injury), early (< 1-week post-injury), and late (> 1-week post-injury). A post-traumatic seizure (PTS) is a seizure that occurs in the immediate or early timeframe following a TBI. PTS may be transient, as 75% of patients with PTS do not develop a seizure disorder (Ding et al., 2016). PTS is believed to occur because the trauma and inflammation that results from a TBI stimulates brain tissue that has a low threshold for seizures (Ding et al., 2016). PTS occurs in 2-17% of people with a TBI (Anwer et al., 2021). Risk factors for PTS include acute intracerebral or subdural

hematoma, younger age, increased TBI severity, and alcohol use disorder (Verellen & Cavazos, 2010).

PTS is distinct from post-traumatic epilepsy (PTE), which is a seizure disorder diagnosed after the occurrence of at least one late post-traumatic seizure. The risk of developing PTE corresponds with the severity of the TBI, with 2% of mTBI, 4% of moderate TBI, and 15% of severe TBI patients developing PTE (Anwer et al., 2021; Ding et al., 2016). Other risk factors for PTE include acute intracerebral or subdural hematoma, brain contusion, increased TBI severity, brain lesions, and PTS (Verellen & Cavazos, 2010). Recent examinations of neuroimaging found that lesions in the temporal lobe may predict PTE with higher specificity than injury severity (Garner et al., 2019). Potential post-TBI epileptogenic pathogens include alterations to the blood brain barrier, increased GABAergic excitability, inflammation, and glucose metabolism dysregulation (Anwer et al., 2021; Garner et al., 2019).

Psychiatric Outcomes of TBIs

Compared to individuals who experienced physical trauma without the presence of TBI, persons with past TBI are significantly more likely to endorse a broad array of psychiatric complaints. Specifically, apathy, anxiety, suicidal ideation, depression, pain, and substance use are potential outcomes of TBI (Felde et al., 2006; Moore et al., 2014; Stéfan & Mathe, 2016).

One of the most common psychiatric disorders following a TBI is posttraumatic stress disorder (PTSD), which may develop in direct relation to the attack or accident occurring at the time the TBI was acquired (Brady et al., 2009). Evaluation of U.S. military veterans found that 44% of individuals with severe TBI met criteria for PTSD whereas only 16% of veterans with non-TBI injuries developed PTSD (Hoge et al., 2008). People with TBI also tend to experience

more severe symptoms of PTSD than matched controls of people diagnosed with PTSD yet negative for TBI (Gros et al., 2017; Ragsdale et al., 2013).

Chronic pain is more prevalent among individuals with TBI than other neurological disorders (Salsitz, 2016). Hoffman et al. (2005) found that 72.5% of individuals surveyed reported pain 1-year post-TBI. Posttraumatic headaches are the most common cause of chronic pain due to TBI, followed by pain in the neck, shoulders, back, and arms (Khoury & Benavides, 2018; Moye & Pradhan, 2017). Paradoxically, chronic pain is seen in mTBIs at twice the rate of moderate-severe TBIs (Nampiaparampil, 2008). The exact mechanism by which chronic pain and TBI are associated is unclear. Past research has posited activation of brainstem structures, PTSD, depression, hopelessness, and sleep disturbances may contribute to the development of chronic pain post-TBI (Mollayeva et al., 2017).

Substance use is consistently linked with TBI (Bjork & Grant, 2009; Corrigan & Adams, 3029; Olsen & Corrigan, 2022). Although there is often a period of decreased substance use following TBI, it has been shown to increase over the subsequent months and years (Adams et al., 2021; Corrigan et al., 2012). Beaulieu-Bonneau et al. examined the trajectory of substance use post-TBI and found it returned to pre-injury levels for most participants by 12 months post-injury (2018). Risks with post TBI substance use disorder included younger age, being single, and intoxication at the time of injury (Beaulieu-Bonneau et al., 2018). Individuals with pre-injury substance use are 10 times more likely to use substances non-medically post-TBI as compared to those with no prior substance use (Corrigan et al., 2012). One potential mechanism through which TBI could increase non-medical substance use is via neuropsychological alterations to brain regions linked to craving and reward response (Koob & Volkow, 2016; Merkel et al., 2017). However, other studies have concluded that the presence of many confounding variables

(e.g., personality, socioeconomic status) and mixed findings via animal models have rendered the temporal relation between substance use and TBI unclear (Bjork & Grant, 2009; Olsen & Corrigan, 2022).

TBI is associated with an elevated risk of overdose and accidental poisoning (Byers et al., 2020; Fonda et al., 2020). The risk of overdose is over 3-times greater among opioid-prescribed U.S. veterans with a history of TBI compared to veterans without TBI (Fonda et al., 2020). Compared to the general U.S. population, there is an 11-fold increase in accidental death due to drug poisoning for individuals with TBIs (Hammond et al., 2020).

Neuropsychological Outcomes of TBIs

The chronicity and domain of post-TBI neuropsychological impairment varies widely based on the severity, point of impact, diffuse or focal nature, and classification as an open or closed head injury. However, clusters of symptoms tend to appear based on severity of TBI.

mTBI. Common symptoms of mTBI include dizziness, headache, and fatigue (Katz et al., 2015). Headache is considered acute if it resolves within two months post-TBI and chronic if it persists (Pavlov et al., 2019). The neurocognitive domain most sensitive to the impact of a mTBI is attention, which may manifest as heightened distractibility, poor concentration, and difficulty multitasking (Broshek et al., 2015). Impaired attention, slowed processing speed, and mild confusion are symptoms of post-concussive syndrome (PCS) following a mTBI (Pavlov et al., 2019). PCS typically resolves within two weeks, with 15% of patients reporting symptoms 1-year post-injury (Broshek et al., 2015). PCS is believed to have a psychogenic and neurological etiology (Heslot et al., 2021). Verbal retrieval tends to be impaired but improves with cueing to normal limits (Lezak et al., 2012). Residual problems with memory or learning are rare post-

mTBI (Cooksley et al., 2018; Dikmen et al., 2017). Activities of daily living (ADLs) are rarely impacted, and rates of returning to work are high (Cooksley et al., 2018).

Moderate- Severe TBI. Outcomes of moderate-severe TBI range widely since it encompasses a spectrum of impairment, including persons in a persistent vegetative state. Overall, moderate-severe TBI is likely to result in long-term cognitive impairment (Azouvi et al., 2017). A meta-analytic evaluation of subacute and chronic deficits for moderate-severe TBI was 49% and 21% for memory concerns respectively; 54% and 50% for attention deficits; and 48% and 38% for executive functioning deficits (Tsai et al., 2021). In an evaluation of 147 patients four years after a moderate-severe TBI, 67.5% reported memory deficits, making them the most common neurocognitive complaint (Jourdan et al., 2016). One meta-analysis found that several dimensions of memory are impaired following moderate-severe TBI (e.g., visuospatial memory, global memory), with verbal memory having the largest effect size (Vakil et al., 2019). Free verbal recall is specifically vulnerable to the effects of TBI, with verbal recognition being relatively spared (Vakil et al., 2019). This pattern of impairment is consistent with patients who have frontal lobe injury and disrupted executive functioning rather than compromised memory formation (Broadway et al., 2019). Executive functioning deficits may present as increased impulsivity and risk-taking, disinhibition, and reduced cognitive flexibility (McAllister, 2008; Ozga et al., 2018; Rochat et al., 2010). Severe TBI is a risk factor for the development of neurodegenerative diseases, including Alzheimer's dementia and Parkinson's disease (Brett et al., 2022).

Repeated TBIs. TBIs tend to have a cumulative effect on cognition such that each subsequent TBI increases the risk of impairment and the vulnerability of incurring another TBI (Lezak et al., 2012). Chronic traumatic encephalopathy (CTE) is a term referring to the

degeneration of brain tissue believed to develop years or decades after incurring multiple head traumas (Montenigro et al., 2014). CTE is only diagnosed post-mortem via autopsy, obscuring accurate estimations of prevalence rates (Cantu & Bernick, 2020). However, it is believed to occur most often among individuals who undergo repeated, significant head traumas, such as athletes who play contact sports or persons who serve in the military (Montenigro et al., 2014).

Pathologists theorize that there are two forms of CTE, with the first form developing earlier in life and causing behavioral health issues such as depression, anxiety, deficits in impulse control, and aggression (Fesharaki-Zadeh, 2019). The second form of CTE is believed to have an older age of onset, cause neurological issues, and potentially be a precursor to dementia (Fesharaki-Zadeh, 2019). Researchers have observed a buildup of tau proteins around blood vessels in the brains of individuals with CTE (McKee & Daneshvar, 2015). Abnormal Tau protein accumulation ("tauopathy") is similarly observed in individuals with Pick disease, progressive supranuclear palsy, and Alzheimer's disease (Katsumoto et al., 2019). The shared tauopathy may explain why individuals with CTE sometimes exhibit signs of other neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, or frontotemporal dementia (Katsumoto et al., 2019).

Risk Factors for TBIs

Epidemiological research estimates that men are 40% more likely to suffer a TBI than women (CDC, 2023a; Gupte et al., 2019). However, male gender identity may be an overestimated risk factor as there is growing evidence that TBIs sustained because of intimate partner violence frequently go unreported, which may result in an underestimation of the frequency of TBIs among women (Biegon, 2021). As determined by a chart review in a

hospital's department of neurology, only 21% of individuals with past TBI due to intimate partner violence sought medical treatment at the time of injury (Zieman et al., 2017).

One of the strongest predictors of TBI is acute substance use (Weil et al., 2018). Almost half of the patients who required hospitalization for a TBI in one hospital trauma center were found to be intoxicated at the time of the injury (Andelic et al., 2010). Other research has estimated that between 36-51% of individuals who admit to the emergency department following TBI were intoxicated at the time of injury (Parry-Jones et al., 2006). The most likely reason for this relation is that substances weaken motor control and behavioral inhibition, increasing susceptibility to attacks and accidents causing TBIs (Gjerde et al., 2008; Olson-Madden et al., 2012). Alcohol is the most common substance of use at the time of TBI, potentially due to its role in motor vehicle accidents (Beaulieu-Bonneau et al., 2018).

The impact of chronic substance use on behavioral and motor functioning may increase vulnerability to TBI. Prolonged or excessive substance use of numerous psychotropic drugs is known to induce neurodegeneration and frontal cortical dysfunction (Crews & Boettiger, 2009; Büttner, 2021). These neurological changes, in turn, may contribute to the deficits in learning, mood dysregulation, and inhibited executive functioning often evident after substance use (Stevenson et al., 2009). Consequently, the resulting impairment of substance use on the structure and function of the brain may reduce behavioral inhibition, thus increasing behaviors likely to result in TBI (Allen et al., 2016).

The lifetime prevalence of TBI among individuals experiencing homelessness is high, suggesting housing status may confer specific risks (Stubbs et al., 2020). A systematic review examined studies of TBI among persons experiencing homelessness and found that 53.1% of the almost 10,000 participants examined were positive for past TBI (Stubbs et al., 2020). Of

individuals who had a lifetime history of TBI and were experiencing homelessness, 70% incurred the TBI prior to experiencing homelessness (Hwang et al., 2008). Among persons experiencing homelessness, TBI was consistently associated with suicidality, memory impairments, and criminal justice system involvement (Stubbs et al., 2020). Even after controlling for potential confounders, individuals who are homeless with a lifetime history of TBI are at heightened risk of criminal justice involvement, being a victim of physical assault, and emergency department utilization at one-year follow-up (To et al., 2015).

Given the nature of military training and combat, TBIs are relatively common among military services members. The CDC reported 2.5 million emergency department visits and approximately 300,000 hospitalizations related to TBIs by military service members annually (CDC, 2016). The main cause of TBIs among recent military service members are improvised explosive devices, which also can result in other injuries, chronic pain, and PTSD (Lindberg et al., 2021). Concurrent TBI, chronic pain, and PTSD among military service members has been coined the "polytrauma triad" and occurs regularly (Lindberg et al., 2021).

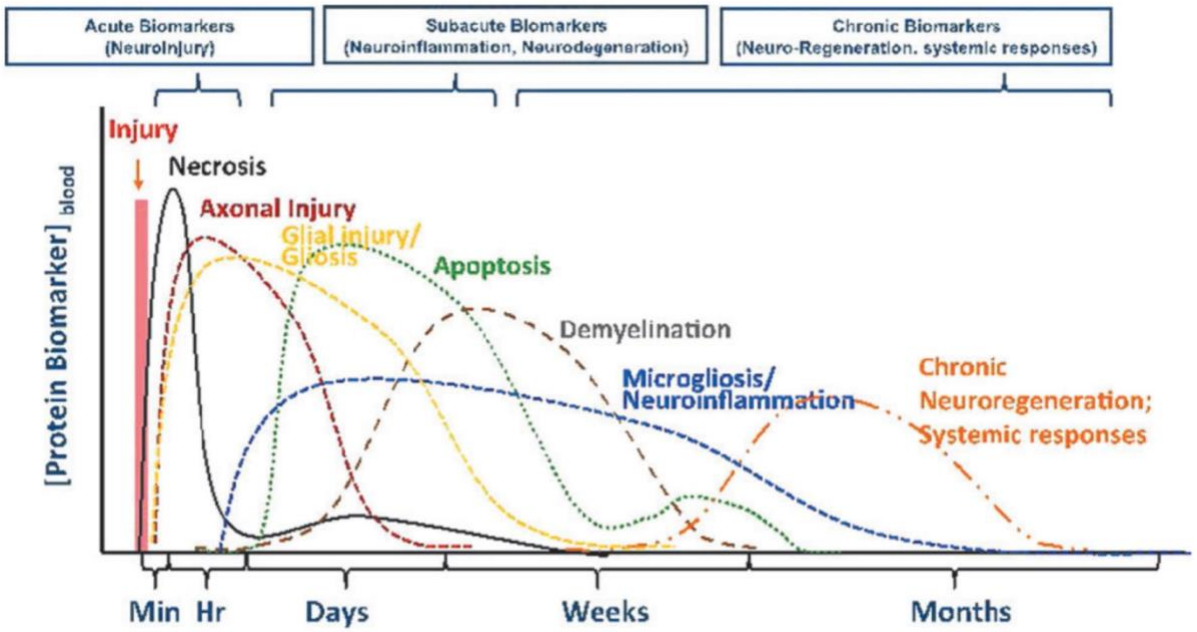
It is plausible that personality and behavioral tendencies could predispose someone to develop a TBI. High levels of risk-taking and impulsivity may underlie the tendency to partake in high-risk behaviors (Jamt et al., 2020; Olson-Madden et al., 2012; Olson-Madden et al., 2010) and sensation-seeking is associated with driving quickly, playing contact sports, and substance use (Jamt et al., 2020; Zuckerman, 2015), all of which may render persons susceptible to accidents involving TBI. Several studies corroborate the connection between impulsivity and TBI (Rochat et al., 2010; Vonder Haar et al., 2017). However, existing research largely assesses personality post-TBI, which is susceptible to the effects of the injury. Future research is needed to establish if personality traits increase the risk of incurring a TBI.

Age and TBI Outcomes

TBIs acquired in childhood are associated with greater behavioral health concerns and alcohol and illicit drug use later in life (Corrigan et al., 2021; Dams-O'Connor et al., 2013). Animal models have proposed that alterations to the brain circuitry implicated in reward during childhood may increase susceptibility to developing SUD (Cannella et al., 2019). TBIs occurring before age 11 are more likely to result in psychiatric disorders as compared to TBIs with later onset, and TBIs occurring between 11-16 years of age are more likely to result in a conduct disorder diagnoses and substance use (Trembley et al., 2019). Furthermore, adults with TBI onset ≥ 65 years of age produce fewer symptoms of post-concussive syndrome, depression, and less impairment in functional outcomes than individuals acquiring TBIs prior to age 65 (Peters et al., 2018).

Figure 1.3

Continuum of Biomarkers for TBI Pathophysiology and its Manifestation Over Time (from Wang et al., 2013)



Treatment of TBI

Acute treatment of TBI includes surgical interventions (craniotomies), medically induced comatose states, reduction of intracranial pressure through hyperventilation, and head elevation (Dash & Chavali, 2018). Post-TBI, occupational therapy, speech-language therapy, and physical rehabilitation may be warranted. (Barman et al., 2016). Although no drugs are U.S. Food & Drug Administration (FDA)-approved for the treatment of TBI, medications are frequently prescribed off-label for the management of neuropsychological sequelae. Antiepileptics, antipsychotics, direct-acting antivirals, and antidepressants are among the most prescribed medications following TBIs (Merino et al., 2019).

Cognitive rehabilitation (CR) may be administered as a means of restoring or compensating for impaired neuropsychological functioning as part of an interdisciplinary treatment plan (Barman et al., 2016). Evidence supports the use of CR for individuals with mild-moderate cognitive impairments and high levels of independence when completing ADLs. CR targets specific neurocognitive domains through tailored interventions; a scoping review evaluated the percent of available studies on CR that treated the following domains: executive function (30%), attention (30%), memory (15%), communication (9%), social cognition (2%) topographic orientation (2%), verbal auditory perception (2%; Julien et al., 2023). Positive effects on at least one outcome measure were reported by 93% of studies examined in the scoping review (Julien et al., 2023). Examples of interventions delivered during CR include training in memory strategy, attention processing, goal management, and compensatory strategies, such as the use of assistive technologies, calendars, and alarms (Barman et al., 2016).

TBIs are associated with extensive financial burden, in part due to the high cost of healthcare allocated to the diagnosis and treatment of TBI (CDC, 2023a). Healthcare costs stem from

emergency department visits, the cost of prescriptions, diagnostic tests such as CT and MRI scans, and the rehabilitation services often necessary to treat TBIs (Marin et al., 2017). The burden of these costs is compounded by the high rate of disability status following TBI and the subsequent financial burden therein (CDC, 2016).

Opioid Use

Opioids are a class of drugs that relieve pain and produce feelings of relaxation (Corder et al., 2018). Whereas opiates are drugs extracted from naturally occurring matter within poppy plants (e.g., opium, morphine, codeine, heroin), the term opioid typically encompasses both opiates and their synthetic counterparts (e.g., hydrocodone/Vicodin, oxycodone/Oxycontin/Percocet, oxymorphone/Opana, methadone/Dolophine, Fentanyl/Ultiva/Sublimaze; FDA, 2021). Opioids may be consumed via transdermal patch, suppository, oral capsule, inhalation, or intravenous administration (FDA, 2021)

Oxycodone, a commonly used opioid, has bioavailability ranging from 60%-70% following oral administration (Huddart et al., 2018). The serum concentration of oxycodone is higher for women and positively correlated with age (Kaiko et al., 1996). Once absorbed, oxycodone is 38-45% protein-bound, mainly to the plasma protein albumin (Huddart et al, 2018). Peak plasma concentrations are typically reached 25 minutes post intravenous administration. Oxycodone is primarily metabolized by liver CYP3A4 and CYP3A5 enzymes which produce the inactive metabolite noroxycodone (Lalovic et al., 2004). O-demethylation via the CYP2D6 enzyme produces the active metabolite oxymorphone (Lalovic et al., 2006). The remaining metabolites are then further metabolized to noroxymorphone, which is then eliminated by the kidneys and excreted (Lalovic et al., 2004).

Despite the low lipophilicity and moderate molecular weight (315.364 g/mol) of oxycodone, current research suggests it can cross the blood-brain barrier without the need of an active transporter (Villesen et al., 2006). Once crossed, Oxycodone acts on opioid receptors in the dorsal horn of the spinal cord (Adan et al., 2016). Oxycodone has high affinity (95.7%) for binding at μ-opioid receptor sites, which then engenders a cascade of neurotransmitter activity (Lalovic et al., 2006). First, binding stimulates the exchange of guanosine-5′-triphosphate (GTP) for guanosine-5′-diphosphate (GDP) on the G-protein complex, thereby obstructing the production of adenylate cyclase and cyclic adenosine-monophosphate (cAMP; Kinnunen et al., 2019). Diminished cAMP then inhibits the release of γ-aminobutyric acid (GABA), dopamine, acetylcholine, and noradrenaline. Simultaneously, oxycodone binding reduces the release of vasopressin, somatostatin, insulin, and glucagon (Huddart et al., 2018). Oxycodone closes N-type voltage-gated calcium channels and opens potassium channels, reducing neuronal excitability (Kinnunen et al., 2019). Overdose from opioids can be reversed by administering a centrally acting pure opioid antagonist with a high affinity at μ-opioid receptors, such as naloxone (FDA, 2023).

Due to their analgesic properties, physicians commonly prescribe opioids to manage moderate-severe pain following injury or surgery or for health conditions such as cancer (Blackwood & Cadet, 2021). Opioid dispensing has declined since its peak in 2012 when the nationwide dispensing rate was 81.3 prescriptions per 100 persons (CDC, 2021a). However, several counties continue to dispense opioids at high rates, especially in the southeastern and Appalachian regions of the United States. In 2020, the following dispensing rates per 100 persons were observed: Washington Co., TN = 140.123; Hamblen Co., TN = 124.684; Sullivan

Co., TN = 126.423; Scott Co., VA = 142.901; Knox Co., TN, 105.76; national average = 43.3 (CDC, 2021a).

Opioid Use Disorder (OUD)

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) defines opioid use disorder as a pattern of problematic opioid use resulting in withdrawal, cravings, tolerance, and continued use despite adverse outcomes (American Psychiatric Association, 2013). Between 2-3 million individuals in the United States are diagnosed with OUD (Azadfard et al., 2023; Chang et al., 2018). Repeated use of opioids can lead to OUD, even when taking opioids as prescribed (CDC, 2021b). The CDC estimates that 1 in 4 individuals prescribed opioids long-term in primary care settings will develop OUD (CDC, 2021b). Non-medical opioid use, or the consumption of opioids with the intent of receiving pleasurable effects from the drug, is also associated with developing OUD (Tetrault & Butner, 2015). Non-medical opioid use is relatively common, with 3.7% of the population over the age of 12 reporting experimenting with opioids in 2018 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2020).

Health disparities in the development of OUD and the risk for overdose are apparent. Individuals with earnings below the national poverty line, criminal justice system involvement, insecure housing, and not attaining a high school degree are at increased risk of opioid-related overdose (Martins et al., 2015). Certain mental health disorders, such as depressive disorders, PTSD, anxiety disorders, and other substance use disorders are associated with increased risk of developing OUD (Kaye et al., 2017). Advanced modeling has been used to capture the relative risk of developing OUD among individuals with repeated exposure to opioids (Cochran et al., 2014). The following characteristics were determined to elevate the risk of OUD: male sex;

younger age; more prescriptions for opioids and longer supply of opioids per prescription; prescriptions filled at more pharmacies per year; a greater number of psychiatric diagnoses; higher healthcare utilization; and a greater number of prescribed medications (Cochran et al., 2014).

Regional differences in rates of OUD are apparent. The high dispense rates of opioid prescriptions in Appalachian regions of the United States increase access to opioids and, therefore the risk of OUD (Cochran et al., 2014). Claims filed to the health insurance company BlueCross BlueShield (BCBS) affirm that long-term prescription opioid use and OUD align geographically, with the highest rates of both seen in the southeastern and Appalachian regions of the United States (BCBS, 2017). The limited access to mental health services, high rates of poverty, and injury-prone employment opportunities further exacerbate the risk of OUD and overdose in this region (Moody et al., 2017).

Personality and behavioral constructs are also linked to OUD. Individuals with OUD demonstrate higher impulsivity, emotion dysregulation, and shorter delay discounting than non-substance using persons (Peck et al., 2022). This association is bidirectional, such that substance use may also prompt higher levels of impulsivity (Evren & Bozkurt, 2017). Additionally, persons with OUD tend to have higher levels of novelty seeking, are more prone to experimentation, and are more easily bored with routines than individuals with other substance use disorders (Milivojevic et al., 2012).

Adverse Health Consequences of OUD

OUD can adversely impact all major systems of the body, including the respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine, and central nervous systems (Baldini et al., 2012; Von Korff et al., 2011). These effects tend to be dose-dependent,

such that a higher daily dose is associated with an increased likelihood of adverse events (Baldini et al., 2012). Additionally, the negative effects of opioids are more pronounced among elderly and immunocompromised persons (Baldini et al., 2012).

Opioid use can paradoxically result in decreased pain threshold and pain tolerance, known as opioid-induced hyperalgesia (OIH; Khan & Mehan, 2021). Studies have confirmed decreased pain tolerance in individuals on methadone as compared to matched controls via cold-pressor tests (Doverty et al., 2001). OIH may occur during rapid dose escalation, while on a low dose, during withdrawal periods, and from both intraoperative and ongoing opioid therapy (Angst & Clark, 2006; Lee et al., 2013; Tompkins & Campbell, 2011). OIH may be reversible following long-term abstinence from all opioid use, which does not extend to persons being treated via medications for opioid use disorder (MOUD; Treister et al., 2012). Of approximately 15,000 patients enrolled in OUD treatment, 47% reported worsening pain after beginning MOUD (Ellis et al., 2021). Given that pain is commonly reported to be a primary reason for opioid relapse, the presence of OIH may be a risk factor for unsuccessful OUD treatment outcomes (Ellis et al., 2021).

Given the depressive effect of opioids on the respiratory system, OUD is associated with a higher rate of overdose than any other substance use disorder (Baldini et al., 2012). In 2020, 75% of all overdoses in the United States involved opioids, with synthetic opioids such as fentanyl contributing to most opioid-involved overdoses (CDC, 2022). Fentanyl caused more deaths due to overdose in 2021 than the next three leading causes of overdose combined (i.e., synthetic opioids (fentanyl): 71, 238; psychostimulants (methamphetamine): 32,856; cocaine: 24,538; natural/semi-synthetic: 13,503; CDC, 2022). In 2017, the U.S. Department of Health and Human Services declared a national state of emergency in response to the rapidly growing

number of opioid-induced overdoses (U.S. Administration for Strategic Preparedness and Response, 2017). The rate of overdose from opioids continues to rise, increasing approximately 17.14% from 2020 to 2021 (CDC, 2022). The most serious outcomes of overdose are death and brain and other organ damage (CDC, 2022). Varying degrees of brain damage may occur depending on the duration of hypoxia the overdose causes (Rubenson Wahlin et al., 2018). Falling during an overdose is common, which can result in TBI (Rubenson Wahlin et al., 2018). There is evidence that concurrent TBI and hypoxia result in more extensive cumulative damage than the sum of the separate events (Rubenson Wahlin et al., 2018).

Adverse Neuropsychological Consequences of OUD

Specific patterns of neuroanatomical changes following the onset of OUD are consistently found (Stewart et al., 2019). Bilateral volumetric loss in the frontal lobes, frontotemporal brain region, and amygdala are displayed by individuals with OUD as compared to matched controls (Leong & Yuan, 2017; Upadhyay et al., 2010). Dysconnectivity in axonal pathways associated with emotion and stress (e.g., the anterior insula, nucleus accumbens and portions of the amygdala) is also displayed by individuals with OUD (Leong & Yuan, 2017). Importantly, the neurological changes evident among persons with OUD are implicated in executive functioning and reward response (Stewart et al., 2019). The extent of functional and structural changes is exacerbated by length of OUD duration (Upadhyay et al., 2010). Conversely, neurological changes are attenuated by prolonged abstinence, but this effect varies for patients treated with methadone (Leong & Yuan, 2017).

Meta-analyses of neuropsychological consequences of OUD have found deficits in a range of domains (Baldacchino et al., 2012; Wollman et al., 2019). Robust impairments are evident in verbal working memory, executive functioning, cognitive flexibility (Baldacchino et

al., 2012), and complex psychomotor ability (Wollman et al., 2019). Domains apparently spared from the impact of OUD are motor and processing speed (Wollman et al., 2019). There is evidence of group differences between opioid subtypes, such that use of heroin is associated with impaired strategic planning and highest risk-taking (Baldaccino et al., 2015). Fentanyl use may be most highly associated with overall neurocognitive impairment due to its potency in causing hypoxia, which is 20-times that of heroin (Solis et al., 2018). Patients using MOUD demonstrate poorer verbal fluency, executive functioning, and verbal memory abilities as compared to non-drug using controls (Mazhari et al., 2015). Evaluation of the neuropsychological impact of methadone is mixed, with some studies concluding it directly hinders neurocognition (Verdejo et al., 2005) and others finding comparable impairment within persons with OUD with and without MOUD (Prosser et al., 2006). Regardless, the neuropsychological consequences of OUD and its treatment may contribute to the inherent difficulties of treating the disease (Mazhari et al., 2015).

Treatment of OUD

MOUD is an evidence-based treatment of OUD using certain medications (e.g., methadone, buprenorphine, naltrexone) to reduce urges and cravings for substance use and mitigate the pleasurable impact of opioids (Mattick et al., 2014). Methadone is a full opioid agonist that activates opioid receptors in the brain more slowly than other forms of prescription opioids, therefore not resulting in feelings of euphoria or withdrawal (SAMHSA, 2015). Buprenorphine is a partial opioid agonist that similarly prevents opioid craving and withdrawal. Buprenorphine may be used alone or in conjunction with naloxone, an opioid antagonist which reverses or diminishes the pleasurable effects of opioids (National Institute on Drug Abuse, 2023). Although methadone and buprenorphine may be diverted and misused, it is relatively rare

and most often occurs as a form of "self-treatment" to reduce heroin use and alleviate withdrawal symptoms (Schuman-Olivier et al., 2010).

Although MOUD is efficacious, rates of treatment retention and abstinence from non-medical use of opioids varies. A systematic review examining randomized controlled trials of MOUD found 1-year retention rates ranging from 37.0% to 90.7% (Timko et al., 2016). The necessary length of a MOUD treatment course is not clearly defined, and tapering or cessation of MOUD tends to result in resumed non-medical use of opioids (Oesterle et al., 2019). Therefore, low rates of retention are believed to be indicative of relapse/return to non-medical use, rather than successful cessation of opioid use. Established psychosocial characteristics associated with poor MOUD outcomes include being female, never married, homeless, using other drugs, and having comorbid psychiatric disorders (Parpouchi et al., 2017). To date, TBI has not yet been examined as a risk factor for adverse MOUD outcomes.

The Relation Between OUD and TBI

Most literature examining the relation between substance use and TBI has focused on alcohol use, partially due to the prominent role of alcohol intoxication in motor vehicle accidents and, thus, TBI development (Corrigan & Adams, 2019). However, recent research found relatively high rates of TBI among individuals with OUD (Jacotte-Simancas et al., 2021). Cross-sectional data has found that almost three times as many respondents with past TBI reported non-medically using opioids compared to respondents without a history of TBI (Ilie et al., 2015). Accordingly, there is growing concern that TBI is an overlooked yet essential behavioral health concern related to the development and prognosis of OUD (Corrigan & Adams, 2019; Ilie et al., 2015).

Underlying Mechanism: Pain

Given that opioids are commonly prescribed to treat injury-related pain, TBIs may increase the risk of opioid use and thereafter OUD. Between 52%-58% of individuals with TBI develop subsequent chronic pain (Khoury & Benavides, 2018; Trexler et al., 2020). One multi-hospital study found that approximately 70% of individuals hospitalized after TBI were prescribed opioids for pain management (Hammond et al., 2015). Another study found that 52% of patients requiring an ICU stay related to a TBI were given an opioid prescription upon discharge, and 30% of those patients continued to use opioids one-year post-injury (Starosta et al., 2021).

Although opioids are medically indicated as a form of pain management for some patients, it is estimated that between 21-29% of patients prescribed opioids misuse them, and 8-12% of patients prescribed opioids later develop OUD (Vowles et al., 2015). Pain is a commonly cited reason for initiation of opioid use, prolonged non-medical opioid use, use of riskier forms of opioids such as heroin, and a risk factor for relapse (Salsitz, 2016). Pain is also a prominent feature of withdrawal from opioids which may be especially intense for individuals with premorbid chronic pain, potentially leading to lower rates of sustained abstinence (Chang & Compton, 2013). If treating TBI and post-concussive symptoms through opioid prescriptions lowers the risk threshold for acquiring OUD, there is concern that TBIs may be a common pathway to developing OUD.

Underlying Mechanism: Psychiatric Comorbidities

TBIs may also increase susceptibility to OUD due to self-medicating for mental health disorders that developed in concert with the TBI. Patients with a TBI, mood disorder, and opioid prescription were found to use opioids after the pain subsided due to the positive impact opioids

have on mood (Corrigan & Adams, 2019; Ilie et al., 2015). Furthermore, providers appear to be prescribing opioids at higher rates for patients with TBI and psychiatric comorbidities. Specifically, patients positive for PTSD, depression, and TBI were 3.6 times more likely to be prescribed an opioid than those with a TBI but with no psychiatric comorbidities (Seal et al., 2018). Therefore, the increase in opioid prescribing and prolonged opioid use for individuals with both psychiatric illnesses and TBIs may be a risk factor for OUD following a TBI.

Underlying Mechanism: Shared Psychosocial Risks

Although the direct research in this area is more nascent and theoretical, there is also support for shared predispositions for developing TBI and OUD (Starosta et al., 2021). For instance, it has been posited that personality traits (e.g., impulsivity, sensation-seeking) are confounding variables that explain the bi-directional link between TBI and substance use (Corrigan et al., 2021; Milivojevic et al., 2012). It may be that more impulsive persons are at higher risk of separately developing OUD and incurring TBIs. Male sex and younger age are also linked to both TBI and OUD, potentially contributing to their intersection (CDC, 2023a; CDC, 2023b; Cochran et al., 2014; Gupte et al., 2019).

Underlying Mechanism: Neuropsychological Impairment

The impact of TBI on neuropsychological functioning may lead to poor regulation of substance use, thereby increasing the risk of OUD. The neurophysiological damage inflicted by TBIs is directly tied to many skills critical for self-regulation and abstinence from substances (Allen et al., 2016; Niehmer et al., 2016; Vonder Haar et al., 2017). Additionally, the effect of OUD on brain functioning and impulse control may increase engagement in high-risk behaviors that may result in TBI (Wollman et al., 2019). Opioid use also disrupts motor control and

balance, increasing the risk of falls and accidents that could cause TBI (Corrigan & Adams, 2019).

Underlying Mechanism: Adverse Treatment Prognosis

TBI may also result in poorer OUD treatment outcomes, prolonging the condition. For instance, executive function underpins the ability to remember and follow medical recommendations, such as taking medications as prescribed and participating in OUD treatment (Allen et al., 2016; Graham & Cordon, 2008; Niehmer et al., 2016; Trexler et al., 2020; Vonder Haar et al., 2017). Impulsivity is associated with both TBI and OUD and is predictive of poor psychotherapy treatment outcomes (Loree et al., 2015). Cognitive behavioral treatment for OUD emphasizes psychoeducation, cognitive restructuring, and affect regulation, which may be challenging for individuals with neuropsychological impairment after TBI (Dugosh et al., 2016). TBI may also weaken factors associated with positive SUD treatment outcomes, such as gainful employment and high self-efficacy (Harvey et al., 2020; Yehene et al., 2020).

Statement of the Problem

Despite a known association between OUD and TBI, many characteristics of this relation have yet to be empirically evaluated. Clarifying the relation between OUD and TBI is imperative for preventing, understanding, and treating these two common diseases. Across three discrete manuscripts, this project will explore TBI characteristics among persons with OUD, evaluate the moderating effect of depression, pain, anxiety, and PTSD on the relation between TBI and OUD treatment outcomes, examine substance use behaviors for persons positive and negative for a lifetime history of TBI, and finally, review treatment modifications designed to improve substance use disorder treatment effectiveness for persons with TBIs.

Hypotheses and Aims

Manuscript 1 – Traumatic Brain Injury Characteristics among Individuals Seeking Treatment for Opioid Use Disorder

1. *Aim*
    a. Explore TBI characteristics (number of TBIs, age of TBI onset, TBI severity) and demographic and psychosocial characteristics of participants with comorbid TBI and OUD.
2. *Hypothesis*
    a. Among persons with TBI and OUD, TBI will be proportionally more likely to precede OUD.

Manuscript 2 – Evaluation of the Role of Traumatic Brain Injury in Predicting Risky Health Behaviors Associated with Opioid Use Disorder Severity

1. *Aim*
    a. Evaluate the relation between TBI and risky health behaviors among persons with OUD.
2. *Hypotheses*
    a. Compared to persons without TBI, the substance use behaviors of persons with TBI will have greater harm potential (i.e., have more overdoses, shorter time to overdose, younger age of first use, use of fentanyl, polysubstance use, and use of opioids via riskier routes of administration).
    b. Variables that correspond with adverse OUD treatment outcomes (i.e., younger age of first substance use, comorbid mental health conditions, chronic pain) will correspond with increased odds of having a TBI. Should mental health outcomes

significantly correspond with TBI, an exploratory aim will determine if symptoms of chronic pain, PTSD, anxiety, and depression moderate the relation between TBI and markers of poor OUD prognosis.

Manuscript 3 - A Systematic Review of Psychotherapy for Substance Use Disorder among Patients with Traumatic Brain Injury

1. *Aim*
    a. Evaluate treatment for substance use disorders for persons with TBI and compile succinct treatment recommendations for this population.

Chapter 2. Traumatic Brain Injury Characteristics among Individuals Seeking Treatment for Opioid Use Disorder

Hannah G. Mitchell, M.A.[1]

Department of Psychology, East Tennessee State University

ABSTRACT

Introduction. Research has consistently linked substance use and traumatic brain injury (TBI), and there is now growing concern regarding the involvement of opioids in the development and prognosis of TBIs. However, little is known about the prevalence, characteristics, and trajectory of TBIs reported by persons undergoing treatment for opioid use disorder (OUD). *Aim.* The present study sought to identify the rate, severity, and temporal progression of TBI among patients in outpatient treatment for OUD. *Methods.* Researchers administered a battery of assessments, including the Ohio State University TBI Identification Method, to patients enrolled in OUD treatment. *Results.* Participants (N = 158) were 52.1% female and 47.9% male with an average age of 44 (Range: 23-75; SD = 11.4). A history of at least one TBI was reported by 48.7% of the sample. Of persons with TBI, 44.2% reported repeated TBIs, and most TBIs reportedly occurred in childhood. The odds of incurring a TBI before ever using opioids was 1.5 times higher than the reverse progression. Approximately 90% of participants with a TBI had been prescribed an opioid medication by a healthcare professional at some point, significantly higher than for persons without TBI. Few differences in psychosocial characteristics were found between persons with and without TBI, TBI with and without LOC, and TBI with childhood or adult onset. *Conclusions*. These results conclude that TBI is a relatively frequent comorbidity for patients enrolled in OUD treatment. TBI most often proceeds OUD, warranting caution when

prescribing opioids for someone with a history of TBI and supporting the consistent screening of both substance use and TBI in medical settings.

Keywords: Opioid use disorder, TBI, mood, pain

[1] Manuscript is co-authored by Meredith K. Ginley

Traumatic Brain Injury Characteristics among Individuals Seeking Treatment for Opioid Use Disorder

An estimated 6.7 to 7.6 million adults in the United States are living with opioid use disorder (OUD), making it more common than Alzheimer's disease or seizure disorders (CDC, 2023; National Institute of Health, 2022). After the opioid epidemic was declared a national public health emergency in 2017, substantial research and public health policy has been dedicated to mitigating opioid-related harms. Despite these efforts, opioid-related mortality increased by 38% between 2019 to 2020 (CDC, 2022), and analgesics remain one of the most frequently prescribed classes of medication in the United States (CDC, 2021). Additionally, some regions remain at high risk for over-prescription, as evidenced by the counties clustered in the southeastern United States that prescribe opioids at rates 8-10 times the national average (CDC, 2021). Since as many as one in four persons prescribed an opioid long-term will later develop an opioid use disorder (OUD), excessively prescribing opioids introduces vulnerability to OUD (Boscarino et al., 2010).

Persons with OUD are at increased risk of a host of neuropsychological and physical disorders, including infectious diseases, chronic pain, and heart disease (National Institute on Drug Abuse, 2023). There is also growing evidence that opioid use is associated with traumatic brain injury (TBI; Adams et al., 2020; Adams et al., 2021; Starosta et al., 2021). Although the causal role of substance use in the development of TBI is well-established, opioids may have a uniquely bidirectional relation with TBI due to the use of opioids for pain management, its effect on neuropsychological and motor function, and the risk of overdose (Ponsford et al., 2018). Persons with TBI are more likely to be prescribed opioids as compared to their peers without a history of TBI (Adams et al., 2021; Molero et al., 2021; Seal et al., 2018). Additionally, over

75% of persons with TBI are diagnosed with a behavioral health disorder one-year postinjury, such as PTSD or depression (Alway et al., 2016; Nampiaparampil, 2008), which may subsequently increase susceptibility to developing OUD (Cochran et al., 2014). A cognitive predisposition towards risk-taking (i.e., impulsivity) may also contribute to high-risk behaviors likely to result in both opioid use and accidents causing TBI (Bakhshani, 2014). Overlapping psychosocial characteristics (i.e., gender, age, health disparities of persons historically marginalized) of persons at risk for both OUD and TBI may also strengthen the relation between the two diseases (Biegon, 2021; Cochran et al., 2014; Manhapra et al., 2021; Ponsford et al., 2018; Stubbs et al., 2020). The convergence of risk factors for opioid-related harms for persons with TBI has been recently coined a "perfect storm" (Adams et al., 2021).

Outcomes of TBI are highly variable, ranging from no long-term symptoms to severe respiratory failure and death (Bramlett & Dietrich, 2015). Severity of TBI, typically gauged via assessment of length of loss of consciousness (LOC), presence of posttraumatic amnesia, and/or results of neuroimaging, is predictive of long-term TBI outcomes (Hawryluk & Manley, 2015; Levin et al., 1979; Teasdale & Jennett, 1974). Moderate-severe TBI is most likely to result in physical limitations and neuropsychological impairment (Ponsford et al., 2016; Venkatesan et al., 2021). Paradoxically, mild TBI (mTBI) is associated with an elevated likelihood of chronic headaches and some specific mental health concerns (Pavlov et al., 2019). Repeated TBIs, especially those incurred over a brief period (i.e., over the span of a few months), and TBIs occurring prior to age 15 are also associated with a greater chance of long-term neuropsychological symptoms (Fesharaki-Zadeh, 2019; Trembley et al., 2019). Altogether, knowledge of the presence or absence of TBI provides much less insight into the risk of persisting symptoms than does a comprehensive understanding of the severity, age of onset, and

number of TBIs sustained. However, prior research on the link between substance use and TBI has predominantly examined TBI as a dichotomous variable. The present study will advance upon existing research by evaluating the prevalence and characteristics of TBIs reported by patients undergoing treatment for OUD. This aim is exploratory in nature and seeks to provide insight into a presently understudied comorbid condition. Additionally, the present study will evaluate the predictive ability of impulsivity to determine TBI status.

Although the temporal progression of TBI and OUD has been postulated, it has not yet been empirically evaluated among individuals seeking treatment for OUD (Adams et al., 2020). The present study seeks to fill this gap through evaluating the progression between TBI and OUD among persons undergoing treatment for OUD. It is hypothesized that a pattern of TBIs temporarily preceding OUD will emerge and that a portion of patients first used opioids as medically prescribed to alleviate pain related to their TBI.

Method

Participants

Participants enrolled in treatment at one of two OUD treatment clinics located in a rural-serving, Appalachian region of the southeastern United States. Both clinics prescribe medications for opioid use disorder (MOUD; e.g., methadone, suboxone, naloxone), and individual and group outpatient therapy. Clinics were a convenience sample of locations with which the investigators had at least some prior research-related engagement but were purposively sampled to include at least one clinic that provided methadone as a treatment option.

Procedures

Research assistants were seated in a private patient room that was dedicated to data collection. Patients were made aware of the study via word-of-mouth from clinic staff and flyers advertising the study that were placed in the waiting rooms. Patients were free to approach the research assistant and initiate enrollment in the study. All adult patients of the clinics were eligible to participate.

Interested patients were given an informed consent form to read via REDCap link on an iPad, which detailed the risks, benefits, and compensation for participating in the study. The informed consent document also informed participants they needed to be 18 years of age or older to consent to the study. If participants agreed to the informed consent, they were immediately enrolled in the study. Participants then completed a short battery of assessments that took approximately 20 minutes. No personally identifiable information was collected. After the assessments were completed, participants were thanked for their time with the chance to win a $5, $10, or $15 gift card to a previously designated store. Participants spun a pre-programmed wheel that provided a 25% chance of winning $5, 50% chance of winning $10, and 25% chance of winning $15. Gift cards were immediately delivered to participants. The affiliated University's Institutional Review Board approved all study procedures.

Measures

Traumatic Brain Injury

The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) is a commonly used structured interview assessing for lifetime history of head injuries (Bogner & Corrigan, 2009; Corrigan & Bogner, 2007). The OSU-TBI-ID includes summary indices that have been established as reliable and valid (Bogner & Corrigan, 2009; Corrigan & Bogner,

2007). Index scores include the Worst (moderate-severe), First (before age 15), Multiple (repeated TBIs within short timespan), and Recent (mTBI in recent weeks or moderate-severe TBI in recent months), corresponding to TBI characteristics likely to result in current symptoms (Corrigan et al., 2012; Gardner et al., 2020). The OSU-TBI-ID has been successfully used in community settings (Smith & Rothschild, 2023), substance use disorder treatment clinics (Corrigan et al., 2012; Olson-Madden et al., 2010), and behavioral healthcare settings (Coxe-Hyzak et al., 2022). To establish interrater reliability, 33% (N = 200) of OSU-TBI-ID scores were randomly selected for a second research assistant to independently code. The researchers' index scores were found to have 99% consistency. The 2 scores with discrepant coding were resolved through discussion.

Impulsivity

Impulsivity was assessed through the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), a 30-item self-report questionnaire that assesses the multi-dimensional construct of rash impulsivity. The BIS-11 is the most often-cited instrument to assess impulsivity and has been validated in a wide range of populations. Higher sum scores correspond with increased impulsivity. The BIS-11 demonstrates strong test-retest reliability (Spearman's Rho = 0.83) and internal consistency (Cronbach's α = .83; Stanford et al., 1996).

Substance Use

To establish the temporal relation between substance use and TBI, participants were asked to estimate how old they were when they first used specific substances. Directions prompted participants to provide their best estimate if they did not precisely recall.

Initial opioid exposure was assessed by asking participants which opioid they used first and how old they were when they first used opioids. Participants were asked to report how they

obtained the first opioid they used. Response options included: given by a friend; given by a family member; given by a romantic partner; prescribed by a doctor or medical provider; bought on the internet; bought from drug dealer/stranger; bought or took from friend; bought or took from family member; bought or took from romantic partner; and other (please describe). If participants reported first using opioids after being prescribed them by a medical professional, they were given a free text box and asked to report what it was prescribed for. Participants were also asked if they had ever been prescribed an opioid by a medical professional (not including a MOUD prescription).

Demographic and Psychosocial Information

Relevant demographic and psychosocial information was obtained by asking participants to self-report their age, gender, race/ethnicity, sexual orientation, marital status, annual household income, educational attainment, and employment status. Participants were asked if they had ever experienced homelessness and if they were enrolled in SUD treatment due to a court order/mandate.

Analyses

SPSS was used to conduct all statistical analyses (version 29; IBM). Missing data were addressed using listwise deletion and full information maximum likelihood (FIML) methodology. Descriptive statistics were calculated to explore the demographic and psychosocial characteristics of participants reporting TBI, the number of TBIs with and without LOC, average age of first TBI, and the severity of TBIs reported by participants. Descriptive statistics were calculated to identify the proportion of patients who used opioids prior to acquiring a TBI and the initial source of opioids for individuals with and without TBI. A Pearson correlation was used to examine the association between age of TBI and age of first opioid use. X^2 tests

evaluated group differences based on the presence of TBI, TBI with LOC, and adult or childhood-onset TBI. No corrections for multiple comparisons were made because analyses were exploratory and not hypothesis-led, but results with $p > .01$ should be interpreted with caution. Lastly, a binary logistic regression was calculated to evaluate the predictive ability of impulsivity to determine TBI status.

Results

Participants (N = 158) were patients ages 23-75 (M = 44.1; SD = 11.4) undergoing treatment for OUD. The sample was 52.1% female and 47.9% male. The ethnic makeup of the sample was predominantly White (90.9%), followed by Black (5.6%), Hispanic/Latino(a) (1.4%), Multiracial (1.4 %), and other (0.7%). The following education level was reported to be the highest attained: grade school (3.5%), some high school (14.8%), GED (12.7%), high school degree (46.5%), Associate's or technical degree (11.3%), bachelor's degree (7.0%), master's degree (0.7%), and other (3.5%). Annual household income was reported to be less than $14,999 by 48.6% of participants, $15,000-$24,999 by 36.6% of participants, and ≥ $25,000 by 14.8% of participants. Participants reported being employed full-time (35.2%), on disability (24.6%), unemployed (23.2%), employed part-time (11.3%), retired (4.2%), and attending school full-time (1.4%). Of the overall sample, 49.3% reported having experienced homelessness. Approximately 5% of the sample reported being enrolled in OUD treatment due to a court order/mandate. Having a prior or current diagnosis of a mental or behavioral illness was reported by 47.9% of participants.

TBI Prevalence and Characteristics

As assessed via the OSU-TBI-ID, 48.7% of the sample had experienced at least one TBI. The number of TBIs incurred by participants is presented in Table 2.1 and range from 0-5.

Estimates of the length of LOC are reported in Table 2.2. For participants with multiple TBIs, the longest length of LOC is reported. TBIs were classified as mild (59.8%) or moderate-severe (26%) depending on the length of LOC. For participants with multiple TBIs, the most severe instance was classified. Some (14.3%) TBIs were unable to be classified due to participants' inability to estimate their length of LOC. Of participants with a TBI, 3.6% reported having had a TBI within the past 12 months. The average time since the only or most recent TBI was 18.9 years (*SD* = 12.9; range = 0 – 57 years).

Table 2.1

Number of TBIs Reported by Participants

Number of TBIs	
	n(%)
0	81(51.3)
1	43(27.2)
2	23(14.6)
3	7(4.4)
4	3(1.9)
5	1(0.6)

Table 2.2

Length of LOC Among Participants with TBI

Length of Loss of Consciousness	n(%)
No LOC	13(16.9%)
< 30 minutes	33(42.9%)
30 minutes – 24 hours	18(23.4%)
> 24 hours	2(2.6%)
Unable to estimate	11(14.3%)

Timeline of TBI and OUD Onset

Of participants with a history of TBI, 55.7% had experienced at least one TBI prior to age 16. The age at which participants experienced a TBI ranged from < 1 year of age to 57 years old (M = 17.28; SD = 11.67). Age of TBI and age of first opioid use was significantly correlated $r(72) = .26$, $p < .05$. Most participants (55.6%) with TBI reported incurring their TBI prior to initiating opioid use, while 35.8% reported using opioids prior to experiencing their TBI, and 8.6% reported these events happening at the same point in time. For participants who incurred a TBI prior to using opioids, the length of time between TBI and opioid use ranged from 1 – 38 years, (M = 11.80; SD = 9.90). Of persons who first used opioids prior to incurring a TBI, the length of time between first opioid use and TBI ranged from 1 – 36 years (M = 7.72; SD = 8.49). Notably, 36% of all TBIs that occurred prior to using opioids occurred within two years of first using opioids.

First Opioid Use

Although no significant differences were observed between individuals with and without TBI in terms of the source of opioids first used, a higher percentage of persons with TBI reported first using opioids as prescribed by a medical professional as compared to participants without TBI (see Table 2.3 for complete statistics). Of the overall sample, 86.3% reported having ever been prescribed an opioid by a medical professional, excluding MOUD. Of participants with TBI, 89.6% reported having been prescribed an opioid at some point, excluding MOUD. A χ 2 test of independence revealed that persons with TBI were significantly more likely to have been prescribed an opioid medication than participants without TBI, χ^2 (2, N=140) =6.34, $p < 0.05$. Participants with TBI reported being prescribed opioid medications for acute pain following injury (36.4%), head or back pain (25%), chronic medical conditions (20.5%), and dental procedures or toothache (15.9%).

Table 2.3

Source of Initial Opioid Used by Participants

Source of Opioid First Used	TBI + n(%)	TBI – n(%)
Prescribed by medical provider	46(61.3%)	29(49.2%)
Given by a friend or romantic partner	14(18.7%)	15(25.4%)
Given by a family member	6(8.0%)	9(15.3%)
Bought or took from stranger or dealer	1(1.3%)	1(1.7%)
Bought or took from friend or romantic partner	4(5.3%)	4(6.8%)
Bought or took from family member	4(5.3%)	1(1.7%)

Differences in Psychosocial Characteristics and Diagnoses by TBI Status

A series of chi-square tests of independence examined the relation between participants' psychosocial characteristics and history of TBI, severity of TBI, and age of TBI onset. No significant differences were observed on any level for gender, marital status, sexual orientation, race/ethnicity, history of homelessness, employment status, mandated treatment status, educational attainment, or annual income. Group differences were observed such that persons with TBI with or without LOC were more likely to have been diagnosed with a mental or behavioral illness χ^2 (2, N=142) = 8.12, p = 0.01. No differences in diagnostic status were observed based on if the TBI was child or adult onset. See Table 2.4 for complete statistics.

Table 2.4

Psychosocial Characteristics by TBI Status

		TBI		Statistic
		Yes	No	
Gender				χ 2 (1, N = 142) = 2.99
	Man	54.5%	40.0%	
	Woman	45.5%	60.0%	
Marital status				χ 2 (4, N = 141) = 4.22
	Never married/single	23.7%	26.2%	
	In a committed relationship	14.5%	15.4%	
	Married	34.2%	30.8%	
	Divorced/Separated	23.7%	16.9%	
	Widowed	3.9%	7.7%	
	Other	0.0%	3.1%	
Sexual orientation				χ 2 (3, N = 142) = 4.30
	Straight/heterosexual	89.6%	93.5%	
	Gay/lesbian/bisexual	10.4%	6.5%	
Race/ethnicity				χ 2 (4, N = 143) = 2.17
	White	93.5%	87.9%	
	Black	3.9%	7.6%	
	Hispanic/Latino(a)	1.3%	1.5%	
	Multiracial	1.3%	1.5%	
	Other	0.0%	1.5%	
History of homelessness				χ 2 (1, N = 142) = 1.05
	Yes	54.5%	44.6%	
	No	46.8%	55.4%	

		TBI		Statistic
		Yes	No	
Employment status				χ 2 (5, N = 142) = 4.62
	Full-time	40.3%	29.2%	
	Part-time	10.4%	12.3%	
	Retired	5.2%	3.1%	
	On disability	22.1%	27.7%	
	Unemployed	22.1%	24.6%	
	Full-time student	0.0%	3.1%	
Mandated treatment				χ 2 (2, N = 142) = 2.03
	Yes	6.5%	3.1%	
	No	93.5%	96.9%	
Educational attainment				χ 2 (7, N = 142) = 2.56
	Grade school	3.9%	3.1%	
	Some high school	14.3%	15.4%	
	GED	14.3%	10.8%	
	High school degree	48.1%	44.6%	
	Associate's or technical degree	9.1%	13.8%	
	Bachelor's degree	6.5%	7.7%	
	Master's degree	1.3%	0.0%	
	Other	2.6%	4.6%	
Annual income				χ 2 (2, N = 142) = 1.71
	< $14,999	48.05%	49.23%	
	$15,000 - $24,999	40.3%	32.3%	
	> $25,000	11.7%	18.5%	
Mental health diagnosis				χ 2 (2, N = 142) = 8.12*
	Yes	60.8%	36.5%	
	No	39.2%	63.5%	

*Indicates significance at p =.01.

Impulsivity and TBI

A binary logistic regression was calculated to determine the predictive ability of BIS-11 to determine TBI status. The overall model was statistically significant ($\chi^2(1) = 18.75$, $p < .001$) and explained 17.4% (Nagelkerke R^2) of the variance. Higher reported levels of impulsivity (OR = 1.06, (95% CI = 1.03, 1.10)) were associated with an increased likelihood of having a TBI.

Discussion

Although there is a known association between TBI and opioid use, scarce prior research has evaluated the frequency or development of concurrent TBI and OUD. Therefore, the current study aimed to determine the rate, severity, and chronological development of TBI among patients in outpatient treatment for OUD. Using a validated, structured interview to evaluate TBI status, the present study found that almost half of the patients engaged in MOUD treatment had incurred at least one TBI in their lifetime and that 90% of participants with a TBI had been previously prescribed an opioid. It was also found that TBI most often precedes OUD. Overall, this study concludes that TBI is a common yet currently underappreciated clinical covariate for persons undergoing treatment for OUD.

The prevalence rate finding of this study is comparable to estimations of TBI among persons seeking treatment for substance use and mental health concerns, ranging from 54% to 80% (McHugo et al., 2017; Sacks et al., 2009). Additionally, prior research has found that between 60% and 72.1% of persons who are incarcerated and between 46% and 53% of persons who are experiencing homelessness have experienced TBI with LOC (Shiroma et al., 2010; Stubbs et al., 2020). Given that 49.3% of the sample reported having been homeless at some point in their lives, it is possible that homelessness bolsters the connection between TBI and OUD.

Characteristics associated with an increased likelihood of prolonged symptoms of TBI were apparent. Of participants reporting a TBI history, 44.2% reported multiple TBIs. Approximately 25% of TBIs reported were considered severe based on the length of LOC. The age of TBI onset ranged from infancy to 57 years of age, with an average age of 17.3. Of persons with prior TBI, 55.7% had experienced a TBI before age 16. Given that repeated TBIs, more severe TBIs, and young age of TBI onset are each associated with adverse prognosis following a TBI, these findings provide further support that significant and potentially chronically impairing TBIs are occurring with relative frequency among persons being treated for OUD.

Among persons with TBI, 55.6% experienced their TBI prior to initiating opioid use compared to 35.8% of participants who first used opioids. Although there is substantial evidence of the role of substances in the injury producing TBIs, less is known about how TBI may increase the risk of later developing OUD. This finding supports the value of providing psychoeducation and consistently screening for problematic substance use in trauma and rehabilitation centers as a means of identification and prevention of SUD. Age of TBI and age of first using opioids were positively correlated, and 36% of all TBIs occurred within the first two years of using opioids. Roughly 90% of participants with a TBI had been prescribed an opioid medication by a healthcare professional, which is significantly higher than the prescription rates among participants without TBI. Given that TBI most often proceeds opioid use, and opioid use is often initiated by healthcare professionals, these findings further support the use of caution when prescribing opioids to persons with a history of TBI.

Beyond the medical complication of a history of TBI, social determinants of health associated with barriers to medical care access and health disparities were common among sample participants (Hacker & Houry, 2022). Specifically, 18.3% of participants never earned a

high school diploma or GED, and 77.5% of the sample received no secondary education. Furthermore, 48.6% of participants reported earning annual household incomes of $14,999 or less, approximately 1/5 the national average (U.S. Labor Bureau, 2021). Only 14.8% of participants reported earning ≥ $25,000 per year. One in four participants was on disability, and 23.2% reported being unemployed. Contrary to expectations, these social determinants of health did not significantly differ between participants with and without TBI. Since persons with OUD in rural, Appalachian regions of the United States are already prone to experiencing significant health inequity, it may be that any added risk associated with TBI was not apparent at this sample size. Additionally, OUD treatment requires consistent transportation, frequent in-office visits, and multiple forms of psychotherapy, making it a more cumbersome and intensive treatment than that for some other mental health conditions. As such, treatment may require a baseline level of stability and resources such that persons with more significant symptoms of TBI cannot adhere to treatment requirements and therefore are not captured by these data. However, these findings illuminate the proportional burden TBI may place on persons already likely to experience significant barriers to receiving sufficient medical care.

Participants with a TBI history were also more likely to have been diagnosed with a mental or behavioral illness. This finding is unsurprising given the documented association between TBI and mental health concerns, such as anxiety, depression, and PTSD (Brady et al., 2009; Felde et al., 2006; Moore et al., 2014; Stéfan & Mathe, 2016). Comorbid substance use and mental health conditions are associated with higher rates of psychiatric hospitalization and lower treatment session attendance (Kelly & Daley, 2013; Launders et al., 2022). The poor treatment outcomes for persons with comorbidities may be due to the mismatch between available single-disorder treatment protocols and treatment needs (Kelly & Daley, 2013). Future

research should examine how mental health concerns may facilitate the connection between TBI and OUD, as well as identify the implications of concurrent TBI and mental health diagnoses on OUD treatment outcomes.

Impulsivity was found to be a significant predictor of TBI among persons with OUD. Impulsivity is characterized by favoring smaller, immediate rewards rather than larger, later ones, and increased novelty-seeking (Van Den Berk Clark, 2021). Impulsivity impacts health decisions such that health behaviors with relatively little short-term reinforcement (i.e., substance use cessation, treatment attendance) are less likely to be maintained (Rogers et al., 2021; Van Den Berk Clark, 2021). Past research has successfully implemented novel behavioral interventions that mitigated participants' impulsive behaviors (Smith et al., 2015). Examining the impact of these interventions on individuals most susceptible to developing OUD and TBI may provide meaningful points of intervention for this population.

Study Limitations and Conclusions

These results should be considered with limitations in mind. Participants were treatment-engaged patients in a rural, Appalachian region of the United States, which may not generalize to individuals from other areas or non-treatment-seeking patients with OUD. Clinic staff may have skewed the sample by specifically encouraging patients with a known TBI history to participate, thereby inflating the proportion of the sample with a past TBI. However, researchers regularly reminded staff that all patients were able to participate. Additionally, our results are comparable to other estimates of TBI among a population of patients seeking treatment for substance use disorders.

Overall, the present study is the first to confirm high rates of TBI among persons who had undergone "gold standard" evaluation of OUD and are therefore confirmed to be

experiencing serious and impairing symptoms of opioid addiction. Compared to participants without a history of TBI, participants with TBI are more likely to have been prescribed an opioid medication and to have been previously diagnosed with a mental health condition. For persons with comorbid TBI and OUD, TBI is likely to have preceded the first use of opioids. Future research evaluating how TBI may impact OUD treatment outcomes is needed. Clinicians working in OUD treatment settings should participate in the implementation of best practices concerning the assessment of TBI. Understanding patients' neurological backgrounds and the associated risks of TBI, impulsivity, and comorbid mental health conditions is critical for mitigating threats to treatment success.

References

Adams, R. S., Corrigan, J. D., & Dams-O'Connor, K. (2020). Opioid use among individuals with traumatic brain injury: A perfect storm? *Journal of Neurotrauma*, *37*(1), 211–216. https://doi.org/10.1089/neu.2019.6451

Adams, R. S., Ketchum, J. M., Nakase-Richardson, R., Katz, D. I., & Corrigan, J. D. (2021). Prevalence of drinking within low-risk guidelines during the first 2 years after inpatient rehabilitation for moderate or severe traumatic brain injury. *American Journal of Physical Medicine & Rehabilitation*, *100*(8), 815–819. https://doi.org/10.1097/PHM.0000000000001753

Alway, Y., Gould, K. R., Johnston, L., McKenzie, D., & Ponsford, J. (2016). A prospective examination of Axis I psychiatric disorders in the first 5 years following moderate to severe traumatic brain injury. *Psychological Medicine*, *46*(6), 1331–1341. https://doi.org/10.1017/S0033291715002986

Bakhshani, N.-M. (2014). Impulsivity: A predisposition toward risky behaviors. *International Journal of High-Risk Behaviors and Addiction*, *3*(2). https://doi.org/10.5812/ijhrba.20428

Biegon, A. (2021). Considering biological sex in traumatic brain injury. *Frontiers in Neurology*, *12*, 576366. https://doi.org/10.3389/fneur.2021.576366

Bogner, J., & Corrigan, J. D. (2009). Reliability and predictive validity of the Ohio state university TBI identification method with prisoners. *Journal of Head Trauma Rehabilitation*, *24*(4), 279–291. https://doi.org/10.1097/HTR.0b013e3181a66356

Boscarino, J. A., Rukstalis, M., Hoffman, S. N., Han, J. J., Erlich, P. M., Gerhard, G. S., & Stewart, W. F. (2010). Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system: Risk factors for drug dependence among out-

patients. *Addiction*, *105*(10), 1776–1782. https://doi.org/10.1111/j.1360-0443.2010.03052.x

Brady, K. T., Tuerk, P., Back, S. E., Saladin, M. E., Waldrop, A. E., & Myrick, H. (2009). Combat posttraumatic stress disorder, substance use disorders, and traumatic brain injury. *Journal of Addiction Medicine*, *3*(4), 179–188. https://doi.org/10.1097/ADM.0b013e3181aa244f

Bramlett, H. M., & Dietrich, W. D. (2015). Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. *Journal of Neurotrauma*, *32*(23), 1834–1848. https://doi.org/10.1089/neu.2014.3352

CDC. (2021, a). *U.S. Opioid Dispensing Rate Maps | Drug Overdose | CDC Injury Center*. https://www.cdc.gov/drugoverdose/rxrate-maps/index.html

CDC. (2022). *Death Rate Maps & Graphs | Drug Overdose | CDC Injury Center*. https://www.cdc.gov/drugoverdose/deaths/index.html

CDC. (2023, b). *FastStats*. https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

Cochran, B. N., Flentje, A., Heck, N. C., Van Den Bos, J., Perlman, D., Torres, J., Valuck, R., & Carter, J. (2014). Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a database of commercially-insured individuals. *Drug and Alcohol Dependence*, *138*, 202–208. https://doi.org/10.1016/j.drugalcdep.2014.02.701

Corrigan, J. D., & Bogner, J. (2007). Initial reliability and validity of the Ohio state university TBI identification method. *Journal of Head Trauma Rehabilitation*, *22*(6), 318–329. https://doi.org/10.1097/01.HTR.0000300227.67748.77

Corrigan, J. D., Bogner, J., & Holloman, C. (2012). Lifetime history of traumatic brain injury among persons with substance use disorders. *Brain Injury*, *26*(2), 139–150. https://doi.org/10.3109/02699052.2011.648705

Coxe-Hyzak, K. A., Bunger, A. C., Bogner, J., Davis, A. K., & Corrigan, J. D. (2022). Implementing traumatic brain injury screening in behavioral healthcare: Protocol for a prospective mixed methods study. *Implementation Science Communications*, *3*(1), 17. https://doi.org/10.1186/s43058-022-00261-x

Felde, A. B., Westermeyer, J., & Thuras, P. (2006). Co-morbid traumatic brain injury and substance use disorder: Childhood predictors and adult correlates. *Brain Injury*, *20*(1), 41–49. https://doi.org/10.1080/02699050500309718

Fesharaki-Zadeh, A. (2019). Chronic traumatic encephalopathy: a brief overview. *Frontiers in Neurology*, *10*, 713. https://doi.org/10.3389/fneur.2019.00713

Gardner, R. C., Rivera, E., O'Grady, M., Doherty, C., Yaffe, K., Corrigan, J. D., Bogner, J., Kramer, J., & Wilson, F. (2020). Screening for lifetime history of traumatic brain injury among older American and Irish adults at risk for dementia: development and validation of a web-based survey. *Journal of Alzheimer's Disease*, *74*(2), 699–711. https://doi.org/10.3233/JAD-191138

Hacker, K., & Houry, D. (2022). Social needs and social determinants: the role of the centers for disease control and prevention and public health. *Public Health Reports*, *137*(6), 1049–1052. https://doi.org/10.1177/00333549221120244

Hawryluk, G. W. J., & Manley, G. T. (2015a). Classification of traumatic brain injury. In *Handbook of Clinical Neurology* (Vol. 127, pp. 15–21). Elsevier. https://doi.org/10.1016/B978-0-444-52892-6.00002-7

Hawryluk, G. W. J., & Manley, G. T. (2015b). Classification of traumatic brain injury. In *Handbook of Clinical Neurology* (Vol. 127, pp. 15–21). Elsevier. https://doi.org/10.1016/B978-0-444-52892-6.00002-7

Levin, H. S., O'donnell, V. M., & Grossman, R. G. (1979). The Galveston orientation and amnesia test: A practical scale to assess cognition after head injury. *The Journal of Nervous and Mental Disease*, *167*(11), 675–684. https://doi.org/10.1097/00005053-197911000-00004

Manhapra, A., Stefanovics, E., & Rosenheck, R. (2021). The association of opioid use disorder and homelessness nationally in the veterans health administration. *Drug and Alcohol Dependence*, *223*, 108714. https://doi.org/10.1016/j.drugalcdep.2021.108714

McHugo, G. J., Krassenbaum, S., Donley, S., Corrigan, J. D., Bogner, J., & Drake, R. E. (2017). The prevalence of traumatic brain injury among people with co-occurring mental health and substance use disorders. *Journal of Head Trauma Rehabilitation*, *32*(3), E65–E74. https://doi.org/10.1097/HTR.0000000000000249

Molero, Y., Sharp, D. J., D'Onofrio, B. M., Larsson, H., & Fazel, S. (2021). Psychotropic and pain medication use in individuals with traumatic brain injury—A Swedish total population cohort study of 240,000 persons. *Journal of Neurology, Neurosurgery & Psychiatry*, *92*(5), 519–527. https://doi.org/10.1136/jnnp-2020-324353

Moore, E., Indig, D., & Haysom, L. (2014). traumatic brain injury, mental health, substance use, and offending among incarcerated young people. *Journal of Head Trauma Rehabilitation*, *29*(3), 239–247. https://doi.org/10.1097/HTR.0b013e31828f9876

Nampiaparampil, D. E. (2008). Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA*, *300*(6), 711. https://doi.org/10.1001/jama.300.6.711

National Institute of Health. (2022). 2022 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 18*(4), 700–789. https://doi.org/10.1002/alz.12638

National Institute on Drug Abuse. *Part 2: Co-occurring Substance Use Disorder and Physical Comorbidities*. https://nida.nih.gov/publications/research-reports/common-comorbidities-substance-use-disorders/part-2-co-occurring-substance-use-disorder-physical-comorbidities

Olson-Madden, J. H., Brenner, L., Harwood, J. E. F., Emrick, C. D., Corrigan, J. D., & Thompson, C. (2010). Traumatic brain injury and psychiatric diagnoses in veterans seeking outpatient substance abuse treatment. *Journal of Head Trauma Rehabilitation, 25*(6), 470–479. https://doi.org/10.1097/HTR.0b013e3181d717a7

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774. https://doi.org/10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

Pavlov, V., Thompson-Leduc, P., Zimmer, L., Wen, J., Shea, J., Beyhaghi, H., Toback, S., Kirson, N., & Miller, M. (2019). Mild traumatic brain injury in the United States: Demographics, brain imaging procedures, health-care utilization and costs. *Brain Injury, 33*(9), 1151–1157. https://doi.org/10.1080/02699052.2019.1629022

Ponsford, J., Alway, Y., & Gould, K. R. (2018). Epidemiology and natural history of psychiatric disorders after TBI. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(4), 262–270. https://doi.org/10.1176/appi.neuropsych.18040093

Ponsford, J. L., Spitz, G., & McKenzie, D. (2016). Using post-traumatic amnesia to predict outcome after traumatic brain injury. *Journal of Neurotrauma*, *33*(11), 997–1004. https://doi.org/10.1089/neu.2015.4025

Rogers, M. M., Kelley, K., & McKinney, C. (2021). Trait impulsivity and health risk behaviors: A latent profile analysis. *Personality and Individual Differences*, *171*, 110511. https://doi.org/10.1016/j.paid.2020.110511

Sacks, A. L., Fenske, C. L., Gordon, W. A., Hibbard, M. R., Perez, K., Brandau, S., Cantor, J., Ashman, T., & Spielman, L. A. (2009). Co-morbidity of substance abuse and traumatic brain injury. *Journal of Dual Diagnosis*, *5*(3–4), 404–417. https://doi.org/10.1080/15504260903182755

Seal, K. H., Bertenthal, D., Barnes, D. E., Byers, A. L., Gibson, C. J., Rife, T. L., & Yaffe, K. (2018). Traumatic brain injury and receipt of prescription opioid therapy for chronic pain in Iraq and Afghanistan veterans: Do clinical practice guidelines matter? *The Journal of Pain*, *19*(8), 931–941. https://doi.org/10.1016/j.jpain.2018.03.005

Shiroma, E. J., Ferguson, P. L., & Pickelsimer, E. E. (2010). Prevalence of traumatic brain injury in an offender population: A meta-analysis. *Journal of Correctional Health Care*, *16*(2), 147–159. https://doi.org/10.1177/1078345809356538

Smith, A. P., Marshall, A. T., & Kirkpatrick, K. (2015). Mechanisms of impulsive choice: II. Time-based interventions to improve self-control. *Behavioural Processes*, *112*, 29–42. https://doi.org/10.1016/j.beproc.2014.10.010

Smith, M., & Rothschild, D. (2023). Use of the Ohio state university TBI identification method (OSU-TBI) in community settings. *Archives of Physical Medicine and Rehabilitation*, *104*(3), e60–e61. https://doi.org/10.1016/j.apmr.2022.12.177

Starosta, A. J., Adams, R. S., Marwitz, J. H., Kreutzer, J., Monden, K. R., Dams O'Connor, K., & Hoffman, J. (2021). Scoping review of opioid use after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 36*(5), 310–327. https://doi.org/10.1097/HTR.0000000000000721

Stéfan, A., & Mathé, J.-F. (2016). What are the disruptive symptoms of behavioral disorders after traumatic brain injury? A systematic review leading to recommendations for good practices. *Annals of Physical and Rehabilitation Medicine, 59*(1), 5–17. https://doi.org/10.1016/j.rehab.2015.11.002

Stubbs, J. L., Thornton, A. E., Sevick, J. M., Silverberg, N. D., Barr, A. M., Honer, W. G., & Panenka, W. J. (2020). Traumatic brain injury in homeless and marginally housed individuals: A systematic review and meta-analysis. *The Lancet Public Health, 5*(1), e19–e32. https://doi.org/10.1016/S2468-2667(19)30188-4

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. *The Lancet, 304*(7872), 81–84. https://doi.org/10.1016/S0140-6736(74)91639-0

Tremblay, S., Desjardins, M., Bermudez, P., Iturria-Medina, Y., Evans, A. C., Jolicoeur, P., & De Beaumont, L. (2019). Mild traumatic brain injury: The effect of age at trauma onset on brain structure integrity. *NeuroImage: Clinical, 23*, 101907. https://doi.org/10.1016/j.nicl.2019.101907

Van Den Berk Clark, C. (2021). The role of impulsivity on health behavior related to cardiovascular disease among young adults. *Psychological Trauma: Theory, Research, Practice, and Policy, 13*(3), 271–276. https://doi.org/10.1037/tra0000910

Venkatesan, U. M., Rabinowitz, A. R., Wolfert, S. P., & Hillary, F. G. (2021). Duration of post-traumatic amnesia is uniquely associated with memory functioning in chronic moderate-

to-severe traumatic brain injury. *NeuroRehabilitation*, *49*(2), 221–233. https://doi.org/10.3233/NRE-218022

Chapter 3. The Role of Traumatic Brain Injury in Predicting Risky Behaviors Associated with Opioid Use Disorder Severity

Hannah G. Mitchell, M.A.[1]

Department of Psychology, East Tennessee State University

ABSTRACT

Introduction. Persons with traumatic brain injury (TBI) are at elevated risk of comorbid health conditions, which add to the burden of the disease. Although TBI has a known association with opioid use, the relation between TBI and risky health behaviors associated with opioid use disorder (OUD) severity has yet to be evaluated. *Aim.* The present study aimed to examine the relation between TBI and factors influencing OUD harm potential, including overdose, polysubstance use, route of opioid administration (ROA), and behavioral health comorbidities. *Methods.* Participants undergoing treatment for OUD across two clinics were administered a battery of assessments, including the Ohio State University TBI Identification Method, PHQ-9, GAD-7, PCL-5, and BPI. *Results.* Participants (N = 158) with TBI were at elevated risk of overdose, use of certain other substances, riskier ROA, and higher symptoms of chronic pain and anxiety as compared to patients without TBI. Use of some substances (e.g., alcohol, marijuana) and symptoms of PTSD and depression did not differ by TBI history. *Conclusions*. The data support the relation between TBI and markers of high-risk health behaviors and medical complexities. TBI should be routinely assessed for and considered when creating treatment plans.

Keywords: Opioid use disorder, TBI, disease progression, overdose, hypoxia

[1] Manuscript is co-authored by Meredith K. Ginley

The Role of Traumatic Brain Injury in Predicting Risky Behaviors Associated with Opioid Use Disorder Severity

Traumatic brain injury (TBI) is a leading cause of long-term impairment in social, occupational, recreational, and neuropsychological domains worldwide (Polinder et al., 2015). A growing body of literature proposes a strong association between substance use and TBI (Adams et al., 2021; Ilie et al., 2015; West, 2011). Various substances have unique links with TBI; for instance, alcohol is often implicated in TBIs in part due to the involvement of alcohol in motor vehicle accidents (Weil et al., 2018). In recent years, the link between TBI and opioid use has garnered research attention due to the "perfect storm" of TBI outcomes and risk for opioid use disorder (OUD), including chronic pain, neuropsychological changes, barriers to healthcare, and overprescribing of opioids that frequently occurs following TBI (Adams et al., 2020; Starosta et al., 2021).

Chronic Pain and TBI

Over half of individuals who experience a TBI report chronic pain post-injury (Nampiaparampil, 2008). Evaluation of veterans one-year post-TBI found that 22% had been prescribed an opioid to treat pain, with moderate-severe TBI associated with a higher prescribing rate (Seal et al., 2018). Although clinical guidelines are intended to deter the use of opioids for persons with TBI, overprescribing continues to be a prevalent issue, particularly among rural, Appalachian regions of the southeastern United States (Adams et al., 2020; CDC, 2021). Access to prescription opioids is potentially problematic since pain increases susceptibility to opioid dependence and OUD (Mollayeva et al., 2017; Salsitz, 2016; Vowles et al., 2015). Additionally, pain is associated with riskier use of opioids (i.e., injecting), risk of overdose, and polysubstance

use (Fernandez et al., 2019; Heimer et al., 2015). It is plausible that the relation between TBI and OUD severity is strengthened through the presence of chronic pain.

Behavioral Health Disorders and TBI

Evaluation of persons one-year post-TBI found that over 75% had been diagnosed with one or more behavioral health disorders, with mood and anxiety disorders being the most common sequala (Ilie et al., 2015). TBI is associated with the initial development of mental health disorders and the exacerbation of preexisting ones (Lamontagne et al., 2022). Potential pathways from TBI to mental health concerns include the neurophysiological changes resulting from the TBI, physical or recreational restrictions that are imposed following the TBI, and general stress and worry associated with incurring a major injury (Lamontagne et al., 2022). High rates of anxiety are also evident among individuals with OUD, with estimates that 47%-60% of treatment-seeking persons with OUD meet diagnostic criteria for an anxiety disorder (Conway et al., 2006; Gros et al., 2013). The development of anxiety following TBI may be a causal factor for the use of substances, although this has yet to be evaluated among a population of individuals with OUD.

Given that posttraumatic stress disorder (PTSD) and TBIs may both develop from injury, it is unsurprising that they frequently develop in concert (Monsour et al., 2022). Veterans with a history of TBI were 2-3 times more likely to have a diagnosis of PTSD than veterans without prior TBI (Ragsdale et al., 2013). Concurrent TBI and PTSD is particularly problematic because this specific comorbidity appears to have an additive detrimental effect on health-related quality of life (Monsour et al., 2022). Among persons with TBI, PTSD is associated with an increased risk of suicide attempts, aggressive behavior, and substance use (Barnes et al., 2012; Hale et al., 2022). Longitudinal evaluation of veterans' substance use found that persons with TBI are three

times more likely to overdose from opioids than those without TBI (Fonda et al., 2020) and two to three times more likely to have a substance use disorder (Ragsdale et al., 2013). Veterans with PTSD and TBI are more likely to be prescribed opioids than persons without TBI, potentially increasing vulnerability for OUD (Seal et al., 2018). However, it is unknown if PTSD exacerbates OUD severity among persons with concurrent OUD and TBI.

Qualities of OUD Associated with Greater Harm

OUD has the highest mortality rate of any SUD (Martins et al., 2015). Meta-analysis of crude mortality rates among individuals who use opioids found higher mortality among persons who use injectable drugs, are positive for human immunodeficiency virus (HIV), and live in low- or middle-class areas (Bahji et al., 2020). Other studies have similarly found that the mortality risk is higher for individuals with comorbidities such as HIV, cancer, and other substance use (Hser et al., 2017). Specifically, concurrent use of sedatives (e.g., anxiolytics such as benzodiazepines) significantly increase the risk of hospitalization and death from opioid overdose due to their effect on respiration (Sun et al., 2017). Accordingly, polysubstance use and non-oral routes of administration are meaningful markers of severity of OUD that delineate the risk of future adverse OUD outcomes (Kerr et al., 2007).

Opioids are the leading contributor to overdose and are thereby uniquely associated with hypoxia (Martins et al., 2015). Hypoxia and TBI both may cause a range of neuropsychological impairments and have additive effects when they occur in short succession (Brenner et al., 2012; Spaite et al., 2017). TBI and hypoxia can result in a range of neuropsychological impairments, including executive functioning deficits, that may mitigate the ability to self-regulate substance use (Wilens et al., 2011; Zibbel, 2019). The initiation of OUD treatment represents a unique period wherein the risk of overdose increases, and thus the possibility of hypoxic brain injuries is

higher (Sordo et al., 2017). Further evaluation of the impact of hypoxia from overdose and TBI on OUD treatment outcomes may elucidate a risk factor for poor treatment prognosis.

OUD Treatment

OUD can be difficult to adequately treat, in part due to its variable retention rate (e.g., retention between 9-94%; Timko et al., 2016). Much research has been dedicated to identifying risks for low treatment attendance and treatment-resistant OUD (Patterson Silver Wolf & Gold., 2020). Variables associated with poor treatment outcomes include a history of overdose, young age at first use, unemployment, comorbid mental health concerns, and use of injectable opioids (Gottlieb et al., 2022; Novak & Kral, 2011). It is plausible that persons with TBI are similarly at-risk for adverse treatment outcomes and severe symptoms of OUD, either via direct neuropsychological impairment mitigating the efficacy of OUD treatment, or indirectly through associating with known risk factors for poor prognosis (Scott et al., 2021).

The Present Study

The current study aimed to evaluate the role of TBI in predicting risky health behaviors associated with OUD severity. It was hypothesized that individuals with a lifetime history of TBI have more opioid harm potential (i.e., have more overdoses, shorter time to overdose, younger age of first use, use of fentanyl, polysubstance use, and use of opioids via riskier routes of administration) as compared to their non-TBI experiencing counterparts. It was also hypothesized that variables associated with unfavorable OUD outcomes (i.e., younger age of first substance use, comorbid mental health conditions, chronic pain) will be associated with higher odds of TBI. If mental health outcomes are significantly associated with TBI, an exploratory analysis will investigate whether symptoms of chronic pain, PTSD, anxiety, and depression moderate the connection between TBI and indicators of OUD severity.

Method

Participants

Data were collected across two OUD treatment clinics in an Appalachian region of the Southeast United States. The treatment clinics provide an array of services to treat OUD, including medications for opioid use disorder (MOUD; e.g., suboxone and methadone) and outpatient psychotherapy. All participants (N = 158) were adult patients actively enrolled in treatment.

Procedures

Patients became aware of the study through flyers placed in the clinic waiting rooms and through word-of-mouth from clinic staff. Interested patients informed front office staff or healthcare provider of their desire to enroll in the study and were then taken to a private patient room where the researcher was located.

The risks, benefits, and compensation for study involvement were discussed verbally and written in an informed consent document which patients signed via REDCap link on an iPad. All adult patients were eligible to enroll in the study. Patients were informed that their responses were not linked to their electronic medical record and that no personally identifiable information was to be collected. Upon signing the informed consent document, participants were immediately enrolled in the study.

Data collection required approximately 20 minutes and consisted of one structured interview and several self-report assessments. Once the assessments were completed, participants spun a pre-programmed wheel which offered a 25% chance of winning a $5 gift card, a 50% chance of winning a $10 gift card, and a 25% chance of winning a $15 gift card as thanks for

their time. Gift cards were given to participants immediately. The study was approved by the affiliated University's Institutional Review Board.

Measures

Traumatic Brain Injury

The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) was administered to assess for a lifetime history of TBI (Bogner & Corrigan, 2009; Corrigan & Bogner, 2007). The OSU-TBI-ID and its' index scores have shown acceptable reliability and validity (Bogner & Corrigan, 2009; Corrigan & Bogner, 2007). Indices correspond to the Worst (moderate to severe TBI), First (TBI with LOC before age 15), Multiple (2 or more TBIs in a short timespan), and Recent (mTBI in the last few weeks or moderate to severe TBI in the past few months), since these characteristics are likely to result in current symptoms (Corrigan et al., 2012; Gardner et al., 2020). Use of the OSU-TBI-ID among persons with substance use disorders and mental health concerns has found to be acceptable (Corrigan et al., 2012; Coxe-Hyzak et al., 2022; Olson-Madden et al., 2010). To ensure adequate interrater reliability, 33% (N = 200) of the OSU-TBI-ID scores were randomly selected to be double-coded by an independent research assistant. Discrepancy in scoring was found in 2 cases, which was addressed via consensus. The lead author completed a brief training in administering the OSU-TBI-ID and trained all research assistants (N = 4) before they began collecting data.

Substance Use History

Alcohol use was evaluated by the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001; Saunders et al., 1993). AUDIT scores range from 0-40, with 0-7 indicating low-risk consumption, 8-14 suggesting hazardous alcohol use, and ≥ 15 indicating likely alcohol

dependence (Babor et al., 2001). The AUDIT has strong reliability and validity (De Meneses-Gaya et al., 2009) and has been successfully used among persons with TBI (Bryce et al., 2015).

Participants were given a list of commonly used drugs (e.g., methamphetamine, cocaine, Xanax) and asked to check yes or no regarding lifetime history of use. Participants were asked which opioids they had ever used. Response options included: buprenorphine (Subutex, Suboxone); fentanyl; hydrocodone (Norco, Vicodin, Lortab); hydromorphone (Dilaudid); methadone; morphine; OxyContin; other oxycodone (Tylox, Percocet, Percodan); and heroin. Participants were asked to estimate how old they were when they first used opioids.

Routes of drug administration (ROA) data were ascertained by asking participants how they had ever used opioids. Response options included: crushed and snorted; injected; smoked; swallowed capsules/pills; and applied as a patch. The risk-level of ROA was assigned as follows: swallowing capsules/pills and/or applying as a patch: lower risk; crushing and snorting and/or smoking with or without low-risk behaviors: moderate risk; injecting with any combination of low or moderate-risk behaviors: highest risk. Participants were also asked if they had ever lost consciousness from a drug overdose.

Impairment Due to Chronic Pain

Impairment due to chronic pain was assessed through the Pain Disability Index (PDI) (Pollard, 1984). The PDI is a 7-item measure that produces a total score, a pain interference score, and a severity score, with higher scores indicating more pain-related impairment. The PDI has adequate internal consistency and reliability (McKillop et al., 2018; Tait et al., 1990).

Posttraumatic Stress Disorder

The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) is a 20-item self-report assessment corresponding to the DSM-5 criteria for PTSD (APA, 2013; Blevins et al., 2015;

Weathers et al., 2018). Research suggests a PCL-5 score ≥ 31 is indicative of probable PTSD. The PCL-5 demonstrates high internal consistency (α = .96) and test-retest reliability (r = .84; McKillop et al., 2018).

Anxiety

The GAD-7 is a 7-item measure corresponding with the DSM-5 symptoms of Generalized Anxiety Disorder (GAD; APA, 2013; Spitzer et al., 2006). The GAD-7 demonstrates strong internal consistency (Cronbach α = .92) and test-retest reliability (intraclass correlation = 0.83; Spitzer, 2006). A score ≥ 10 is indicative of significant symptoms of GAD (Spitzer, 2006).

Depression

The Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) is one of the most widely used assessments of depression based on the nine criteria of depression in the DSM-5 (APA, 2013). The PHQ-9 predicts DSM-5 diagnoses of Major Depressive Disorder (MDD) with 80%-90% accuracy (Kroenke et al., 2001). Scores ≥5 are indicative of symptoms consistent with MDD.

Demographic and Psychosocial Information

Participants self-reported their age, gender, and race/ethnicity. Response options were given for gender and race/ethnicity along with free response boxes for participants to self-identify.

Analyses

Statistical analyses were conducted via SPSS (version 29; IBM). Descriptive statistics were calculated to provide insight into the substance use characteristics of the overall sample. Propensity score matching was initially used to summarize covariate effects and adjust for

differences during estimation of TBI effects (Rosenbaum & Rubin, 1984). The predicted probability of TBI derived from a fitted regression model of baseline patient characteristics was used to estimate the propensity score (Austin, 2011). However, participants' psychosocial characteristics (e.g., gender, age) did not differ based on TBI status. Given the lack of apparent confounding variables and the power lost by using propensity score matching, it was not ultimately used (Wang, 2021).

Group differences in history of overdose, use of fentanyl, polysubstance use, AUDIT score, and age of first opioid use were calculated using χ^2 tests and independent samples t-tests based on TBI status.

A one-way analysis of variance analyses (ANOVA) was conducted to evaluate the level of ROA risk by number of TBIs and age of first opioid use by severity of TBI. Significant values were further evaluated post hoc via the Games–Howell test.

Conditional process modeling was initially used to test the extent that symptoms of pain and anxiety moderate the association between TBI and overdose using the PROCESS macro in SPSS. Continuous BPI and GAD-7 scores were not strongly correlated, therefore not violating the assumption of independent causal pathways and acceptable to include in the model. However, the severity and number of TBI and the number of overdoses did not have a linear relation, thereby violating conditions of moderation analysis. Accordingly, a moderation analysis was unable to be conducted.

A series of binary logistic regressions were used to evaluate the predictive ability of GAD-7, PHQ-9, PCL-5, and BPI scores on TBI status. Odds ratios and 95% confidence intervals were calculated.

A Kaplan-Meier survival curve was calculated for overdose as a function of time since opioid initiation, by TBI status. Survival curves appropriately account for the time elapsed between events since participants who are older or initiated opioid use at a younger age have had greater opportunity to experience overdose and therefore require consideration. The log rank Mantel-Cox pairwise comparison was calculated to determine the statistical significance of the survival distributions.

Results

The sample was comprised of 158 patients undergoing outpatient treatment for OUD. Participants were 52.1% women and 47.9% men ages 23-75 (M = 44.1; SD = 11.4). The following racial/ethnic identities were reported: White (90.9%), Black (5.6%), Hispanic/Latino(a) (1.4%), Multiracial (1.4 %), and other (0.7%). A history of at least one TBI was reported by 48.7% of participants. Of persons with TBI, 44.3% reported incurring a TBI prior to 16 years of age. TBIs were considered mild (59.8%), moderate-severe (26%), or unable to be classified due to participants' not being able to provide an estimate of LOC (14.3%).

The most common opioids non-medically used were hydrocodone (81.0%), followed by other oxycodone (i.e., Percocet, Percodan; 75.9%), and OxyContin (65.8%). Of the overall sample, 40.5% had used fentanyl. The age of first opioid use ranged from 7 – 55 (M = 21.3; SD = 8.0). History of overdose was reported by 29.7% of the overall sample. The number of overdoses reported ranged from 0 – 5. ROA was determined to be low-risk for 19.3% of participants, moderate-risk for 35.6% of participants, and high-risk for 45.2% of participants.

Lifetime history of other substance use included marijuana (86.6%), sedatives (64.8%), cocaine (62.4%), amphetamines (62.0%), hallucinogens (48.9%), and inhalants (19.0%). Alcohol use in the last year was reported by 35.4% of participants. Of persons who reported last-year

alcohol use, AUDIT scores classified 71.4% as low-risk, 14.3% as at-risk for hazardous alcohol consumption, and 14.3% as likely experiencing a severe alcohol use disorder. Of the overall sample, 7.6% were classified as at-risk or likely alcohol dependent.

A history of overdose was reported by 40.3% of participants with TBI and 19.8% of persons without TBI, a difference reaching statistical significance (χ^2 (1, N=158) = 7.94, p < 0.01).

Mean total AUDIT scores did not significantly differ by TBI status, although it is notable that 10.4% of persons with TBI reported at-risk or dependent alcohol use compared to 4.9% of persons without TBI, $t(158) = -1.12$, p = .24. χ^2 tests revealed differences in substance use based on TBI status. Specifically, persons with TBI were relatively more likely to have used amphetamines, χ^2 (1, N=129) = 4.39, p < .05; cocaine, χ^2 (1, N=141) = 8.15, p < .01; sedatives, χ^2 (1, N=142) = 5.67, p < .05; and fentanyl, χ^2 (1, N=158) = 17.25, p < .001. Use of hallucinogens (χ^2 (1, N=137) = .62, p = .43); marijuana, χ^2 (1, N=142) = 3.97, p =.052; and inhalants (χ^2 (1, N=142) = .04, p = 1.00) did not differ by TBI status. See Table 3.1 for full statistics.

Table 3.1

Substance Use Behaviors by TBI Status

		TBI		
		Yes	No	
Marijuana				χ 2 (1, N = 142) = 3.97
	Yes	92.0%	80.6%	
	No	8.0%	19.4%	
Sedatives				χ 2 (1, N = 137) = 5.67*
	Yes	73.7%	47.4%	
	No	26.3%	45.5%	
Cocaine				χ 2 (1, N = 141) = 8.15**
	Yes	73.3%	50.0%	
	No	26.7%	50.0%	
Amphetamines				χ 2 (1, N = 129) = 4.39*
	Yes	69.9%	51.8%	
	No	30.1%	48.2%	
Hallucinogens				χ 2 (1, N = 137) = .62
	Yes	52.1%	45.3%	
	No	47.9%	54.7%	
Inhalants				χ 2 (1, N = 142) = .04
	Yes	18.4%	19.7%	
	No	81.6%	80.3%	
Fentanyl				χ 2 (1, N = 158) = 17.25***
	Yes	57.1%	24.7%	
	No	42.9%	75.3%	
Alcohol (last year)				χ 2 (1, N = 158) = .06
	Yes	36.4%	34.6%	
	No	63.6%	65.4%	
Overdose				χ 2 (1, N = 158) = 7.94**
	Yes	40.3%	19.8%	
	No	59.7%	80.2%	

*p <.05; **p < .01; ***p < .001.

Results of an ANOVA revealed differences in ROA risk by the number of TBIs such that the overall model was significant, $F(2, 134) = 3.69$, p <.05. The Games - Howell post hoc test demonstrated that persons with high-risk ROA had a greater number of TBIs than participants

who used a low or moderate-risk ROA (Table 3.2). A second ANOVA found mean differences in the age of first opioid use based on TBI severity. The Games - Howell post hoc test for multiple comparisons revealed that persons with moderate-severe TBIs used opioids at a younger age than persons with mild or no TBIs, $F(2, 119) = 9.55$, $p < .01$ (Table 3.3).

Table 3.2

Mean Number of TBIs and Risk of ROA

		Number of TBI *M*(SD)	
ROA Risk			$F(2, 134) = 3.69$, $p < .05$
	Low	*.65*(1.16)	
	Moderate	*.71*(.77)	
	High	*1.18*(1.15)*	

*$p < .05$.

Table 3.3

TBI Severity by Age of First Opioid Use

		Age of Opioid Initiation *M*(SD)	
TBI Severity			$F(2, 119) = 9.55$, $p < .01$.
	No TBI	*21.25*(6.79)	
	Mild TBI	*24.97*(11.09)	
	Moderate-Severe TBI	*17.00*(4.07)*	

*$p < .01$.

A series of binary logistic regressions were calculated to examine the predictive ability of PHQ-9, GAD-7, PCL-5, and BPI scores on TBI history (see Table 3.4). The model was statistically significant for GAD-7 scores ($\chi^2(1) = 6.67$, $p = .01$) and BPI scores ($\chi^2(1) = 17.67$, $p < .001$). Increased symptoms of anxiety and pain were predictive of positive TBI status. Neither PHQ-9 scores nor PCL-5 scores were associated with increased odds of having had a TBI.

Table 3.4

Symptom Scores by TBI Status

		TBI				
		Yes	No	χ2 Statistic	Odds Ratio	95% CI
PHQ-9				$\chi2(1) = 3.35$	1.06	.99 - 1.12
	M	9.06	7.29			
	SD	5.79	5.7			
GAD-7				$\chi2(1) = 6.67$*	1.08	1.02 - 1.14
	M	9.47	6.78			
	SD	5.98	6.24			
PCL-5				$\chi2(1) = 3.87$	1.02	.99 - 1.04
	M	20.39	14.47			
	SD	17.78	16.17			
BPI				$\chi2(1) = 17.67$**	1.06	1.03 - 1.08
	M	15.64	6.85			
	SD	13.87	11.54			

*p = .01; **p < .001.

A Kaplan-Meier survival distribution was used to depict overdose as a function of time since opioid initiation by TBI status. A log rank test was run to determine if there were differences in the survival distribution for participants with and without TBI. No statistically significant differences were observed ($\chi^2(2) = 2.39$, $p > .05$).

Discussion

Individuals who have experienced TBI have an increased likelihood of developing concurrent adverse health conditions, thereby exacerbating the burden of the disease. While the connection between TBI and opioid use is established, the impact of TBI on risky health behaviors associated with severity of OUD was previously unexplored. The present study examined several facets of the relation between TBI and OUD and concluded that participants

with a history of TBI had higher odds of several behaviors associated with greater harm potential from opioid use (i.e., overdose, fentanyl use). However, other variables expected to correspond to TBI history (e.g., symptoms of PTSD) did not notably differ by TBI status.

Severe symptoms of OUD were reported by participants with and without history of TBI. Of the overall sample, 29.7% reported a history of overdose and 45.2% reported injecting opioids. Lifetime use of other substances non-medically was common, with most participants reporting prior use of marijuana, sedatives, cocaine, and/or amphetamines. These findings align with research demonstrating frequent overdose and high-risk behaviors associated with OUD and speaks to the overall OUD sample severity (Alway et al., 2016; Brandt et al., 2023).

As expected, several markers of OUD severity and risk of mortality were associated with TBI status. Specifically, a history of overdose was significantly more common for persons with TBI as compared to participants without prior TBI. Given that participants tended to report suffering a TBI prior to the first use of opioids, it seems that TBI increases vulnerability to overdose, not that TBIs are developing as a consequence of the overdose. Future research is needed to isolate specific neuropsychological and behavioral correlates of overdose among persons with TBI and OUD to inform prevention methods. One potential point of intervention is ensuring access to opioid antagonist medications, such as naloxone, for persons with a history of TBI receiving opioid therapy. The time between opioid initiation to overdose did not significantly differ by TBI status, indicating that TBI was associated with the presence of overdose, but not the speed with which it occurred.

Persons with TBI were also more likely to report past use of amphetamines, marijuana, cocaine, sedatives, and fentanyl, but not alcohol, hallucinogens, or inhalants. Notably, current alcohol use was relatively infrequent among all participants, with only 8% of the overall sample

reporting at-risk alcohol use or alcohol dependence. History of polysubstance use is associated with poorer treatment prognosis and may exacerbate OUD severity for persons with TBI. It is presently unclear why certain substances, but not others, are associated with TBI. Past research has found personality and behavioral predispositions towards certain substances, which may also increase vulnerability to TBI (Mitchell & Potenza, 2014). The increased use of sedatives among persons with TBI and OUD may have significant consequences since sedatives are often involved in opioid overdose. Similarly, Fentanyl is responsible for a significant portion of opioid-related overdose and mortality. The association between TBI, sedatives, and fentanyl may contribute to the higher rate of overdose among persons with TBI.

Opioid ROA differed by the number of TBIs incurred, such that persons who engaged in the highest-risk ROA had more TBIs than those with lowest or moderate-risk ROAs. Interestingly, the average number of TBIs did not differ between the lowest and moderate-risk ROAs. Given that the highest-risk ROAs are associated with greater instances of infectious disease and mortality, their association with TBI adds an additional layer of risk for adverse health events. The age at first opioid use was also found to be significantly younger for persons with moderate-severe TBI as compared to participants with no TBI history or mild TBI. The age of opioid use did not significantly differ between no TBI and mild TBI, illuminating the significant risks associated with moderate-severe TBIs.

Higher symptoms of pain corresponded with increased odds of having had a TBI. Extensive research has found that pain increases vulnerability to OUD and overdose. Since all persons with TBI have experienced a significant injury, it is unsurprising that they are likely to have increased levels of pain. It is unknown if persons with TBI report increased pain due to

their injury or due to paradoxical hyperalgesia due to more severe OUD. These findings support the need for evidence-based pain management for persons with TBI.

Increased symptoms of anxiety were associated with likelihood of having incurred a TBI. There is definitive evidence of higher rates of anxiety following TBI, potentially due to social, occupational, and physical changes resulting from the injury (Al-Kader et al., 2022; Mallya et al., 2015). Anxiety disorders can increase barriers to treatment and reduce therapy efficacy, thereby warranting identification and separate treatment. Contrary to expectations, symptoms of PTSD and depression were not higher among persons with TBI. It is plausible that TBI is associated with PTSD and depression among persons with OUD, but this relation was not apparent in the present sample due to small sample size or the high symptom severity for all participants. Future research is needed to further evaluate how comorbid mental health conditions associated with TBI may influence treatment efficacy.

Study Limitations and Conclusions

Retrospective self-report questionnaires assessed for past substance use. There is some concern for misreporting and underreporting given the sensitive nature of substance use. However, it is hoped that this effect will be minimized by collecting data through anonymous surveys. Additionally, other self-report retrospective assessments of substance use (e.g., the Timeline Followback) have shown acceptable reliability and validity (Sobell & Sobell, 1992).

Although past research has demonstrated poor treatment results for individuals with TBIs, these findings have yet to be explored for OUD treatment specifically. This study found evidence that persons with TBI are at elevated risk of several markers of OUD severity and poor treatment prognosis, including risk of overdose, polysubstance use, risky ROA, and symptoms of comorbid chronic pain and anxiety. These findings support routine screening of TBI as a risk

factor for medical complexities. Additionally, these findings isolate specific psychiatric comorbidities which warrant detection and treatment, potentially improving OUD treatment outcomes for patients with TBI.

References

Adams, R. S., Corrigan, J. D., & Dams-O'Connor, K. (2020). Opioid use among individuals with traumatic brain injury: A perfect storm? *Journal of Neurotrauma*, *37*(1), 211–216. https://doi.org/10.1089/neu.2019.6451

Adams, R. S., Ketchum, J. M., Nakase-Richardson, R., Katz, D. I., & Corrigan, J. D. (2021). Prevalence of drinking within low-risk guidelines during the first 2 years after inpatient rehabilitation for moderate or severe traumatic brain injury. *American Journal of Physical Medicine & Rehabilitation*, *100*(8), 815–819. https://doi.org/10.1097/PHM.0000000000001753

Al-Kader, D. A., Onyechi, C. I., Ikedum, I. V., Fattah, A., Zafar, S., Bhat, S., Malik, M. A., Bheesham, N., Qadar, L. T., & Sajjad Cheema, M. (2022). Depression and anxiety in patients with a history of traumatic brain injury: A case-control study. *Cureus*. https://doi.org/10.7759/cureus.27971

Alway, Y., Gould, K. R., Johnston, L., McKenzie, D., & Ponsford, J. (2016). A prospective examination of Axis I psychiatric disorders in the first 5 years following moderate to severe traumatic brain injury. *Psychological Medicine*, *46*(6), 1331–1341. https://doi.org/10.1017/S0033291715002986

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Austin, P. C. (2011). An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research*, *46*(3), 399–424. https://doi.org/10.1080/00273171.2011.568786

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., Monteiro, M. G., & World Health Organization. (2001). *AUDIT: The alcohol use disorders identification test: Guidelines for use in primary health care*. https://doi.org/(No. WHO/MSD/MSB/01.6 a)

Bahji, A., Cheng, B., Gray, S., & Stuart, H. (2020). Mortality among people with opioid use disorder: A systematic review and meta-analysis. *Journal of Addiction Medicine*, *14*(4), e118–e132. https://doi.org/10.1097/ADM.0000000000000606

Barnes, S. M., Walter, K. H., & Chard, K. M. (2012). Does a history of mild traumatic brain injury increase suicide risk in veterans with PTSD? *Rehabilitation Psychology*, *57*(1), 18–26. https://doi.org/10.1037/a0027007

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The posttraumatic stress disorder checklist for *DSM-5* (PCL-5): Development and initial psychometric evaluation. *Journal of Traumatic Stress*, *28*(6), 489–498. https://doi.org/10.1002/jts.22059

Bogner, J., & Corrigan, J. D. (2009). Reliability and predictive validity of the Ohio State University TBI identification method with prisoners. *Journal of Head Trauma Rehabilitation*, *24*(4), 279–291. https://doi.org/10.1097/HTR.0b013e3181a66356

Brandt, L., Hu, M.-C., Liu, Y., Castillo, F., Odom, G. J., Balise, R. R., Feaster, D. J., Nunes, E. V., & Luo, S. X. (2023). Risk of experiencing an overdose event for patients undergoing treatment with medication for opioid use disorder. *American Journal of Psychiatry*, *180*(5), 386–394. https://doi.org/10.1176/appi.ajp.20220312

Brenner, M., Stein, D., Hu, P., Kufera, J., Wooford, M., & Scalea, T. (2012). Association between early hyperoxia and worse outcomes after traumatic brain injury. *Archives of Surgery*, *147*(11), 1042. https://doi.org/10.1001/archsurg.2012.1560

Bryce, S., Spitz, G., & Ponsford, J. (2015). Screening for substance use disorders following traumatic brain injury: examining the validity of the AUDIT and the DAST. *Journal of Head Trauma Rehabilitation*, *30*(5), E40–E48. https://doi.org/10.1097/HTR.0000000000000091

CDC. (2021, a). *U.S. Opioid Dispensing Rate Maps | Drug Overdose | CDC Injury Center*. https://www.cdc.gov/drugoverdose/rxrate-maps/index.html

Conway, K. P., Compton, W., Stinson, F. S., & Grant, B. F. (2006). Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: Results from the national epidemiologic survey on alcohol and related conditions. *The Journal of Clinical Psychiatry*, *67*(02), 247–258. https://doi.org/10.4088/JCP.v67n0211

Corrigan, J. D., & Bogner, J. (2007). initial reliability and validity of the Ohio State University TBI identification method. *Journal of Head Trauma Rehabilitation*, *22*(6), 318–329. https://doi.org/10.1097/01.HTR.0000300227.67748.77

Corrigan, J. D., Bogner, J., & Holloman, C. (2012). Lifetime history of traumatic brain injury among persons with substance use disorders. *Brain Injury*, *26*(2), 139–150. https://doi.org/10.3109/02699052.2011.648705

Coxe-Hyzak, K. A., Bunger, A. C., Bogner, J., Davis, A. K., & Corrigan, J. D. (2022). Implementing traumatic brain injury screening in behavioral healthcare: Protocol for a prospective mixed methods study. *Implementation Science Communications*, *3*(1), 17. https://doi.org/10.1186/s43058-022-00261-x

De Meneses-Gaya, C., Zuardi, A. W., Loureiro, S. R., & Crippa, J. A. S. (2009). Alcohol Use Disorders Identification Test (AUDIT): An updated systematic review of psychometric

properties. *Psychology & Neuroscience*, *2*(1), 83–97. https://doi.org/10.3922/j.psns.2009.1.12

Fernandez, A. C., Bush, C., Bonar, E. E., Blow, F. C., Walton, M. A., & Bohnert, A. S. B. (2019). Alcohol and drug overdose and the influence of pain conditions in an addiction treatment sample. *Journal of Addiction Medicine*, *13*(1), 61–68. https://doi.org/10.1097/ADM.0000000000000451

Gardner, R. C., Rivera, E., O'Grady, M., Doherty, C., Yaffe, K., Corrigan, J. D., Bogner, J., Kramer, J., & Wilson, F. (2020). Screening for lifetime history of traumatic brain injury among older American and Irish adults at risk for dementia: Development and validation of a web-based survey. *Journal of Alzheimer's Disease*, *74*(2), 699–711. https://doi.org/10.3233/JAD-191138

Gottlieb, A., Yatsco, A., Bakos-Block, C., Langabeer, J. R., & Champagne-Langabeer, T. (2022). Machine learning for predicting risk of early dropout in a recovery program for opioid use disorder. *Healthcare*, *10*(2), 223. https://doi.org/10.3390/healthcare10020223

Gros, D. F., Milanak, M. E., Brady, K. T., & Back, S. E. (2013). Frequency and severity of comorbid mood and anxiety disorders in prescription opioid dependence: Comorbid disorders in prescription opioid dependence. *The American Journal on Addictions*, *22*(3), 261–265. https://doi.org/10.1111/j.1521-0391.2012.12008.x

Hale, W., Vacek, S., & Swan, A. (2022). Associations between PTSD, depression, aggression, and TBI screening status: Test of a conditional process model. *Aggression and Violent Behavior*, *66*, 101744. https://doi.org/10.1016/j.avb.2022.101744

Heimer, R., Zhan, W., & Grau, L. E. (2015). Prevalence and experience of chronic pain in suburban drug injectors. *Drug and Alcohol Dependence*, *151*, 92–100. https://doi.org/10.1016/j.drugalcdep.2015.03.007

Hser, Y.-I., Mooney, L. J., Saxon, A. J., Miotto, K., Bell, D. S., Zhu, Y., Liang, D., & Huang, D. (2017). High mortality among patients with opioid use disorder in a large healthcare system. *Journal of Addiction Medicine*, *11*(4), 315–319. https://doi.org/10.1097/ADM.0000000000000312

Ilie, G., Adlaf, E. M., Mann, R. E., Ialomiteanu, A., Hamilton, H., Rehm, J., Asbridge, M., & Cusimano, M. D. (2015). Associations between a history of traumatic brain injuries and current cigarette smoking, substance use, and elevated psychological distress in a population sample of Canadian adults. *Journal of Neurotrauma*, *32*(14), 1130–1134. https://doi.org/10.1089/neu.2014.3619

Kerr, T., Fairbairn, N., Tyndall, M., Marsh, D., Li, K., Montaner, J., & Wood, E. (2007). Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and Alcohol Dependence*, *87*(1), 39–45. https://doi.org/10.1016/j.drugalcdep.2006.07.009

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lamontagne, G., Belleville, G., Beaulieu-Bonneau, S., Souesme, G., Savard, J., Sirois, M.-J., Giguère, M., Tessier, D., Le Sage, N., & Ouellet, M.-C. (2022). Anxiety symptoms and disorders in the first year after sustaining mild traumatic brain injury. *Rehabilitation Psychology*, *67*(1), 90–99. https://doi.org/10.1037/rep0000422

Mallya, S., Sutherland, J., Pongracic, S., Mainland, B., & Ornstein, T. J. (2015). The Manifestation of anxiety disorders after traumatic brain injury: A review. *Journal of Neurotrauma*, *32*(7), 411–421. https://doi.org/10.1089/neu.2014.3504

Martins, S. S., Sampson, L., Cerdá, M., & Galea, S. (2015). Worldwide prevalence and trends in unintentional drug overdose: A systematic review of the literature. *American Journal of Public Health*, *105*(11), 2373–2373. https://doi.org/10.2105/AJPH.2015.302843a

McKillop, A. B., Carroll, L. J., Dick, B. D., & Battié, M. C. (2018). Measuring participation in patients with chronic back pain—The 5-Item Pain Disability Index. *The Spine Journal*, *18*(2), 307–313. https://doi.org/10.1016/j.spinee.2017.07.172

Mitchell, M. R., & Potenza, M. N. (2014). Addictions and personality traits: impulsivity and related constructs. *Current Behavioral Neuroscience Reports*, *1*(1), 1–12. https://doi.org/10.1007/s40473-013-0001-y

Monsour, M., Ebedes, D., & Borlongan, C. V. (2022). A review of the pathology and treatment of TBI and PTSD. *Experimental Neurology*, *351*, 114009. https://doi.org/10.1016/j.expneurol.2022.114009

Nampiaparampil, D. E. (2008). Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA*, *300*(6), 711. https://doi.org/10.1001/jama.300.6.711

Novak, S. P., & Kral, A. H. (2011). Comparing injection and non-injection routes of administration for heroin, methamphetamine, and cocaine users in the United States. *Journal of Addictive Diseases*, *30*(3), 248–257. https://doi.org/10.1080/10550887.2011.581989

Olson-Madden, J. H., Brenner, L., Harwood, J. E. F., Emrick, C. D., Corrigan, J. D., & Thompson, C. (2010). Traumatic brain injury and psychiatric diagnoses in veterans

seeking outpatient substance abuse treatment. *Journal of Head Trauma Rehabilitation*, *25*(6), 470–479. https://doi.org/10.1097/HTR.0b013e3181d717a7

Patterson Silver Wolf, D. A., & Gold, M. (2020). Treatment resistant opioid use disorder (TROUD): Definition, rationale, and recommendations. *Journal of the Neurological Sciences*, *411*, 116718. https://doi.org/10.1016/j.jns.2020.116718

Polinder, S., Haagsma, J. A., Van Klaveren, D., Steyerberg, E. W., & Van Beeck, E. F. (2015). Health-related quality of life after TBI: A systematic review of study design, instruments, measurement properties, and outcome. *Population Health Metrics*, *13*(1), 4. https://doi.org/10.1186/s12963-015-0037-1

Pollard, C. A. (1984). Preliminary validity study of the Pain Disability Index. *Perceptual and Motor Skills*, *59*(3), 974–974. https://doi.org/10.2466/pms.1984.59.3.974

Ragsdale, K. A., Neer, S. M., Beidel, D. C., Frueh, B. C., & Stout, J. W. (2013). Posttraumatic stress disorder in OEF/OIF veterans with and without traumatic brain injury. *Journal of Anxiety Disorders*, *27*(4), 420–426. https://doi.org/10.1016/j.janxdis.2013.04.003

Rosenbaum, P. R., & Rubin, D. B. (1984). Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American Statistical Association*, *79*(387), 516–524. https://doi.org/10.1080/01621459.1984.10478078

Salsitz, E. A. (2016). Chronic pain, chronic opioid addiction: A complex nexus. *Journal of Medical Toxicology*, *12*(1), 54–57. https://doi.org/10.1007/s13181-015-0521-9

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*, *88*(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Scott, J. C., Lynch, K. G., Cenkner, D. P., Kehle-Forbes, S. M., Polusny, M. A., Gur, R. C., Chen, S., Foa, E. B., & Oslin, D. W. (2021). Neurocognitive predictors of treatment outcomes in psychotherapy for comorbid PTSD and substance use disorders. *Journal of Consulting and Clinical Psychology*, *89*(11), 937–946. https://doi.org/10.1037/ccp0000693

Seal, K. H., Bertenthal, D., Barnes, D. E., Byers, A. L., Gibson, C. J., Rife, T. L., & Yaffe, K. (2018). Traumatic brain injury and receipt of prescription opioid therapy for chronic pain in Iraq and Afghanistan veterans: Do clinical practice guidelines matter? *The Journal of Pain*, *19*(8), 931–941. https://doi.org/10.1016/j.jpain.2018.03.005

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-Back. In R. Z. Litten & J. P. Allen (Eds.), *Measuring Alcohol Consumption* (pp. 41–72). Humana Press. https://doi.org/10.1007/978-1-4612-0357-5_3

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., Ferri, M., & Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ*, j1550. https://doi.org/10.1136/bmj.j1550

Spaite, D. W., Hu, C., Bobrow, B. J., Chikani, V., Barnhart, B., Gaither, J. B., Denninghoff, K. R., Adelson, P. D., Keim, S. M., Viscusi, C., Mullins, T., & Sherrill, D. (2017). The effect of combined out-of-hospital hypotension and hypoxia on mortality in major traumatic brain injury. *Annals of Emergency Medicine*, *69*(1), 62–72. https://doi.org/10.1016/j.annemergmed.2016.08.007

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A Brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092. https://doi.org/10.1001/archinte.166.10.1092

Starosta, A. J., Adams, R. S., Marwitz, J. H., Kreutzer, J., Monden, K. R., Dams O'Connor, K., & Hoffman, J. (2021). Scoping review of opioid use after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *36*(5), 310–327. https://doi.org/10.1097/HTR.0000000000000721

Sun, E. C., Dixit, A., Humphreys, K., Darnall, B. D., Baker, L. C., & Mackey, S. (2017). Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ*, j760. https://doi.org/10.1136/bmj.j760

Tait, R. C., Chibnall, J. T., & Krause, S. (1990). The Pain Disability Index: Psychometric properties. *Pain*, *40*(2), 171–182. https://doi.org/10.1016/0304-3959(90)90068-O

Timko, C., Schultz, N. R., Cucciare, M. A., Vittorio, L., & Garrison-Diehn, C. (2016). Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of Addictive Diseases*, *35*(1), 22–35. https://doi.org/10.1080/10550887.2016.1100960

Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & Van Der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*, *156*(4), 569–576. https://doi.org/10.1097/01.j.pain.0000460357.01998.f1

Wang, J. (2021). To use or not to use propensity score matching? *Pharmaceutical Statistics*, *20*(1), 15–24. https://doi.org/10.1002/pst.2051

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The clinician-administered PTSD Scale for DSM–5 (CAPS-

5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, *30*(3), 383–395. https://doi.org/10.1037/pas0000486

Weil, Z. M., Corrigan, J. D., & Karelina, K. (2018). Alcohol use disorder and traumatic brain injury. *Alcohol Research: Current Reviews*, *39*(2), 171–180.

West, S. L. (2011). Substance use among persons with traumatic brain injury: A review. *NeuroRehabilitation*, *29*(1), 1–8. https://doi.org/10.3233/NRE-2011-0671

Wilens, T. E., Martelon, M., Fried, R., Petty, C., Bateman, C., & Biederman, J. (2011). Do executive function deficits predict later substance use disorders among adolescents and young adults? *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(2), 141–149. https://doi.org/10.1016/j.jaac.2010.11.010

Zibbel, J. (2019). *Non-Fatal Opioid Overdose and Associated Health Outcomes: Final Summary Report*. ASPE. https://aspe.hhs.gov/reports/non-fatal-opioid-overdose-associated-health-outcomes-final-summary-report-0

Chapter 4. A Systematic Review of Psychotherapy for Substance Use Disorder among Patients with Traumatic Brain Injury

Hannah G. Mitchell, M.A.[1]

Department of Psychology, East Tennessee State University

ABSTRACT

Introduction: Despite extensive epidemiological data demonstrating the presence of substance use disorder (SUD) among persons with TBIs, limited research has evaluated the effectiveness of treatments tailored for this population. The present study is a systematic review of the available peer-reviewed literature related to treatment for SUD among adults who have experienced TBIs. *Method:* PubMed, PsycInfo, and Scopus were searched for relevant articles. Of the 373 abstracts evaluated, 10 (2.7%) met study inclusion criteria. The following information was collected from each study: study design, sample size, mean age of the sample, mean time since TBI, location of participants, treatment modality and accommodations for the impact of TBI, treatment duration, treatment outcome variables, and study results. *Results:* Motivational enhancement/interviewing was found to decrease substance use in four studies and have no effect in two studies. Comprehensive TBI services, including resource and service coordination, were found to significantly decrease substance use in two studies. Prolonged exposure was implemented for patients with comorbid posttraumatic stress disorder with a successful reduction in substance use, although this effect was less than for individuals without TBI. An adapted screening and brief intervention protocol was found to decrease substance use significantly in one study. Interventions were adapted to mitigate the impact of TBI through memory cues, visual aids, role plays, large print items, and ample repetition. *Conclusion:* These studies provide evidence for the feasibility and efficacy of adapting SUD treatments to meet the needs of patients with TBI.

Findings from this review may be used to develop an evidence-based pathway for the identification and treatment of SUD among patients with TBI in a variety of healthcare settings.

Keywords: traumatic brain injury, substance use, neuropsychology, addiction

[1] Manuscript is co-authored by Meredith K. Ginley

A Systematic Review of Psychotherapy for Substance Use Disorder among Patients with Traumatic Brain Injury

The association between substance use and traumatic brain injury (TBI) is well-established (Andelic et al., 2010; Corrigan & Adams, 2019; Corrigan et al., 2012). Among persons with a history of TBI, upwards of 79% report problematic alcohol use and 10%-44% report non-medical drug use (Taylor et al., 2003). More than half of persons seeking substance use disorder (SUD) treatment report having a prior TBI (Sacks et al., 2009). Persons who sustain a TBI while intoxicated are also at heightened risk of incurring subsequent TBIs (Vaaramo et al., 2014). Given that 1.5 million persons in the United States sustain a TBI and 40.3 million persons are diagnosed with a SUD annually, the intersection of these medical conditions warrants clinical and research attention (Allen at al., 2016; CDC, 2023a; CDC, 2023b).

Substance use is a reliable predictor of TBI, largely due to its effect on motor control and decision making, thereby increasing vulnerability to attacks and accidents (Allen et al., 2016; Chen et al., 2012; Gjerde et al., 2008; Olson-Madden et al., 2012). Acute substance use is involved in one-half to one-third of TBI-causing accidents and injuries among hospitalized persons (MacLeod & Hungerford, 2011; Weil et al., 2018). Behavioral predispositions and similar environmental risks (i.e., criminal justice system involvement, experiencing homelessness) may further contribute to the connection between TBI and substance use (McKinlay et al., 2014).

There is evidence that a history of TBI may increase the risk of SUD (Merkel et al., 2017). Brain regions damaged by TBIs, including the prefrontal cortex, nucleus accumbens, and ventral tegmental area, are central to executive functioning and emotion regulation (Merkel et al., 2017). Accordingly, they are often implicated in the development and continuation of SUDs

(Nestler, 2005). It has been posited that substance use may be a maladaptive method of coping with the unpleasant biopsychosocial consequences of a TBI (Cox et al., 2003). Of persons with TBI, 32-75% report chronic pain (Nampiaparampil, 2008), 43–72% depression (Lavoie et al., 2017; Scholten et al., 2016), 9%-19% posttraumatic stress disorder (Stein et al., 2019), and 6% are on long-term disability (CDC, 2016). Given the well-established connection between mental health disorders, life stress, and addiction, the collection of symptoms surrounding TBI may render persons vulnerable to developing a SUD (Lin et al., 2020).

Of persons enrolled in SUD treatment, a history of TBI is associated with more SUD symptoms, more prior unsuccessful treatment attempts, earlier age of SUD onset, and a higher number of concurrent physical and behavioral health disorders (Graham & Cardon, 2008; Gros et al., 2017; Merkel et al., 2017; Parry-Jones et al., 2006). Characteristics of the TBI, such as the age of onset and the severity, moderate the relation between TBI and SUD treatment outcomes (Cannella et al., 2019; Merkel et al., 2017). The resultant neuropsychological impairment of both TBI and SUD may be contributing to the poor SUD treatment prognosis for individuals with TBI. Research has established that comorbid TBI and SUD patients have higher mortality rates, greater brain atrophy, degraded white matter, and increased neuropsychological impairments (Fazel et al., 2014; Jourdan et al., 2016; Unsworth & Mathias, 2017; West, 2011). These neuropsychological changes may limit patients' ability to fully participate in and benefit from treatment (Adams et al., 2020; Scott et al., 2021). Additionally, comorbid behavioral health conditions and chronic pain may attenuate the efficacy of SUD treatment (Ilgen et al., 2020; Murthy et al., 2019).

Alterations to SUD treatment may mitigate the effect of TBI on SUD treatment (Bogner & Corrigan, 2013). For instance, financial incentives, immediate rewards for treatment

participation, and mindfulness interventions increase SUD treatment adherence for individuals with TBI (Corrigan & Cole, 2008; Cox et al., 2003; Kristofersson et al., 2016). However, there is substantial diversity in the interventions evaluated for SUD treatment post-TBI, especially when considering the range of providers, healthcare settings, and treatment modalities that have been researched. The lack of concise, evidence-based guidelines for SUD treatment following TBI may serve as a barrier to the appropriate implementation of these interventions.

Although previous reviews have examined the available literature (N = 6 studies) for SUD treatment following TBI (Bogner & Corrigan, 2013), four treatment studies have been published over the last 10 years, warranting an updated review. The present study intends to further update previous reviews by systematically reviewing treatments of SUD adapted for individuals with TBI in terms of efficacy and operational components. Given the prevalence and implications of comorbid TBI and SUD, updated treatment guidelines will provide useful direction for clinicians and researchers.

Method

Inclusion and Exclusion Criteria

First, the scope and limits of the review was specified. For inclusion, studies must: 1) evaluate a treatment for SUD, 2) use a design that is either multiarmed (randomized or non-randomized) or pretest-posttest, and 3) include an outcome measure related to substance use. The end date of the review was March 30, 2023, when the database searches were conducted. Studies were excluded if they 1) evaluated prevention rather than treatment, 2) were review or theoretical, or 3) were not available in English.

Search Strategy

PubMed, PsycInfo, and Scopus were searched using the following combination of search terms: [‘drug dependence’ OR ‘drug use’ OR ‘addiction’ OR ‘substance use’] AND [‘treatment’ OR ‘intervention’ OR ‘therapy’ OR ‘rehabilitation’] AND [‘traumatic brain injury’ OR ‘TBI’ OR ‘concussion’ OR ‘head injury’]. For this review, alcohol use disorder was not differentiated from other forms of substance use disorder in accordance with how the reviewed articles operationalized substance use disorder treatment (e.g., Gros et al., 2017). Secondary reference searching was conducted on all included studies. Finally, the reference lists of similar reviews were hand-searched for relevant studies.

Screening Abstracts

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened for inclusion in the study. First, the primary research screened abstracts to eliminate clearly non-relevant articles. To establish inter-rater reliability, 40% (150) of these articles were randomly selected for a second researcher to code independently. The researchers had 97.5% agreement. All discrepancies were resolved through consensus. Full articles were then collected and evaluated for study inclusion.

Data Extraction and Management

The following information was collected from each study: study design, sample size, mean age of the sample, mean time since TBI, location of participants, treatment modality and accommodations for the impact of TBI, treatment duration, treatment outcome variables, and study results. The extracted data were reviewed for accuracy and completeness by another researcher. A meta-analysis was not conducted due to the notable heterogeneity in study design and treatment modality, as well as the paucity of relevant research available to analyze.

Results

The initial database search yielded 298 abstracts that were evaluated by the primary investigator (HGM). The initial review of abstracts produced 16 articles warranting further evaluation. After evaluating the full manuscript, three articles met criteria for study inclusion. Of the references listed within these studies, 75 were pulled as potential studies of interest. After review of these manuscripts, seven met the inclusion criteria. Ultimately, 10 of the 373 abstracts evaluated met the study criteria (2.4%). See Figure 4.1 for the PRISMA Flow Diagram of article selection (Page et al., 2021). Study characteristics are listed in Table 4.1

Figure 4.1

PRISMA Flow Diagram

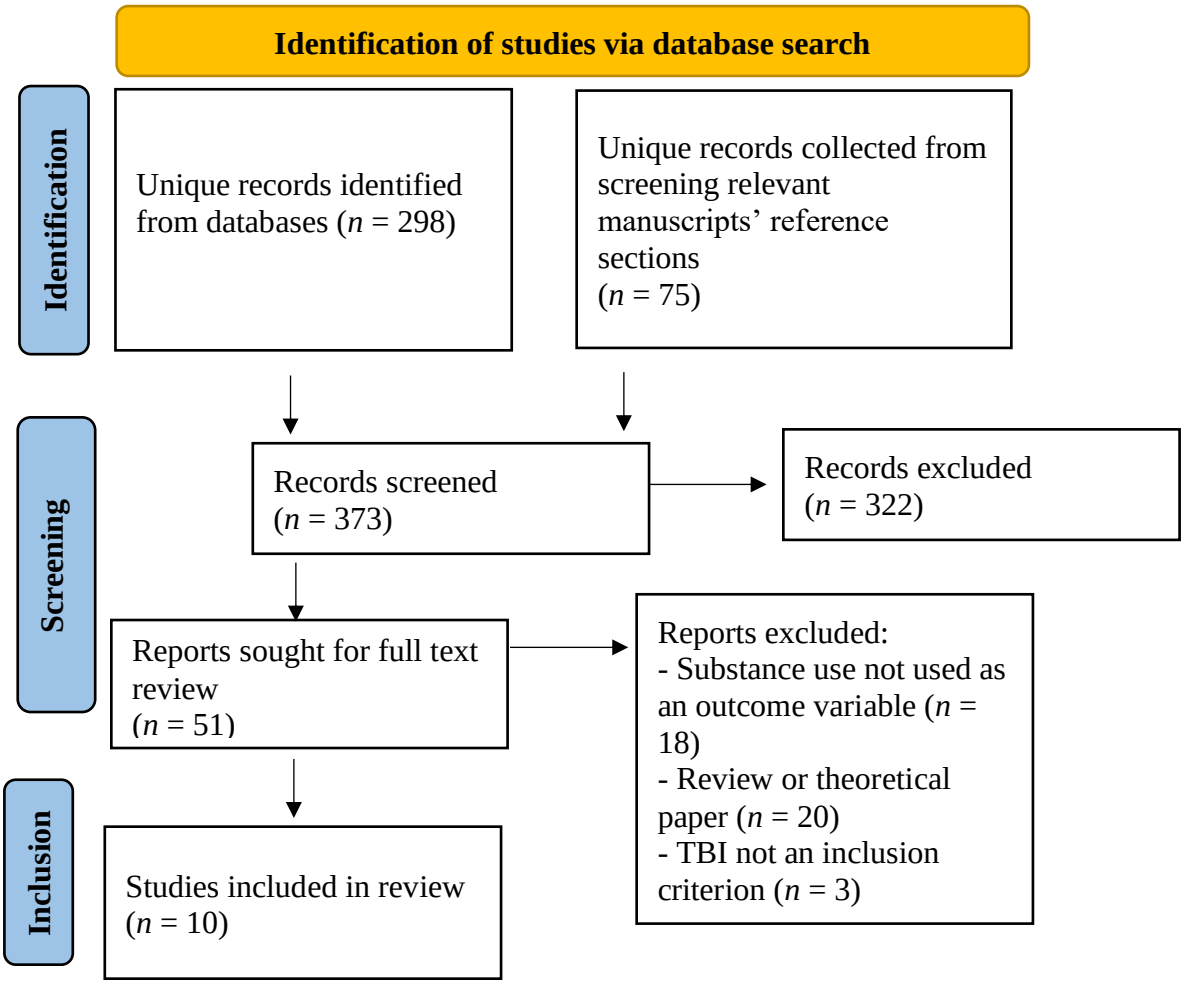


Table 4.1

Study Characteristics

Author, year	*N*	Age M (SD)	Time since TBI M (SD) or range	Study design	Location of participants	Treatment	Explicitly accommodates cognitive impact of TBI	Treatment duration	Outcome assessments administered	Significant result
Bogner et al., 2021	58	39.2 (14.6) years	33.8 (21.7) days	Single-masked, parallel group, randomized controlled trial	Academic medical center's inpatient rehabilitation facility	Adapted Screening, and Brief Intervention	Yes	Single session lasting 25–30 minutes + single booster session lasting 10–15	Timeline follow-back (TLFB); Alcohol Expectancies Questionnaire (AEQ-III)	No significant effect on drinks/week, but intervention group less likely to resume alcohol use
Gros et al., 2017	51	39.9 (10.8)	-	Non-randomized controlled study	Recruited from the community	Concurrent Treatment for PTSD and Substance Use Disorders Using Prolonged Exposure (COPE)	No	12 weekly, individual, 90-minute sessions	TLFB	Significantly fewer days per month of alcohol use were found post-treatment
Tweedly et al., 2012	60	35.2 (16.5)	6 - 9 months	Randomized controlled study	Post-discharge from inpatient hospitalization into the community	Informational discussion and motivational interviewing	Yes	Single 2-hour session	TLFB	No statistical difference found
Vungkhanching et al., 2007	117	32.8 (7.3)	9.0 (6.8) years	Non-randomized controlled study	Vocational rehabilitation programs	Systematic motivational counseling	Yes	12 1-hour sessions	Alcohol and Drug Inventory (ADI); Alcohol Use Inventory	Intervention group participants decreased alcohol and drug use relative to the comparison group.
Zatzick et al., 2014	878	36.9 (14.3)	< 7 days	Cluster randomized trial	Hospital trauma unit	Screening + brief motivational interviewing	No	Single session lasting M = 33.4 minutes	Alcohol Use Disorders Identification Test (AUDIT); Short Inventory of Problems (SIP); Form 90 alcohol	Intervention patients demonstrated an 8% reduction in AUDIT, although this effect was

									timeline follow-back	weakened for patients with TBI
Sander et al., 2012	104	36.1 (14)	30 (26) days	Randomized controlled study	Level I trauma centers	Brief intervention consisting of education and motivational interviewing	Yes	Single session lasting 20-30 minutes	AEQ-III	No statistical difference found
Heinemann et al., 2004	319	36 (9.5)	1.4 (8.3) years	Non-randomized controlled study	Long-term postinjury services, either through vocational rehabilitation or case management	Comprehensive case management services	Yes	9 months; median appointments completed = 56	Addiction Severity Index (ASI)	No statistical difference found
Bombardier & Rimmele, 1999	32	37.2 (14.8)	2.6 (18.3) days	Historical-controlled trial	Rehabilitation hospital inpatient unit	Motivational interviewing	Yes	2 sessions lasting 20-60 minutes each	Unstructured interview assessment	No statistical difference found
Bogner et al., 1997	69	26.0 (10)	44.3 (67.1) months	Non-controlled trial	Community members	TBI Network: comprehensive services	Yes	12-15 months	ASI	Intervention group participants were more likely to achieve substance abstinence relative to the comparison group.
Cox et al., 2003	94	35.6 (11.9)	4.0 (4.3) years	Non-randomized controlled study	Rehabilitation hospital inpatient or outpatient units	Systematic motivational counseling	No	12 sessions over 10 months	ADI	Intervention group participants decreased alcohol and/or drug use relative to the comparison group.

Overview of Studies Included

Patient Characteristics

Across the 10 included studies, there were 1,782 participants. The average age of participants ranged from *M* = 26.0-39.9 years. Two studies recruited participants from hospital trauma centers, three from rehabilitation units of hospitals, three from the community, and two from postinjury rehabilitation programs, such as vocational rehabilitation programs and/or case management services. The length of time between the TBI and the intervention varied widely. One study did not specify, two studies intervened within seven days post-TBI, three studies intervened between one and nine months post-TBI, and four studies intervened over one-year post-TBI. The longest average time between TBI and intervention was 9.0 years (Vungkhanching et al., 2007). All studies were predominantly male (e.g., 82.5% [Cox et al., 2003], 96.7% [Gros et al., 2017], 78% [Bogner et al., 1997]). Three studies provided insight into the substances used by participants. Bogner et al., 2021 reported that 77.6% of participants had alcohol use disorder, and 43.1% of participants had non-medically used drugs in their lifetime. As assessed through the Alcohol and Drug Inventory, 62.9% of participants used alcohol, followed by marijuana (18.5%), cocaine (11.1%), and other drugs (7.4%; Cox et al., 2003). The "drug of choice" for 81% of participants was alcohol, followed by crack/cocaine (8%), marijuana (7%), and other drugs (3%; Bogner et al., 1997).

Method of Assessing Substance Use Outcomes

Substance use outcomes were assessed via self-report measures in each study. The Alcohol Use Inventory (Wanberg et al., 1977) and Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) were each used by one study each to assess for symptoms of alcohol use disorder. The Alcohol Expectancies Questionnaire (AEQ-III; Brown et al., 1987)

was used by two studies to examine the anticipated outcomes of alcohol use. An unstructured interview assessment was used in one study. Alcohol and drug use was examined via the Form-90 Timeline Follow back or the Timeline Follow-Back (Sobell & Sobell, 1992) in four studies, the Addiction Severity Index (McLellan et al., 1992) in two studies, and Alcohol and Drug Inventory (Blount & Cox, 1996) in two studies.

Accommodations for the Impact of TBI

Bogner et al. (2021) described accommodations for cognitive/memory impairment following TBI. Written documentation of the Brain Health Plan (BHP), methods of remembering the BHP, and a reminder of the follow-up appointment were sent via letter following the intervention. The intervention also included a discussion of strategies for recalling and implementing the BHP, including the use of technological and visual reminders (e.g., phone alerts, wearing a bracelet, use of a calendar; Bogner et al., 2021). Vungkhanching et al. (2007) specified a flexible approach to implementing the intervention based on the neuropsychological profiles of each participant. The potential impact of learning and memory deficits was mitigated through an active retraining process and ample rehearsal.

One study offered participants information via verbal, written, and visual formats to mitigate the impact of cognitive difficulties (Tweedly et al., 2012). Participants were also encouraged to take their written notes and informational booklet home with them following the intervention (Tweedly et al., 2012). Bombardier & Rimmele (1999) implemented the intervention following patients' discharge to allow time for cognitive recovery. Cue cards were offered throughout the screening and assessment to remind patients of response options, and information was presented via multiple formats (e.g., verbal, written, graphic; Bombardier & Rimmele, 1999).

Three studies did not explicitly adapt the content or method of delivering the intervention to accommodate the potential impact of the TBI (Cox et al., 2003; Gros et al., 2017; Zatzick et al., 2014). Although several studies did not describe methods of developing or modifying the intervention to be suitable for patients post-TBI, it is assumed that adaptations were standard care due to having been created and/or delivered within TBI rehabilitation units. For example, Cox et al. (2003), Heinemann et al. (2004), and Sander et al. (2012) examined interventions within existing programs that serve patients post-TBI, wherein TBI adaptations are assumed to be standard care. However, the only explicit accommodation Heinemann et al. note is that services and treatment plans are adapted to suit individual patients' abilities. Similarly, the video portion of the intervention presented by Sander et al. (2012) was developed by faculty in a brain injury rehabilitation center which is assumed to be specifically tailored to accommodate the cognitive impact of TBI, although this is not specified. No studies scientifically evaluated the merits of these adaptations.

Treatment Modality

Motivational Interviewing/Counseling

Six studies implemented motivational interviewing or motivational counseling techniques (Bombardier & Rimmele, 1999; Cox et al., 2003; Sander et al., 2012; Tweedly et al., 2012; Vungkhanching et al., 2007; Zatzick et al., 2014). Several authors suggest that MI may be well-suited to inpatient or rehabilitation settings since it can be taught to non-specialists and is brief (Bombardier & Rimmele, 1999; Tweedly et al., 2012). Three studies did not find significant effects of the intervention on substance use (Bombardier & Rimmele, 1999; Sander et al., 2012; Tweedly et al., 2012).

Bombardier & Rimmele (1999) evaluated the effect of two MI sessions on alcohol use by employing the Project Match Motivational Enhancement Therapy manual protocol (Miller, 1992). The first MI visit was dedicated to the assessment of alcohol use, and the second visit was used to provide personalized feedback from the first visit. Feedback, responsibility, advice, a menu of options, empathy, and self-efficacy were emphasized during both visits (Bombardier & Rimmele, 1999). MI was estimated to increase the proportion of participants not drinking from 20% to 34%, as determined by a comparison of intervention to historical control. However, this trend did not reach significance, and it is noted that the historical control group also demonstrated significant reductions in alcohol use post-TBI.

Tweedly et al. (2012) examined the effect of MI on alcohol use. Study staff were trained in MI through multiple MI-training sessions and received feedback regarding fidelity to MI. Common MI strategies, including open-ended questions, affirmations, reflective listening, and summarizing statements were implemented within the study protocol (Tweedly et al., 2012). The goals of MI were to emphasize the impact of current alcohol use, explore ambivalence about alcohol use, and elucidate the discrepancy between current behaviors and long-term goals. Participants undergoing MI did not significantly differ from the control group in terms of alcohol use at follow-up.

Sander et al. (2012) implemented a 20–30-minute interview infused with principles of MI, including open-ended questioning, affirming, reflecting, and summarizing statements. The MI therapist emphasized the benefits of change and the discrepancy between participants' recovery goals and alcohol use. Study staff were instructed by a certified MI trainer and received feedback regarding treatment fidelity via a review of taped MI visits. There was no effect of the intervention on alcohol use as compared to a control group receiving treatment as usual.

Cox et al. (2003) evaluated the benefit of systematic motivational counseling (SMC) + post-TBI rehabilitation services compared to patients only receiving rehabilitation services. SMC included the following treatment components: 1) reviewing personal concerns, 2) interpreting motivational profile, 3) exploring competing goals, 4) identifying treatment goals, 5) creating goal ladders, 6) creating between-session goals, 7) attaining skills essential for meeting goals, 8) resolving conflict between goals, 9) relinquishing unrealistic/emotionally unsatisfying goals, 10) identifying healthy incentives for meeting goals, 11) facilitating positive thinking, and 12) improving self-esteem (Cox et al., 2003). Study staff were trained in SMC through a two-day workshop and evaluated for protocol adherence through weekly review of recorded SMC visits. SMC was delivered over 12 individual visits. Relative to the comparison group, participants who received SMC reported decreased alcohol and/or drug use at follow-up (M = 9.1 months post-intervention).

Zatzick et al., (2014) implemented MI as part of screening and brief intervention within a hospital trauma unit. MI was delivered at an inpatient's bedside in a single 20-minute appointment. Study staff were trained to deliver MI during a 1-day workshop. MI fidelity was evaluated through standardized patient-actor telephone interviews and Motivational Interviewing Treatment Integrity (MITI) coding. Results found an 8% reduction in AUDIT scores for participants who received MI relative to the control group. However, not all participants in this study had experienced a TBI. The presence of a TBI was found to mitigate the effect of the intervention on AUDIT scores, although the exact reduction of the effect was not specified.

The Skills-based Substance Abuse Prevention Counseling (SBSAPC) intervention contains four stages: comprehensive evaluation, motivational enhancement, coping skills training, and structured generalization (Vungkhanching et al., 2007). SBSAPC was delivered

over 12 sessions lasting 60 minutes each. Study staff were trained in SBSAPC through a one-day workshop on biopsychosocial outcomes of TBI and the SBSAPC protocol. Participants who received SBSAPC decreased alcohol and drug use relative to waitlist controls. The extent that this change may be attributed to the motivational enhancement component of this intervention is unknown.

Informational Interventions (Psychoeducation)

Five studies evaluated informational interventions targeting substance use post-TBI. Blackerby & Baumgarten (1990) utilized psychoeducation on SUD and information on the Alcoholics Anonymous/Narcotics Anonymous 12-step program. Family members also received written information regarding the process of discharging from the hospital. Of note, patients must have had a cognitive ability of seven or higher on the Rancho Scale to participate in this intervention (Blackerby & Baumgarten, 1990; Madonna Rehabilitation Hospitals, n.d.).

The TBI Network also includes educational components to promote change among individuals with SUD and TBI (Bogner et al., 1997; Heinemann et al., 2004). Staff from the TBI Network work closely with an inpatient team within a specialized brain injury rehabilitation unit by providing information on alcohol and drug use following TBI, as well as facilitating weekly substance use educational groups for the psychologists (Bogner et al., 1997; Heinemann et al., 2004). This program was replicated at other treatment sites, including the Consumer Advocacy Model (CAM) Program at Wright University (Heinemann et al., 2004).

Sander and colleagues (2012) created a single-session treatment that consisted of a 10-minute educational video that described the adverse effects of alcohol and drug use following a TBI and encouraged patients to consider the pros and cons of substance use.

Lastly, Tweedly and colleagues (2012) examined whether brief MI combined with an information package, information alone, or an informal discussion on changes the participant has exhibited following their TBI (i.e., no discussion on alcohol or drug use) would result in decreased alcohol consumption at follow-up (Tweedly et al., 2012). The informational packet consisted of a seven-minute educational video and a booklet outlining potential cognitive, behavioral, and psychological outcomes of TBI and how alcohol and drug use may exacerbate them (Tweedly et al., 2012).

Case Management

Two studies evaluated the effect of case management programs on SUD. The TBI Network assists patients in "wrap-around services" to address patients' physical, financial, and social health (Bogner et al., 1997; Heinemann et al., 2004). One way they address these concerns is by connecting patients with existing SUD treatment services (Bogner et al., 1997; Heinemann et al., 2004). Case managers/employment service coordinators also assist in the following areas: (1) job-search skills training; (2) job development; (3) job placement; (4) individual and group counseling; and (5) supported employment (Bogner et al., 1997; Heinemann et al., 2004).

Skills-Based

Three studies evaluated skills-based programs for the treatment of SUD. Blackerby & Baumgarten (1990) assessed a post-acute rehabilitation program, Rebound Lifestyle Adjustment Team (RELATE), designed for clients exhibiting dual diagnoses of SUD and TBI (Blackerby & Baumgarten, 1990). The six-month, high-intensity program was implemented in a residential TBI rehabilitation center and was facilitated by staff members with 20 hours of specific training in TBI (Blackerby & Baumgarten, 1990). RELATE required daily structured activities including two educational and discussion sessions, two group counseling sessions, two daily community

meetings (i.e., AA/NA), structured exercise and leisure time, and, when needed, traditional rehabilitation therapies. RELATE also involved peer modeling, coaching, and family support (Blackerby & Baumgarten, 1990).

RELATE implemented a cognitive behavioral approach to assist patients in learning and practicing self-awareness and substance use avoidance behaviors (Blackerby & Baumgarten, 1990). Patients were praised for identifying triggers in their community, taught how to create structured schedules to eliminate free time that may prompt substance use, and role-played ways to navigate triggers for substance use (Blackerby & Baumgarten, 1990).

One stage of SBSAPC entails coping skills training (Vungkhanching et al., 2007). During this stage, participants learned alternative behaviors to substance use, management of difficult feelings and emotions, coping with substance-related triggers, and ways of increasing social competence (Vungkhanching et al., 2007).

Prolonged Exposure

Gros et al. (2017) evaluated prolonged exposure among veterans with PTSD and SUD using COPE (Concurrent Treatment of PTSD and SUD Using Prolonged Exposure). COPE is a 12-session protocol entailing 1) psychoeducation on PTSD, SUD, and the relation between PTSD and SUD; 2) prolonged imaginal exposure and in vivo exposure for PTSD; and 3) relapse prevention for SUD. Either abstinence or adaptive substance use are possible treatment goals using COPE. COPE decreased substance use among all participants, although this relation was stronger in the absence of TBI.

Discussion

The aim of the present systematic review was to provide an updated examination of the current literature on SUD treatment adapted for individuals with TBI. Given the significant costs

and prevalence of TBIs, and the high co-occurrence of TBIs and SUDS, a review of the efficacy and operational components of existing interventions was merited (CDC, 2023a; CDC, 2023b; Chen et al., 2012; Olsen & Corrigan, 2022). This study is an update to a previous systematic review of SUD interventions following TBI by Bogner and Corrigan (2013), and after screening all possible studies for eligibility criteria, includes 66% more published studies. All included studies were assessed for patient characteristics, substance use outcome methods, TBI accommodations, and treatment modality to aid in identifying themes to inform the identification and treatment of SUD among patients with TBI.

Eligible studies included data from a range of settings, including hospital trauma centers, rehabilitation hospital units, community centers, and postinjury rehabilitation programs. It is critical to assess SUD treatment efficacy in these various environments as individuals with TBI present to different treatment settings depending on the level of care required (Colantonio et al., 2015). These findings reinforce the relevance of assessing for and considering the implications of TBI outside of the "traditional" settings where practitioners might be primed to screen for TBIs (i.e., in outpatient psychotherapy offices in addition to hospital trauma centers). Indeed, TBI is a pervasive, chronic condition that may impact treatment efficacy across settings and presenting diagnoses.

Substance use outcomes were assessed using self-report measures in all 10 studies. Self-report data is susceptible to biases and therefore may not accurately portray treatment responses (Macleod et al., 2005). One study (Bombardier & Rimmele, 1999) additionally used an unstructured interview assessment with unknown validity and reliability to assess substance use. Alcohol was assessed via the Alcohol Use Inventory (Wanberg et al., 1977), Alcohol Use Disorders Identification Test (Saunders et al., 1993), and Alcohol Expectancies Questionnaire

(Brown et al., 1987), and substance use generally was assessed via the Timeline Follow-Back (Sobell & Sobell, 1992), Addiction Severity Index (McLellan et al., 1992), and the Alcohol and Drug Inventory (Blount & Cox, 1996). However, three studies (33%) exclusively assessed for alcohol use rather than substance use generally. Assessing solely for alcohol use neglects to consider the elevated risk of non-medical use of other drugs following TBI, including cocaine (Ramesh et el., 2015) and opioids (Adams et al., 2020). Future studies using a range of assessment modalities (i.e., self-report, validated semi-structured interview, behavioral, drug tests) that assess for a broader range of substances may provide additional insight into outcomes of SUD treatment for individuals with TBI.

Accommodations to SUD treatment as usual were assumed to be present in 70% of studies, with four studies explicitly describing the alterations made. Three studies sought to overcome memory impairment following TBI via rehearsal, repetition, and reminders. Given that memory impairment is the most common neuropsychological sequalae of moderate-severe TBI, memory-based adaptations for treatment are fitting (Jourdan et al., 2016). The use of multiple modalities when delivering information (e.g., verbal, written, and graphic formats) was also endorsed by two studies. This adaptation is consistent with evidence-based cognitive rehabilitation following TBI (Velikonja et al., 2023). Three studies did not mention alterations to treatment as usual, and three studies nondescriptly stated they were tailored to compensate for the TBI. Without insight into the specific approach to tailoring implemented, these accommodations are unable to be replicated by clinicians or researchers. Future research objectively stating all interventions and accommodations implemented will render a more practical and scientifically sound guide to treatment.

Treatment modalities incorporated in the eligible studies were organized into five categories: motivational interviewing/counseling (n = 6), psychoeducation (n = 5), case management (n = 2), skills-based (n = 3), and prolonged exposure (n = 1). No modality was found to be superior in the current review. However, the small sample size and significant heterogeneity of studies in the current review (N = 10) prohibited meta-analysis, thereby limiting the precise comparison of effects between studies. Upon publication of additional relevant research, a meta-analysis will provide further insight into the relative efficacy of these interventions. Notably, prolonged exposure was found to be effective in reducing SUD among persons with TBI, but to a lesser extent than for patients without TBI. Motivational interviewing was inconsistent in enhancing outcomes; 3 of the 6 studies (50%) that implemented motivational interviewing or motivational counseling techniques did not find significant effects of the intervention on substance use (Bombardier & Rimmele, 1999; Sander et al., 2012; Tweedly et al., 2012). Plausible explanations for this discrepancy include the caliber of training in motivational interviewing provided to the researchers and the severity of TBI injuries treated between settings.

Limitations and Conclusions

There were several limitations to the current review that should be considered when interpreting the results. Few studies met inclusion criteria, limiting the sample of available evidence to review. The limited sample size combined with the large heterogeneity between studies prevented a meta-analysis from being conducted. Some studies did not provide critical study details, including the length of time between the TBI and the intervention and information on how protocols were adapted to accommodate patients with TBI. Lastly, publication bias may

skew the available pool of studies to review, therefore distorting the findings of the current study (Dalton et al., 2016).

The current systematic review examined psychotherapy for SUD among persons with TBI and updated a previous review through the inclusion of recent research. The findings highlight the need for rigorous randomized clinical trials of psychotherapy for SUD that has been adapted for persons with TBI. Studies should explicitly describe their treatment accommodation strategies so that the scientific merit of such adaptations can be evaluated.

References

Adams, R. S., Corrigan, J. D., & Dams-O'Connor, K. (2020). Opioid use among individuals with traumatic brain injury: A perfect storm? *Journal of Neurotrauma*, *37*(1), 211–216. https://doi.org/10.1089/neu.2019.6451

Allen, S., Stewart, S. H., Cusimano, M., & Asbridge, M. (2016). Examining the relationship between traumatic brain injury and substance use outcomes in the Canadian population. *Substance Use & Misuse*, *51*(12), 1577–1586. https://doi.org/10.1080/10826084.2016.1188955

Andelic, N., Jerstad, T., Sigurdardottir, S., Schanke, A.-K., Sandvik, L., & Roe, C. (2010). Effects of acute substance use and pre-injury substance abuse on traumatic brain injury severity in adults admitted to a trauma centre. *Journal of Trauma Management & Outcomes*, *4*(1), 6. https://doi.org/10.1186/1752-2897-4-6

Blackerby, W. F., & Baumgarten, A. (1990). A model treatment program for the head–injured substance abuser: Preliminary findings: *Journal of Head Trauma Rehabilitation*, *5*(3), 47–59. https://doi.org/10.1097/00001199-199009000-00009

Blount, J., & Cox, W. (1996). *Alcohol and drug Inventory*.

Bogner, J. A., Corrigan, J. D., Spafford, D. E., & Lamb-Hart, G. L. (1997). Integrating substance abuse treatment and vocational rehabilitation after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *12*(5), 57–71. https://doi.org/10.1097/00001199-199710000-00006

Bogner, J., & Corrigan, J. D. (2013). Interventions for substance misuse following TBI: A systematic review. *Brain Impairment*, *14*(1), 77–91. https://doi.org/10.1017/BrImp.2013.5

Bogner, J., Corrigan, J. D., Peng, J., Kane, C., & Coxe, K. (2021). Comparative effectiveness of a brief intervention for alcohol misuse following traumatic brain injury: A randomized controlled trial. *Rehabilitation Psychology*, *66*(4), 345–355. https://doi.org/10.1037/rep0000405

Bombardier, C. H., & Rimmele, C. T. (1999). Motivational interviewing to prevent alcohol abuse after traumatic brain injury: A case series. *Rehabilitation Psychology*, *44*(1), 52–67. https://doi.org/10.1037/0090-5550.44.1.52

Brown, S. A., Christiansen, B. A., & Goldman, M. S. (1987). The Alcohol Expectancy Questionnaire: An instrument for the assessment of adolescent and adult alcohol expectancies. *Journal of Studies on Alcohol*, *48*(5), 483–491. https://doi.org/10.15288/jsa.1987.48.483

CDC. (2016). *Report to Congress on Traumatic Brain Injury Epidemiology and Rehabilitation | Concussion | Traumatic Brain Injury | CDC Injury Center*. https://www.cdc.gov/traumaticbraininjury/pubs/congress_epi_rehab.html

CDC. (2023a, b). *FastStats*. https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

CDC. (2023b, a). *TBI Data | Concussion | Traumatic Brain Injury | CDC Injury Center*. https://www.cdc.gov/traumaticbraininjury/data/index.html

Chen, C. M., Yi, H.-Y., Yoon, Y.-H., & Dong, C. (2012). Alcohol use at time of injury and survival following traumatic brain injury: Results from the national trauma data bank. *Journal of Studies on Alcohol and Drugs*, *73*(4), 531–541. https://doi.org/10.15288/jsad.2012.73.531

Colantonio, A., Hsueh, J., Petgrave, J., Hirdes, J. P., & Berg, K. (2015). A profile of patients with traumatic brain injury within home care, long-term care, complex continuing care,

and institutional mental health settings in a publicly insured population. *Journal of Head Trauma Rehabilitation*, *30*(6), E18–E29. https://doi.org/10.1097/HTR.0000000000000112

Corrigan, J. D., & Adams, R. S. (2019). The intersection of lifetime history of traumatic brain injury and the opioid epidemic. *Addictive Behaviors*, *90*, 143–145. https://doi.org/10.1016/j.addbeh.2018.10.030

Corrigan, J. D., Bogner, J., & Holloman, C. (2012). Lifetime history of traumatic brain injury among persons with substance use disorders. *Brain Injury*, *26*(2), 139–150. https://doi.org/10.3109/02699052.2011.648705

Corrigan, J. D., & Cole, T. B. (2008). Substance use disorders and clinical management of traumatic brain injury and posttraumatic stress disorder. *JAMA*, *300*(6), 720. https://doi.org/10.1001/jama.300.6.720

Cox, W. M., Heinemann, A. W., Miranti, S. V., Schmidt, M., Klinger, E., & Blount, J. (2003). Outcomes of systematic motivational counseling for substance use following traumatic brain injury. *Journal of Addictive Diseases*, *22*(1), 93–110. https://doi.org/10.1300/J069v22n01_07

Dalton, J. E., Bolen, S. D., & Mascha, E. J. (2016). Publication bias: The elephant in the review. *Anesthesia & Analgesia*, *123*(4), 812–813. https://doi.org/10.1213/ANE.0000000000001596

Fazel, S., Wolf, A., Pillas, D., Lichtenstein, P., & Långström, N. (2014). Suicide, fatal injuries, and other causes of premature mortality in patients with traumatic brain injury: A 41-year Swedish population study. *JAMA Psychiatry*, *71*(3), 326. https://doi.org/10.1001/jamapsychiatry.2013.3935

Gjerde, H., Normann, P. T., Pettersen, B. S., Assum, T., Aldrin, M., Johansen, U., Kristoffersen, L., Øiestad, E. L., Christophersen, A. S., & Mørland, J. (2008). Prevalence of alcohol and drugs among Norwegian motor vehicle drivers: A roadside survey. *Accident Analysis & Prevention*, *40*(5), 1765–1772. https://doi.org/10.1016/j.aap.2008.06.015

Graham, D. P., & Cardon, A. L. (2008). An update on substance use and treatment following traumatic brain injury. *Annals of the New York Academy of Sciences*, *1141*(1), 148–162. https://doi.org/10.1196/annals.1441.029

Gros, D. F., Lancaster, C. L., Horner, M. D., Szafranski, D. D., & Back, S. E. (2017). The influence of traumatic brain injury on treatment outcomes of concurrent treatment for PTSD and substance use disorders using prolonged exposure (COPE) in veterans. *Comprehensive Psychiatry*, *78*, 48–53. https://doi.org/10.1016/j.comppsych.2017.07.004

Heinemann, A. W., Corrigan, J. D., & Moore, D. (2004). Case management for traumatic brain injury survivors with alcohol problems. *Rehabilitation Psychology*, *49*(2), 156–166. https://doi.org/10.1037/0090-5550.49.2.156

Ilgen, M. A., Coughlin, L. N., Bohnert, A. S. B., Chermack, S., Price, A., Kim, H. M., Jannausch, M., & Blow, F. C. (2020). Efficacy of a psychosocial pain management intervention for men and women with substance use disorders and chronic pain: A randomized clinical trial. *JAMA Psychiatry*, *77*(12), 1225. https://doi.org/10.1001/jamapsychiatry.2020.2369

Jourdan, C., Bayen, E., Pradat-Diehl, P., Ghout, I., Darnoux, E., Azerad, S., Vallat-Azouvi, C., Charanton, J., Aegerter, P., Ruet, A., & Azouvi, P. (2016). A comprehensive picture of 4-year outcome of severe brain injuries. Results from the PariS-TBI study. *Annals of*

Physical and Rehabilitation Medicine, *59*(2), 100–106. https://doi.org/10.1016/j.rehab.2015.10.009

Kristofersson, G. K., Beckers, T., & Krueger, R. (2016). Perceptions of an adapted mindfulness program for persons experiencing substance use disorders and traumatic brain injury. *Journal of Addictions Nursing*, *27*(4), 247–253. https://doi.org/10.1097/JAN.0000000000000144

Lavoie, S., Sechrist, S., Quach, N., Ehsanian, R., Duong, T., Gotlib, I. H., & Isaac, L. (2017). Depression in men and women one year following traumatic brain injury (TBI): A TBI model systems study. *Frontiers in Psychology*, *8*, 634. https://doi.org/10.3389/fpsyg.2017.00634

Lin, S.-Y., Fried, E. I., & Eaton, N. R. (2020). The association of life stress with substance use symptoms: A network analysis and replication. *Journal of Abnormal Psychology*, *129*(2), 204–214. https://doi.org/10.1037/abn0000485

MacLeod, J. B. A., & Hungerford, D. W. (2011). Alcohol-related injury visits: Do we know the true prevalence in U.S. trauma centres? *Injury*, *42*(9), 922–926. https://doi.org/10.1016/j.injury.2010.01.098

Macleod, J., Hickman, M., & Smith, G. D. (2005). Reporting bias and self-reported drug use. *Addiction*, *100*(4), 562–563. https://doi.org/10.1111/j.1360-0443.2005.01099.x

McKinlay, A., Corrigan, J., Horwood, L. J., & Fergusson, D. M. (2014). Substance abuse and criminal activities following traumatic brain injury in childhood, adolescence, and early adulthood. *Journal of Head Trauma Rehabilitation*, *29*(6), 498–506. https://doi.org/10.1097/HTR.0000000000000001

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. (1992). The fifth edition of the addiction severity index. *Journal of Substance Abuse Treatment*, *9*(3), 199–213. https://doi.org/10.1016/0740-5472(92)90062-S

Merkel, S. F., Cannella, L. A., Razmpour, R., Lutton, E., Raghupathi, R., Rawls, S. M., & Ramirez, S. H. (2017). Factors affecting increased risk for substance use disorders following traumatic brain injury: What we can learn from animal models. *Neuroscience & Biobehavioral Reviews*, *77*, 209–218. https://doi.org/10.1016/j.neubiorev.2017.03.015

Miller, W. R. (1992). *Motivational enhancement therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence*. U.S. Dept. of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Alcohol Abuse and Alcoholism; For sale by the U.S. G.P.O., Supt. of Docs.

Murthy, P., Mahadevan, J., & Chand, P. K. (2019). Treatment of substance use disorders with co-occurring severe mental health disorders. *Current Opinion in Psychiatry*, *32*(4), 293–299. https://doi.org/10.1097/YCO.0000000000000510

Nampiaparampil, D. E. (2008). Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA*, *300*(6), 711. https://doi.org/10.1001/jama.300.6.711

Nestler, E. J. (2005). Is there a common molecular pathway for addiction? *Nature Neuroscience*, *8*(11), 1445–1449. https://doi.org/10.1038/nn1578

Olsen, C. M., & Corrigan, J. D. (2022). Does traumatic brain injury cause risky substance use or substance use disorder? *Biological Psychiatry*, *91*(5), 421–437. https://doi.org/10.1016/j.biopsych.2021.07.013

Olson-Madden, J. H., Forster, J. E., Huggins, J., & Schneider, A. (2012). Psychiatric diagnoses, mental health utilization, high-risk behaviors, and self-directed violence among veterans with comorbid history of traumatic brain injury and substance use disorders. *Journal of Head Trauma Rehabilitation*, *27*(5), 370–378. https://doi.org/10.1097/HTR.0b013e318268d496

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, n71. https://doi.org/10.1136/bmj.n71

Parry-Jones, B. L., Vaughan, F. L., & Miles Cox, W. (2006). Traumatic brain injury and substance misuse: A systematic review of prevalence and outcomes research (1994–2004). *Neuropsychological Rehabilitation*, *16*(5), 537–560. https://doi.org/10.1080/09602010500231875

Ramesh, D., Keyser-Marcus, L. A., Ma, L., Schmitz, J. M., Lane, S. D., Marwitz, J. H., Kreutzer, J. S., & Moeller, F. G. (2015). Prevalence of traumatic brain injury in cocaine-dependent research volunteers: Cocaine use and traumatic brain injury. *The American Journal on Addictions*, *24*(4), 341–347. https://doi.org/10.1111/ajad.12192

Sacks, A. L., Fenske, C. L., Gordon, W. A., Hibbard, M. R., Perez, K., Brandau, S., Cantor, J., Ashman, T., & Spielman, L. A. (2009). Co-morbidity of substance abuse and traumatic brain injury. *Journal of Dual Diagnosis*, *5*(3–4), 404–417. https://doi.org/10.1080/15504260903182755

Sander, A. M., Bogner, J., Nick, T. G., Clark, A. N., Corrigan, J. D., & Rozzell, M. (2012). A Randomized controlled trial of brief intervention for problem alcohol use in persons with traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *27*(5), 319–330. https://doi.org/10.1097/HTR.0b013e318269838c

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*, *88*(6), 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F., & Polinder, S. (2016). Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: A systematic review. *Journal of Neurotrauma*, *33*(22), 1969–1994. https://doi.org/10.1089/neu.2015.4252

Scott, J. C., Lynch, K. G., Cenkner, D. P., Kehle-Forbes, S. M., Polusny, M. A., Gur, R. C., Chen, S., Foa, E. B., & Oslin, D. W. (2021). Neurocognitive predictors of treatment outcomes in psychotherapy for comorbid PTSD and substance use disorders. *Journal of Consulting and Clinical Psychology*, *89*(11), 937–946. https://doi.org/10.1037/ccp0000693

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-Back. In R. Z. Litten & J. P. Allen (Eds.), *Measuring Alcohol Consumption* (pp. 41–72). Humana Press. https://doi.org/10.1007/978-1-4612-0357-5_3

Stein, M. B., Jain, S., Giacino, J. T., Levin, H., Dikmen, S., Nelson, L. D., Vassar, M. J., Okonkwo, D. O., Diaz-Arrastia, R., Robertson, C. S., Mukherjee, P., McCrea, M., Mac Donald, C. L., Yue, J. K., Yuh, E., Sun, X., Campbell-Sills, L., Temkin, N., Manley, G.

T., … Zafonte, R. (2019). Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: A TRACK-TBI study. *JAMA Psychiatry*, *76*(3), 249. https://doi.org/10.1001/jamapsychiatry.2018.4288

Taylor, L. A., Kreutzer, J. S., Demm, S. R., & Meade, M. A. (2003). Traumatic brain injury and substance abuse: A review and analysis of the literature. *Neuropsychological Rehabilitation*, *13*(1–2), 165–188. https://doi.org/10.1080/09602010244000336

Tweedly, L., Ponsford, J., & Lee, N. (2012). Investigation of the effectiveness of brief interventions to reduce alcohol consumption following traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *27*(5), 331–341. https://doi.org/10.1097/HTR.0b013e318262200a

Unsworth, D. J., & Mathias, J. L. (2017). Traumatic brain injury and alcohol/substance abuse: A Bayesian meta-analysis comparing the outcomes of people with and without a history of abuse. *Journal of Clinical and Experimental Neuropsychology*, *39*(6), 547–562. https://doi.org/10.1080/13803395.2016.1248812

Vaaramo, K., Puljula, J., Tetri, S., Juvela, S., & Hillbom, M. (2014). Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: A long-term follow-up study. *European Journal of Neurology*, *21*(2), 293–298. https://doi.org/10.1111/ene.12302

Velikonja, D., Ponsford, J., Janzen, S., Harnett, A., Patsakos, E., Kennedy, M., Togher, L., Teasell, R., McIntyre, A., Welch-West, P., Kua, A., & Bayley, M. T. (2023). INCOG 2.0 Guidelines for cognitive rehabilitation following traumatic brain injury, Part V: Memory. *Journal of Head Trauma Rehabilitation*, *38*(1), 83–102. https://doi.org/10.1097/HTR.0000000000000837

Vungkhanching, M., Heinemann, A. W., Langley, M. J., Ridgely, M., & Kramer, K. M. (2007). Feasibility of a skills-based substance abuse prevention program following traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *22*(3), 167–176. https://doi.org/10.1097/01.HTR.0000271117.19652.98

Wanberg, K. W., Horn, J. L., & Foster, F. M. (1977). A differential assessment model for alcoholism. The scales of the Alcohol Use Inventory. *Journal of Studies on Alcohol*, *38*(3), 512–543. https://doi.org/10.15288/jsa.1977.38.512

Weil, Z. M., Corrigan, J. D., & Karelina, K. (2018). Alcohol use disorder and traumatic brain injury. *Alcohol Research: Current Reviews*, *39*(2), 171–180.

West, S. L. (2011). Substance use among persons with traumatic brain injury: A review. *NeuroRehabilitation*, *29*(1), 1–8. https://doi.org/10.3233/NRE-2011-0671

Zatzick, D., Russo, J., Lord, S. P., Varley, C., Wang, J., Berliner, L., Jurkovich, G., Whiteside, L. K., O'Connor, S., & Rivara, F. P. (2014). Collaborative care intervention targeting violence risk behaviors, substance use, and posttraumatic stress and depressive symptoms in injured adolescents: A randomized clinical trial. *JAMA Pediatrics*, *168*(6), 532. https://doi.org/10.1001/jamapediatrics.2013.4784

Chapter 5. Integrated Discussion

TBIs are a common cause of disability and death in the United States (CDC, 2016; CDC, 2023). Consequences of TBIs include an array of neuropsychological, physical, social, occupational, and psychiatric detriments. Despite their wide-reaching impact, TBIs are under-detected and insufficiently considered in the context of medical decisions and treatment planning (Powell et al., 2008; Ware & Jha, 2015). Although there has been cause for concern regarding the role of TBI in the development and prognosis of opioid use disorder (OUD) this has yet to be thoroughly and empirically tested. Evaluation of the association between TBI and OUD is imperative given the ongoing epidemic of OUD and opioid-involved overdose in the United States (CDC, 2022).

The current project sought to make novel contributions to the scientific understanding of how TBI relates to the onset and progression of OUD. Across three related manuscripts, the project determined the frequency and characteristics of TBI among persons with OUD, explored high-risk health behaviors associated with TBI and OUD that can increase OUD severity and/or adversely impact treatment progress, and examined evidence-based methods of altering substance use disorder (SUD) treatment to accommodate the impact of TBI. To accomplish the aforementioned aims, data were collected within two OUD outpatient treatment clinics. Participants were 158 adult patients attending treatment in an Appalachian region of the southeastern United States.

In the first study, the frequency and characteristics of TBIs among persons with OUD were determined. Roughly half of the sample reported incurring at least one TBI in their lifetime, which is comparable to other estimates of TBIs among persons with substance use and mental health diagnoses (Moore et al., 2014; Olson-Madden et al., 2012). Among persons with a history

of TBI, 44.2% reported multiple TBIs and 55.7% reported having had a TBI prior to age 16. TBI was associated with an increased risk of receiving an opioid prescription, which is aligned with past research regarding opioid prescription patterns among veterans with TBI (Seal et al., 2018). Compared to estimates that 75-80% of all TBIs are mild, a relatively small 59.8% of TBIs in the present study were classified as mild (Jacotte-Simancas et al., 2021). Most participants with both TBI and OUD had incurred a TBI prior to first using opioids. Contrary to expectations, there were few group differences in psychosocial characteristics based on TBI.

In the second study, participants with TBI were found to have higher odds of several behaviors associated with adverse health events. Specifically, they were more likely to have had an overdose, used other substances, and have used riskier ROAs. The relation between TBIs, risky behavior, impulsivity, and poor health has been previously well-documented (Colantonio et al., 2015; Dams-O'Connor et al., 2013; Rogers et al., 2021). More symptoms of chronic pain and anxiety were associated with increased odds of having had a TBI. Anxiety and chronic pain are both known outcomes of TBI and are associated with increased odds of opioid use (Al-Kader et al., 2022; Mehalick & Glueck, 2018; Polinder et al., 2015). Surprisingly, symptoms of PTSD and depression did not predict TBI history. Although past research consistently supports a connection between PTSD, depression, and TBI, this pattern was not apparent in the current study, possibly due to high symptoms across all participants.

In the last study, available peer-reviewed literature related to SUD treatment for persons with TBI was systematically reviewed. PubMed, PsycInfo, and Scopus searches found 373 abstracts related to SUD treatment individuals with TBI. Ultimately, 10 studies met all eligibility criteria for inclusion. Across all studies, four treatment modalities were found to successfully decrease substance use. Specifically, motivational enhancement/interviewing, comprehensive

TBI services, (i.e., case management, service coordination), prolonged exposure, and an adapted screening and brief intervention were found to decrease substance use. Specific adaptations were made to mitigate the impact of TBI on treatment efficacy, including memory cues, visual aids, role plays, large print items, and repetition.

Limitations

The results of the current project should be considered within the context of its limitations. Data were only collected in a relatively rural, Appalachian region of the United States which is disproportionally afflicted by poor social determinants of health. The social location of the sample may be a confounding variable and limit the generalizability of the findings. Additionally, all participants were actively engaged in treatment, which indicates a certain level of motivation, resources, and independence. These findings may not represent persons with more acute or severe cases of OUD or TBI who are not able to receive treatment. Substance use and TBIs were assessed via retrospective and self-report assessments that may be impacted by biased or inaccurate reporting, especially given the potentially sensitive nature of some questions. However, this risk was minimized by ensuring anonymity and using validated assessments of TBI.

Because there was a relatively small sample of available peer-reviewed papers to review, a meta-analysis regarding SUD treatment among persons with TBI was unable to be conducted. Many of the available studies did not provide details regarding the specific methods of accommodating TBIs or specify the psychotherapy treatment protocol. Therefore, the ability to determine and synthesize specific treatment recommendations was limited. Lastly, publication bias may have inherently reduced the available pool of manuscripts to review, consequently skewing the results portrayed by the present study.

Implications and Conclusions

Altogether, the results of the present project conclude that a substantial proportion of patients seeking treatment for OUD have incurred at least one TBI. TBI most often proceeds the first use of opioids, which supports the role of underlying behavioral tendencies (i.e., impulsivity), clinical covariates of TBIs (i.e., pain and anxiety), and neuropsychological consequences of TBIs in the initiation of opioid use and development of OUD. Indeed, results demonstrate that higher levels of impulsivity, anxiety, and chronic pain increase the odds of having had a TBI for persons with OUD. Whether symptoms of impulsivity, anxiety, and chronic pain are an outcome of the TBI or due to a confounding unmeasured variable is presently unknown but warrants further exploration. Additionally, the knowledge that TBI often proceeds opioid initiation supports the use of caution when prescribing opioids to persons with a history of TBI.

TBI was also found to correspond to indicators of high-risk health behaviors and OUD severity, including increased risk of overdose, riskier ROAs, and use of certain other substances. Given the role of opioids in overdose and mortality, there is a strong rationale to identify and mitigate additional risks for adverse opioid-related outcomes among persons with TBI. Accordingly, the results of the present study support a recommendation for healthcare professionals to engage in accurate and consistent screening for TBI so that TBI history may be factored into treatment planning (Coxe-Hyzak et al., 2022).

Lastly, the results of the current project conclude that SUD treatment can reduce substance use among persons with TBI. There is evidence of the feasibility and efficacy of specifically adapting treatment to counteract the negative effects of TBI on treatment response. However, given the lack of details regarding treatment accommodations in the available

literature, a comprehensive protocol is unable to be supplied. Accommodations may include increased rehearsal, repetition, reminders, and the use of multiple modalities to convey information to patients. Findings support the need to consistently screen for TBI and develop a pathway to sufficiently meet the needs of patients with TBI across healthcare settings.

References

Adams, R. S., Ketchum, J. M., Nakase-Richardson, R., Katz, D. I., & Corrigan, J. D. (2021). Prevalence of drinking within low-risk guidelines during the first 2 years after inpatient rehabilitation for moderate or severe traumatic brain injury. *American Journal of Physical Medicine & Rehabilitation*, *100*(8), 815–819. https://doi.org/10.1097/PHM.0000000000001753

Adan, A., Benaiges, I., & Forero, D. A. (2016). *Chapter 36 - Heavy Episodic Drinking or Binge Drinking: A Booming Consumption Pattern*.

Albrecht, J. S., Hirshon, J. M., McCunn, M., Bechtold, K. T., Rao, V., Simoni-Wastila, L., & Smith, G. S. (2016). Increased rates of mild traumatic brain injury among older adults in US emergency departments, 2009-2010. *Journal of Head Trauma Rehabilitation*, *31*(5), E1–E7. https://doi.org/10.1097/HTR.0000000000000190

Al-Kader, D. A., Onyechi, C. I., Ikedum, I. V., Fattah, A., Zafar, S., Bhat, S., Malik, M. A., Bheesham, N., Qadar, L. T., & Sajjad Cheema, M. (2022). Depression and anxiety in patients with a history of traumatic brain injury: A case-control study. *Cureus*. https://doi.org/10.7759/cureus.27971

Allen, S., Stewart, S. H., Cusimano, M., & Asbridge, M. (2016). Examining the relationship between traumatic brain injury and substance use outcomes in the Canadian population. *Substance Use & Misuse*, *51*(12), 1577–1586. https://doi.org/10.1080/10826084.2016.1188955

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Andelic, N., Jerstad, T., Sigurdardottir, S., Schanke, A.-K., Sandvik, L., & Roe, C. (2010). Effects of acute substance use and pre-injury substance abuse on traumatic brain injury severity in adults admitted to a trauma centre. *Journal of Trauma Management & Outcomes*, *4*(1), 6. https://doi.org/10.1186/1752-2897-4-6

Angst, M. S., & Clark, J. D. (2006). Opioid-induced hyperalgesia. *Anesthesiology*, *104*(3), 570–587. https://doi.org/10.1097/00000542-200603000-00025

Anwer, F., Oliveri, F., Kakargias, F., Panday, P., Arcia Franchini, A. P., Iskander, B., & Hamid, P. (2021). Post-traumatic seizures: A deep-dive into pathogenesis. *Cureus*. https://doi.org/10.7759/cureus.14395

Azadfard, M., Huecker, M. R., & Leaming, J. M. (2023). Opioid Addiction. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK448203/

Azouvi, P., Arnould, A., Dromer, E., & Vallat-Azouvi, C. (2017). Neuropsychology of traumatic brain injury: An expert overview. *Revue Neurologique*, *173*(7–8), 461–472. https://doi.org/10.1016/j.neurol.2017.07.006

Bagri, K., Kumar, P., & Deshmukh, R. (2021). Neurobiology of traumatic brain injury. *Brain Injury*, *35*(10), 1113–1120. https://doi.org/10.1080/02699052.2021.1972152

Baldacchino, A., Balfour, D. J. K., & Matthews, K. (2015). Impulsivity and opioid drugs: Differential effects of heroin, methadone and prescribed analgesic medication. *Psychological Medicine*, *45*(6), 1167–1179. https://doi.org/10.1017/S0033291714002189

Baldacchino, A., Balfour, D. J. K., Passetti, F., Humphris, G., & Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: A quantitative review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *36*(9), 2056–2068. https://doi.org/10.1016/j.neubiorev.2012.06.006

Baldini, A., Von Korff, M., & Lin, E. H. B. (2012). A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. *The Primary Care Companion for CNS Disorders*. https://doi.org/10.4088/PCC.11m01326

Barman, A., Chatterjee, A., & Bhide, R. (2016). Cognitive impairment and rehabilitation strategies after traumatic brain injury. *Indian Journal of Psychological Medicine, 38*(3), 172–181. https://doi.org/10.4103/0253-7176.183086

Beaulieu-Bonneau, S., St-Onge, F., Blackburn, M.-C., Banville, A., Paradis-Giroux, A.-A., & Ouellet, M.-C. (2018). Alcohol and drug use before and during the first year after traumatic brain injury. *Journal of Head Trauma Rehabilitation, 33*(3), E51–E60. https://doi.org/10.1097/HTR.0000000000000341

Biegon, A. (2021). Considering biological sex in traumatic brain injury. *Frontiers in Neurology, 12*, 576366. https://doi.org/10.3389/fneur.2021.576366

Bjork, J. M., & Grant, S. J. (2009). Does traumatic brain injury increase risk for substance abuse? *Journal of Neurotrauma, 26*(7), 1077–1082. https://doi.org/10.1089/neu.2008.0849

Blackwood, C. A., & Cadet, J. L. (2021). The molecular neurobiology and neuropathology of opioid use disorder. *Current Research in Neurobiology, 2*, 100023. https://doi.org/10.1016/j.crneur.2021.100023

BlueCross BlueShield. (2017). *America's opioid epidemic and its effect on the nation's commercially insured population | Blue Cross Blue Shield*. https://www.bcbs.com/the-health-of-america/reports/americas-opioid-epidemic-and-its-effect-on-the-nations-commercially-insured

Bodanapally, U. K., Sours, C., Zhuo, J., & Shanmuganathan, K. (2015). Imaging of traumatic brain injury. *Radiologic Clinics of North America*, *53*(4), 695–715.

Brady, K. T., Tuerk, P., Back, S. E., Saladin, M. E., Waldrop, A. E., & Myrick, H. (2009). Combat posttraumatic stress disorder, substance use disorders, and traumatic brain injury. *Journal of Addiction Medicine*, *3*(4), 179–188. https://doi.org/10.1097/ADM.0b013e3181aa244f

Brett, B. L., Gardner, R. C., Godbout, J., Dams-O'Connor, K., & Keene, C. D. (2022). Traumatic brain injury and risk of neurodegenerative disorder. *Biological Psychiatry*, *91*(5), 498–507. https://doi.org/10.1016/j.biopsych.2021.05.025

Broadway, J. M., Rieger, R. E., Campbell, R. A., Quinn, D. K., Mayer, A. R., Yeo, R. A., Wilson, J. K., Gill, D., Fratzke, V., & Cavanagh, J. F. (2019). Executive function predictors of delayed memory deficits after mild traumatic brain injury. *Cortex*, *120*, 240–248. https://doi.org/10.1016/j.cortex.2019.06.011

Broshek, D. K., De Marco, A. P., & Freeman, J. R. (2015). A review of post-concussion syndrome and psychological factors associated with concussion. *Brain Injury*, *29*(2), 228–237. https://doi.org/10.3109/02699052.2014.974674

Büttner, A. (2021). *Neuropathology of drug abuse*. Springer.

Cannella, L. A., McGary, H., & Ramirez, S. H. (2019). Brain interrupted: Early life traumatic brain injury and addiction vulnerability. *Experimental Neurology*, *317*, 191–201. https://doi.org/10.1016/j.expneurol.2019.03.003

Cantu, R. C., & Bernick, C. (2020). History of chronic traumatic encephalopathy. *Seminars in Neurology*, *40*(04), 353–358. https://doi.org/10.1055/s-0040-1713622

CDC. (2016). *Report to Congress on Traumatic Brain Injury Epidemiology and Rehabilitation | Concussion | Traumatic Brain Injury | CDC Injury Center*. https://www.cdc.gov/traumaticbraininjury/pubs/congress_epi_rehab.html

CDC. (2021a, b). *Prescription Opioids | Opioids | CDC*. https://www.cdc.gov/opioids/basics/prescribed.html

CDC. (2021b, a). *U.S. Opioid Dispensing Rate Maps | Drug Overdose | CDC Injury Center*. https://www.cdc.gov/drugoverdose/rxrate-maps/index.html

CDC. (2022). *Death Rate Maps & Graphs | Drug Overdose | CDC Injury Center*. https://www.cdc.gov/drugoverdose/deaths/index.html

CDC. (2023a, b). *FastStats*. https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

CDC. (2023b, a). *TBI Data | Concussion | Traumatic Brain Injury | CDC Injury Center*. https://www.cdc.gov/traumaticbraininjury/data/index.html

Chang, H.-Y., Kharrazi, H., Bodycombe, D., Weiner, J. P., & Alexander, G. C. (2018). Healthcare costs and utilization associated with high-risk prescription opioid use: A retrospective cohort study. *BMC Medicine*, *16*(1), 69. https://doi.org/10.1186/s12916-018-1058-y

Chang, Y.-P., & Compton, P. (2013). Management of chronic pain with chronic opioid therapy in patients with substance use disorders. *Addiction Science & Clinical Practice*, *8*(1), 21. https://doi.org/10.1186/1940-0640-8-21

Cochran, B. N., Flentje, A., Heck, N. C., Van Den Bos, J., Perlman, D., Torres, J., Valuck, R., & Carter, J. (2014). Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a

database of commercially insured individuals. *Drug and Alcohol Dependence*, *138*, 202–208. https://doi.org/10.1016/j.drugalcdep.2014.02.701

Colantonio, A., Hsueh, J., Petgrave, J., Hirdes, J. P., & Berg, K. (2015). A profile of patients with traumatic brain injury within home care, long-term care, complex continuing care, and institutional mental health settings in a publicly insured population. *Journal of Head Trauma Rehabilitation*, *30*(6), E18–E29. https://doi.org/10.1097/HTR.0000000000000112

Cooksley, R., Maguire, E., Lannin, N. A., Unsworth, C. A., Farquhar, M., Galea, C., Mitra, B., & Schmidt, J. (2018). Persistent symptoms and activity changes three months after mild traumatic brain injury. *Australian Occupational Therapy Journal*, *65*(3), 168–175. https://doi.org/10.1111/1440-1630.12457

Corder, G., Castro, D. C., Bruchas, M. R., & Scherrer, G. (2018). Endogenous and exogenous opioids in pain. *Annual Review of Neuroscience*, *41*(1), 453–473. https://doi.org/10.1146/annurev-neuro-080317-061522

Corrigan, J. D., & Adams, R. S. (2019). The intersection of lifetime history of traumatic brain injury and the opioid epidemic. *Addictive Behaviors*, *90*, 143–145. https://doi.org/10.1016/j.addbeh.2018.10.030

Corrigan, J. D., Bogner, J., & Holloman, C. (2012). Lifetime history of traumatic brain injury among persons with substance use disorders. *Brain Injury*, *26*(2), 139–150. https://doi.org/10.3109/02699052.2011.648705

Coxe-Hyzak, K. A., Bunger, A. C., Bogner, J., Davis, A. K., & Corrigan, J. D. (2022). Implementing traumatic brain injury screening in behavioral healthcare: Protocol for a

prospective mixed methods study. *Implementation Science Communications*, *3*(1), 17. https://doi.org/10.1186/s43058-022-00261-x

Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology Biochemistry and Behavior*, *93*(3), 237–247. https://doi.org/10.1016/j.pbb.2009.04.018

Dams-O'Connor, K., Spielman, L., Singh, A., Gordon, W. A., Lingsma, H. F., Maas, A. I. R., Manley, G. T., Mukherjee, P., Okonkwo, D. O., Puccio, A. M., Schnyer, D. M., Valadka, A. B., Yue, J. K., Yuh, E. L., Casey, A. T. T.-T. I. I., Cooper, S. R., Cheong, M., Hricik, A. J., Knight, E. E., Menon, D. K., Morabito, D. J., Pacheco, J. L., Sinha, T. K., Vassar, M. J. (2013). The impact of previous traumatic brain injury on health and functioning: A TRACK-TBI study. *Journal of Neurotrauma*, *30*(24), 2014–2020. https://doi.org/10.1089/neu.2013.3049

Dash, H. H., & Chavali, S. (2018). Management of traumatic brain injury patients. *Korean Journal of Anesthesiology*, *71*(1), 12. https://doi.org/10.4097/kjae.2018.71.1.12

Dikmen, S., Machamer, J., & Temkin, N. (2017). Mild traumatic brain injury: Longitudinal study of cognition, functional status, and post-traumatic symptoms. *Journal of Neurotrauma*, *34*(8), 1524–1530. https://doi.org/10.1089/neu.2016.4618

Ding, K., Gupta, P. K., & Diaz-Arrastia, R. (2016). Epilepsy after Traumatic Brain Injury. In D. Laskowitz & G. Grant (Eds.), *Translational Research in Traumatic Brain Injury*. CRC Press/Taylor and Francis Group. http://www.ncbi.nlm.nih.gov/books/NBK326716/

Doverty, M., White, J. M., Somogyi, A. A., Bochner, F., Ali, R., & Ling, W. (2001). Hyperalgesic responses in methadone maintenance patients. *Pain*, *90*(1), 91–96. https://doi.org/10.1016/S0304-3959(00)00391-2

Dugosh, K., Abraham, A., Seymour, B., McLoyd, K., Chalk, M., & Festinger, D. (2016). A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *Journal of Addiction Medicine*, *10*(2), 93–103. https://doi.org/10.1097/ADM.0000000000000193

Ellis, M. S., Kasper, Z., & Cicero, T. (2021). Assessment of chronic pain management in the treatment of opioid use disorder: Gaps in care and implications for treatment outcomes. *The Journal of Pain*, *22*(4), 432–439. https://doi.org/10.1016/j.jpain.2020.10.005

Evren, C., & Bozkurt, M. (2017). Impulsivity and opioid use disorder. *Dusunen Adam: The Journal of Psychiatry and Neurological Sciences*, 75–78.

Felde, A. B., Westermeyer, J., & Thuras, P. (2006). Co-morbid traumatic brain injury and substance use disorder: Childhood predictors and adult correlates. *Brain Injury*, *20*(1), 41–49. https://doi.org/10.1080/02699050500309718

Fesharaki-Zadeh, A. (2019). Chronic traumatic encephalopathy: A brief overview. *Frontiers in Neurology*, *10*, 713. https://doi.org/10.3389/fneur.2019.00713

Food & Drug Administration. (2021). Opioid Medications. *Center for Drug Evaluation and Research*. https://www.fda.gov/drugs/information-drug-class/opioid-medications

Garner, R., La Rocca, M., Vespa, P., Jones, N., Monti, M. M., Toga, A. W., & Duncan, D. (2019). Imaging biomarkers of posttraumatic epileptogenesis. *Epilepsia*, *60*(11), 2151–2162. https://doi.org/10.1111/epi.16357

Gjerde, H., Normann, P. T., Pettersen, B. S., Assum, T., Aldrin, M., Johansen, U., Kristoffersen, L., Øiestad, E. L., Christophersen, A. S., & Mørland, J. (2008). Prevalence of alcohol and drugs among Norwegian motor vehicle drivers: A roadside survey. *Accident Analysis & Prevention*, *40*(5), 1765–1772. https://doi.org/10.1016/j.aap.2008.06.015

Graham, D. P., & Cardon, A. L. (2008). An update on substance use and treatment following traumatic brain injury. *Annals of the New York Academy of Sciences*, *1141*(1), 148–162. https://doi.org/10.1196/annals.1441.029

Gupte, R. P., Brooks, W. M., Vukas, R. R., Pierce, J. D., & Harris, J. L. (2019). Sex differences in traumatic brain injury: What we know and what we should know. *Journal of Neurotrauma*, *36*(22), 3063–3091. https://doi.org/10.1089/neu.2018.6171

Hammond, F. M., Barrett, R., Dijkers, M. P., Zanca, J. M., Horn, S. D., Smout, R. J., Guerrier, T., Hauser, E., & Dunning, M. R. (2015). Group therapy use and its impact on the outcomes of inpatient rehabilitation after traumatic brain injury: Data from traumatic brain injury–practice-based evidence project. *Archives of Physical Medicine and Rehabilitation*, *96*(8), S282-S292.e5. https://doi.org/10.1016/j.apmr.2014.11.029

Hammond, F. M., Ketchum, J., Dams-O'Connor, K., Corrigan, J. D., Miller, C., Haarbauer-Krupa, J., Faul, M., Trexler, L. E., & Harrison-Felix, C. (2020). Mortality secondary to unintentional poisoning after inpatient rehabilitation among individuals with moderate to severe traumatic brain injury. *Journal of Neurotrauma*, *37*(23), 2507–2516. https://doi.org/10.1089/neu.2020.7038

Hawryluk, G. W. J., & Manley, G. T. (2015). Classification of traumatic brain injury. In *Handbook of Clinical Neurology* (Vol. 127, pp. 15–21). Elsevier. https://doi.org/10.1016/B978-0-444-52892-6.00002-7

Heslot, C., Cogné, M., Guillouët, E., Perdrieau, V., Lefevre-Dognin, C., Glize, B., Bonan, I., & Azouvi, P. (2021). Management of unfavorable outcome after mild traumatic brain injury: Review of physical and cognitive rehabilitation and of psychological care in post-

concussive syndrome. *Neurochirurgie*, *67*(3), 283–289. https://doi.org/10.1016/j.neuchi.2020.09.001

Hoffman, J., Pagulayan, K., Zawaideh, N., & Bell, K. (2005). Poster 46. *Archives of Physical Medicine and Rehabilitation*, *86*(10), e17. https://doi.org/10.1016/j.apmr.2005.08.069

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. soldiers returning from Iraq. *New England Journal of Medicine*, *358*(5), 453–463. https://doi.org/10.1056/NEJMoa072972

Huddart, R., Clarke, M., Altman, R. B., & Klein, T. E. (2018). PharmGKB summary: Oxycodone pathway, pharmacokinetics. *Pharmacogenetics and Genomics*, *28*(10), 230–237. https://doi.org/10.1097/FPC.0000000000000351

Hwang, S. W., Colantonio, A., Chiu, S., Tolomiczenko, G., Kiss, A., Cowan, L., Redelmeier, D. A., & Levinson, W. (2008). The effect of traumatic brain injury on the health of homeless people. *Canadian Medical Association Journal*, *179*(8), 779–784. https://doi.org/10.1503/cmaj.080341

Ilie, G., Adlaf, E. M., Mann, R. E., Ialomiteanu, A., Hamilton, H., Rehm, J., Asbridge, M., & Cusimano, M. D. (2015). Associations between a history of traumatic brain injuries and current cigarette smoking, substance use, and elevated psychological distress in a population sample of Canadian adults. *Journal of Neurotrauma*, *32*(14), 1130–1134. https://doi.org/10.1089/neu.2014.3619

Jacotte-Simancas, A., Fucich, E. A., Stielper, Z. F., & Molina, P. E. (2021). Traumatic brain injury and the misuse of alcohol, opioids, and cannabis. In *International Review of Neurobiology* (Vol. 157, pp. 195–243). Elsevier. https://doi.org/10.1016/bs.irn.2020.09.003

Jamt, R. E. G., Gjerde, H., Furuhaugen, H., Romeo, G., Vindenes, V., Ramaekers, J. G., & Bogstrand, S. T. (2020). Associations between psychoactive substance use and sensation seeking behavior among drivers in Norway. *BMC Public Health*, *20*(1), 23. https://doi.org/10.1186/s12889-019-8087-0

Javeed, F., Rehman, L., Afzal, A., & Abbas, A. (2021). Outcome of diffuse axonal injury in moderate and severe traumatic brain injury. *Surgical Neurology International*, *12*, 384. https://doi.org/10.25259/SNI_573_2020

Jourdan, C., Bayen, E., Pradat-Diehl, P., Ghout, I., Darnoux, E., Azerad, S., Vallat-Azouvi, C., Charanton, J., Aegerter, P., Ruet, A., & Azouvi, P. (2016). A comprehensive picture of 4-year outcome of severe brain injuries. Results from the PariS-TBI study. *Annals of Physical and Rehabilitation Medicine*, *59*(2), 100–106. https://doi.org/10.1016/j.rehab.2015.10.009

Julien, A., Danet, L., Loisel, M., Brauge, D., Pariente, J., Péran, P., & Planton, M. (2023). Update on the efficacy of cognitive rehabilitation after moderate to severe traumatic brain injury: A scoping review. *Archives of Physical Medicine and Rehabilitation*, *104*(2), 315–330. https://doi.org/10.1016/j.apmr.2022.07.007

Kaiko, R. F., Benziger, D. P., Fitzmartin, R. D., Burke, B. E., Reder, R. F., & Goldenheim, P. D. (1996). Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone*. *Clinical Pharmacology & Therapeutics*, *59*(1), 52–61. https://doi.org/10.1016/S0009-9236(96)90024-7

Katsumoto, A., Takeuchi, H., & Tanaka, F. (2019). Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: Similarities and differences. *Frontiers in Neurology*, *10*, 980. https://doi.org/10.3389/fneur.2019.00980

Katz, D. I., Cohen, S. I., & Alexander, M. P. (2015). Mild traumatic brain injury. In *Handbook of Clinical Neurology* (Vol. 127, pp. 131–156). Elsevier. https://doi.org/10.1016/B978-0-444-52892-6.00009-X

Kaye, A. D., Jones, M. R., Kaye, A. M., Ripoll, J. G., Galan, V., Beakley, B. D., Calixto, F., Bolden, J. L., Urman, R. D., & Manchikanti, L. (2017). Prescription opioid abuse in chronic pain: An updated review of opioid abuse predictors and strategies to curb opioid abuse: Part 1. *Pain Physician*, *20*(2S), S93–S109.

Khan, F., & Mehan, A. (2021). Addressing opioid tolerance and opioid-induced hypersensitivity: Recent developments and future therapeutic strategies. *Pharmacology Research & Perspectives*, *9*(3). https://doi.org/10.1002/prp2.789

Khoury, S., & Benavides, R. (2018). Pain with traumatic brain injury and psychological disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *87*, 224–233. https://doi.org/10.1016/j.pnpbp.2017.06.007

Kinnunen, M., Piirainen, P., Kokki, H., Lammi, P., & Kokki, M. (2019). Updated clinical pharmacokinetics and pharmacodynamics of oxycodone. *Clinical Pharmacokinetics*, *58*(6), 705–725. https://doi.org/10.1007/s40262-018-00731-3

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Koval, R. R., Zalesky, C. C., Moran, T. P., Moore, J. C., Ratcliff, J. J., Wu, D. T., & Wright, D. W. (2020). Concussion care in the emergency department: A prospective observational brief report. *Annals of Emergency Medicine*, *75*(4), 483–490. https://doi.org/10.1016/j.annemergmed.2019.08.419

Lalovic, B., Kharasch, E., Hoffer, C., Risler, L., Liuchen, L., & Shen, D. (2006). Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. *Clinical Pharmacology & Therapeutics*, *79*(5), 461–479. https://doi.org/10.1016/j.clpt.2006.01.009

Lalovic, B., Phillips, B., Risler, L. L., Howald, W., & Shen, D. D. (2004). Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. *Drug Metabolism and Disposition*, *32*(4), 447–454. https://doi.org/10.1124/dmd.32.4.447

Lee, C., Lee, H.-W., & Kim, J.-N. (2013). Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean Journal of Anesthesiology*, *64*(1), 19. https://doi.org/10.4097/kjae.2013.64.1.19

Leong, H. F., & Yuan, Z. (2017). Resting-state neuroimaging and neuropsychological findings in opioid use disorder during abstinence: A review. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00169

Levin, H. S., O'donnell, V. M., & Grossman, R. G. (1979). The Galveston Orientation and Amnesia Test: A practical scale to assess cognition after head injury. *The Journal of Nervous and Mental Disease*, *167*(11), 675–684. https://doi.org/10.1097/00005053-197911000-00004

Lezak, M. D. (Ed.). (2012). *Neuropsychological assessment* (5th ed). Oxford University Press.

Lindberg, M., Sloley, S., Ivins, B., Marion, D., & Moy Martin, E. (2021). Military TBI—What civilian primary care providers should know. *Journal of Family Medicine and Primary Care*, *10*(12), 4391. https://doi.org/10.4103/jfmpc.jfmpc_98_21

Loree, A. M., Lundahl, L. H., & Ledgerwood, D. M. (2015). Impulsivity as a predictor of treatment outcome in substance use disorders: Review and synthesis: Impulsivity in substance use treatment. *Drug and Alcohol Review*, *34*(2), 119–134. https://doi.org/10.1111/dar.12132

Marin, J. R., Weaver, M. D., & Mannix, R. C. (2017). Burden of USA hospital charges for traumatic brain injury. *Brain Injury*, *31*(1), 24–31. https://doi.org/10.1080/02699052.2016.1217351

Martins, S. S., Sampson, L., Cerdá, M., & Galea, S. (2015). Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. *American Journal of Public Health*, *105*(11), 2373–2373. https://doi.org/10.2105/AJPH.2015.302843a

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD002207.pub4

Mazhari, S., Keshvari, Z., Sabahi, A., & Mottaghian, S. (2015). Assessment of cognitive functions in methadone maintenance patients. *Addiction & Health*, *7*(3–4), 109–116.

Mcallister, T. W. (2008). Neurobehavioral sequelae of traumatic brain injury: Evaluation and management. *World Psychiatry*, *7*(1), 3–10. https://doi.org/10.1002/j.2051-5545.2008.tb00139.x

McCrea, M. A., Nelson, L. D., & Guskiewicz, K. (2017). Diagnosis and management of acute concussion. *Physical Medicine and Rehabilitation Clinics of North America*, *28*(2), 271–286. https://doi.org/10.1016/j.pmr.2016.12.005

Mckee, A. C., & Daneshvar, D. H. (2015). The neuropathology of traumatic brain injury. In *Handbook of Clinical Neurology* (Vol. 127, pp. 45–66). Elsevier. https://doi.org/10.1016/B978-0-444-52892-6.00004-0

Mehalick, M. L., & Glueck, A. C. (2018). Examining the relationship and clinical management between traumatic brain injury and pain in military and civilian populations. *Brain Injury*, *32*(11), 1307–1314. https://doi.org/10.1080/02699052.2018.1495339

Merino, R., Pérez, A., Fierro, J., & Terré, R. (2019). Prevalence of medication and off-label medication use in acquired brain injury at a neurorehabilitation hospital. *European Journal of Clinical Pharmacology*, *75*(7), 985–994. https://doi.org/10.1007/s00228-019-02651-y

Merkel, S. F., Cannella, L. A., Razmpour, R., Lutton, E., Raghupathi, R., Rawls, S. M., & Ramirez, S. H. (2017). Factors affecting increased risk for substance use disorders following traumatic brain injury: What we can learn from animal models. *Neuroscience & Biobehavioral Reviews*, *77*, 209–218. https://doi.org/10.1016/j.neubiorev.2017.03.015

Milivojevic, D., Milovanovic, S. D., Jovanovic, M., Svrakic, D. M., Svrakic, N. M., Svrakic, S. M., & Cloninger, C. R. (2012). Temperament and character modify risk of drug addiction and influence choice of drugs: Personality factors in drug addiction. *The American Journal on Addictions*, *21*(5), 462–467. https://doi.org/10.1111/j.1521-0391.2012.00251.x

Mollayeva, T., Cassidy, J. D., Shapiro, C. M., Mollayeva, S., & Colantonio, A. (2017). Concussion/mild traumatic brain injury-related chronic pain in males and females: A diagnostic modelling study. *Medicine*, *96*(7), e5917. https://doi.org/10.1097/MD.0000000000005917

Montenigro, P. H., Baugh, C. M., Daneshvar, D. H., Mez, J., Budson, A. E., Au, R., Katz, D. I., Cantu, R. C., & Stern, R. A. (2014). Clinical subtypes of chronic traumatic encephalopathy: Literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimer's Research & Therapy*, *6*(5–8), 68. https://doi.org/10.1186/s13195-014-0068-z

Moody, L. N., Satterwhite, E., & Bickel, W. K. (2017). Substance use in rural Central Appalachia: Current status and treatment considerations. *Journal of Rural Mental Health*, *41*(2), 123–135. https://doi.org/10.1037/rmh0000064

Moore, E., Indig, D., & Haysom, L. (2014). Traumatic brain injury, mental health, substance use, and offending among incarcerated young people. *Journal of Head Trauma Rehabilitation*, *29*(3), 239–247. https://doi.org/10.1097/HTR.0b013e31828f9876

Moye, L. S., & Pradhan, A. A. A. (2017). Animal model of chronic migraine-associated pain. *Current Protocols in Neuroscience*, *80*(1). https://doi.org/10.1002/cpns.33

Nampiaparampil, D. E. (2008). Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA*, *300*(6), 711. https://doi.org/10.1001/jama.300.6.711

National Institute of Health. (2022). 2022 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, *18*(4), 700–789. https://doi.org/10.1002/alz.12638

National Institute on Drug Abuse. (2023, March 17). *Opioid Use Disorder Treatment*. National Institute on Drug Abuse. https://nida.nih.gov/nidamed-medical-health-professionals/treatment/opioid-use-disorder-treatment

Niemeier, J. P., Leininger, S. L., Whitney, M. P., Newman, M. A., Hirsch, M. A., Evans, S. L., Sing, R. F., Huynh, T. T., Guerrier, T. P., & Perrin, P. B. (2016). Does history of

substance use disorder predict acute traumatic brain injury rehabilitation outcomes? *NeuroRehabilitation*, *38*(4), 371–383. https://doi.org/10.3233/NRE-161328

Oesterle, T. S., Thusius, N. J., Rummans, T. A., & Gold, M. S. (2019). Medication-assisted treatment for opioid-use disorder. *Mayo Clinic Proceedings*, *94*(10), 2072–2086. https://doi.org/10.1016/j.mayocp.2019.03.029

Olson-Madden, J. H., Brenner, L., Harwood, J. E. F., Emrick, C. D., Corrigan, J. D., & Thompson, C. (2010). Traumatic brain injury and psychiatric diagnoses in veterans seeking outpatient substance abuse treatment. *Journal of Head Trauma Rehabilitation*, *25*(6), 470–479. https://doi.org/10.1097/HTR.0b013e3181d717a7

Olson-Madden, J. H., Forster, J. E., Huggins, J., & Schneider, A. (2012). Psychiatric diagnoses, mental health utilization, high-risk behaviors, and self-directed violence among veterans with comorbid history of traumatic brain injury and substance use disorders. *Journal of Head Trauma Rehabilitation*, *27*(5), 370–378. https://doi.org/10.1097/HTR.0b013e318268d496

Ozga, J. E., Povroznik, J. M., Engler-Chiurazzi, E. B., & Haar, C. V. (2018). Executive (dys)function after traumatic brain injury: Special considerations for behavioral pharmacology. *Behavioural Pharmacology*, *29*(7), 617–637. https://doi.org/10.1097/FBP.0000000000000430

Parpouchi, M., Moniruzzaman, A., Rezansoff, S. N., Russolillo, A., & Somers, J. M. (2017). Characteristics of adherence to methadone maintenance treatment over a 15-year period among homeless adults experiencing mental illness. *Addictive Behaviors Reports*, *6*, 106–111. https://doi.org/10.1016/j.abrep.2017.09.001

Parry-Jones, B. L., Vaughan, F. L., & Miles Cox, W. (2006). Traumatic brain injury and substance misuse: A systematic review of prevalence and outcomes research (1994–2004). *Neuropsychological Rehabilitation*, *16*(5), 537–560. https://doi.org/10.1080/09602010500231875

Pavlov, V., Thompson-Leduc, P., Zimmer, L., Wen, J., Shea, J., Beyhaghi, H., Toback, S., Kirson, N., & Miller, M. (2019). Mild traumatic brain injury in the United States: Demographics, brain imaging procedures, health-care utilization and costs. *Brain Injury*, *33*(9), 1151–1157. https://doi.org/10.1080/02699052.2019.1629022

Peck, K. R., Nighbor, T. D., & Price, M. (2022). Examining associations between impulsivity, opioid use disorder, and posttraumatic stress disorder: The additive relation between disorders. *Experimental and Clinical Psychopharmacology*, *30*(5), 486–493. https://doi.org/10.1037/pha0000507

Peters, M. E., & Gardner, R. C. (2018). Traumatic brain injury in older adults: Do we need a different approach? *Concussion (London, England)*, *3*(3), CNC56. https://doi.org/10.2217/cnc-2018-0001

Peters, M. E., Hsu, M., Rao, V., Roy, D., Narapareddy, B. R., Bechtold, K. T., Sair, H. I., Van Meter, T. E., Falk, H., Hall, A. J., Lyketsos, C. G., & Korley, F. K. (2018). Influence of study population definition on the effect of age on outcomes after blunt head trauma. *Brain Injury*, *32*(13–14), 1725–1730. https://doi.org/10.1080/02699052.2018.1520301

Polinder, S., Haagsma, J. A., Van Klaveren, D., Steyerberg, E. W., & Van Beeck, E. F. (2015). Health-related quality of life after TBI: A systematic review of study design, instruments, measurement properties, and outcome. *Population Health Metrics*, *13*(1), 4. https://doi.org/10.1186/s12963-015-0037-1

Ponsford, J. L., Spitz, G., & McKenzie, D. (2016). Using post-traumatic amnesia to predict outcome after traumatic brain injury. *Journal of Neurotrauma*, *33*(11), 997–1004. https://doi.org/10.1089/neu.2015.4025

Powell, J. M., Ferraro, J. V., Dikmen, S. S., Temkin, N. R., & Bell, K. R. (2008). Accuracy of mild traumatic brain injury diagnosis. *Archives of Physical Medicine and Rehabilitation*, *89*(8), 1550–1555. https://doi.org/10.1016/j.apmr.2007.12.035

Prosser, J., Cohen, L., Steinfeld, M., Eisenberg, D., London, E., & Galynker, I. (2006). Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. *Drug and Alcohol Dependence*, *84*(3), 240–247. https://doi.org/10.1016/j.drugalcdep.2006.02.006

Ragsdale, K. A., Neer, S. M., Beidel, D. C., Frueh, B. C., & Stout, J. W. (2013). Posttraumatic stress disorder in OEF/OIF veterans with and without traumatic brain injury. *Journal of Anxiety Disorders*, *27*(4), 420–426. https://doi.org/10.1016/j.janxdis.2013.04.003

Rochat, L., Beni, C., Billieux, J., Azouvi, P., Annoni, J.-M., & Van Der Linden, M. (2010). Assessment of impulsivity after moderate to severe traumatic brain injury. *Neuropsychological Rehabilitation*, *20*(5), 778–797. https://doi.org/10.1080/09602011.2010.495245

Rogers, M. M., Kelley, K., & McKinney, C. (2021). Trait impulsivity and health risk behaviors: A latent profile analysis. *Personality and Individual Differences*, *171*, 110511. https://doi.org/10.1016/j.paid.2020.110511

Rowe, B. H., Eliyahu, L., Lowes, J., Gaudet, L. A., Beach, J., Mrazik, M., Cummings, G., & Voaklander, D. (2018). Concussion diagnoses among adults presenting to three Canadian

emergency departments: Missed opportunities. *The American Journal of Emergency Medicine*, *36*(12), 2144–2151. https://doi.org/10.1016/j.ajem.2018.03.040

Rubenson Wahlin, R., Lindström, V., Ponzer, S., & Vicente, V. (2018). Patients with head trauma: A study on initial prehospital assessment and care. *International Emergency Nursing*, *36*, 51–55. https://doi.org/10.1016/j.ienj.2017.10.001

Salsitz, E. A. (2016). Chronic pain, chronic opioid addiction: a complex nexus. *Journal of Medical Toxicology*, *12*(1), 54–57. https://doi.org/10.1007/s13181-015-0521-9

Schuman-Olivier, Z., Albanese, M., Nelson, S. E., Roland, L., Puopolo, F., Klinker, L., & Shaffer, H. J. (2010). Self-treatment: Illicit buprenorphine use by opioid-dependent treatment seekers. *Journal of Substance Abuse Treatment*, *39*(1), 41–50. https://doi.org/10.1016/j.jsat.2010.03.014

Seal, K. H., Bertenthal, D., Barnes, D. E., Byers, A. L., Gibson, C. J., Rife, T. L., & Yaffe, K. (2018). Traumatic brain injury and receipt of prescription opioid therapy for chronic pain in Iraq and Afghanistan veterans: Do clinical practice guidelines matter? *The Journal of Pain*, *19*(8), 931–941. https://doi.org/10.1016/j.jpain.2018.03.005

Solis, E., Cameron-Burr, K. T., Shaham, Y., & Kiyatkin, E. A. (2018). Fentanyl-induced brain hypoxia triggers brain hyperglycemia and biphasic changes in brain temperature. *Neuropsychopharmacology*, 43(4), 810–819. https://doi.org/10.1038/npp.2017.181

Starosta, A. J., Adams, R. S., Marwitz, J. H., Kreutzer, J., Monden, K. R., Dams O'Connor, K., & Hoffman, J. (2021). Scoping review of opioid use after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *36*(5), 310–327. https://doi.org/10.1097/HTR.0000000000000721

Stéfan, A., & Mathé, J.-F. (2016). What are the disruptive symptoms of behavioral disorders after traumatic brain injury? A systematic review leading to recommendations for good practices. *Annals of Physical and Rehabilitation Medicine*, *59*(1), 5–17. https://doi.org/10.1016/j.rehab.2015.11.002

Stevenson, J. R., Schroeder, J. P., Nixon, K., Besheer, J., Crews, F. T., & Hodge, C. W. (2009). Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. *Neuropsychopharmacology*, *34*(5), 1209–1222. https://doi.org/10.1038/npp.2008.90

Stewart, J. L., May, A. C., Aupperle, R. L., & Bodurka, J. (2019). Forging neuroimaging targets for recovery in opioid use disorder. *Frontiers in Psychiatry*, *10*, 117. https://doi.org/10.3389/fpsyt.2019.00117

Stubbs, J. L., Thornton, A. E., Sevick, J. M., Silverberg, N. D., Barr, A. M., Honer, W. G., & Panenka, W. J. (2020). Traumatic brain injury in homeless and marginally housed individuals: A systematic review and meta-analysis. *The Lancet Public Health*, *5*(1), e19–e32. https://doi.org/10.1016/S2468-2667(19)30188-4

Substance Abuse and Mental Health Services Administration. (2020). *2019 NSDUH Annual National Report | CBHSQ Data*. https://www.samhsa.gov/data/report/2019-nsduh-annual-national-report

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. *The Lancet*, *304*(7872), 81–84. https://doi.org/10.1016/S0140-6736(74)91639-0

Tetrault, J. M., & Butner, J. L. (2015). Non-medical prescription opioid use and prescription opioid use disorder: A review. *The Yale Journal of Biology and Medicine*, *88*(3), 227–233.

Timko, C., Schultz, N. R., Cucciare, M. A., Vittorio, L., & Garrison-Diehn, C. (2016). Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of Addictive Diseases*, *35*(1), 22–35. https://doi.org/10.1080/10550887.2016.1100960

To, M. J., O'Brien, K., Palepu, A., Hubley, A. M., Farrell, S., Aubry, T., Gogosis, E., Muckle, W., & Hwang, S. W. (2015). Healthcare utilization, legal incidents, and victimization following traumatic brain injury in homeless and vulnerably housed individuals: A prospective cohort study. *Journal of Head Trauma Rehabilitation*, *30*(4), 270–276. https://doi.org/10.1097/HTR.0000000000000044

Tompkins, D. A., & Campbell, C. M. (2011). Opioid-induced hyperalgesia: Clinically relevant or extraneous research phenomenon? *Current Pain and Headache Reports*, *15*(2), 129–136. https://doi.org/10.1007/s11916-010-0171-1

Treister, R., Eisenberg, Md, E., Lawental, Dsw, E., & Pud, PhD, D. (2012). Is opioid-induced hyperalgesia reversible? A study on active and former opioid addicts and drug naïve controls. *Journal of Opioid Management*, *8*(6), 343–349. https://doi.org/10.5055/jom.2012.0134

Tremblay, S., Desjardins, M., Bermudez, P., Iturria-Medina, Y., Evans, A. C., Jolicoeur, P., & De Beaumont, L. (2019). Mild traumatic brain injury: The effect of age at trauma onset on brain structure integrity. *NeuroImage: Clinical*, *23*, 101907. https://doi.org/10.1016/j.nicl.2019.101907

Trexler, L. E., Corrigan, J. D., Davé, S., & Hammond, F. M. (2020). Recommendations for prescribing opioids for people with traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *101*(11), 2033–2040. https://doi.org/10.1016/j.apmr.2020.07.005

Tsai, Y.-C., Liu, C.-J., Huang, H.-C., Lin, J.-H., Chen, P.-Y., Su, Y.-K., Chen, C.-T., & Chiu, H.-Y. (2021). A meta-analysis of dynamic prevalence of cognitive deficits in the acute, subacute, and chronic phases after traumatic brain injury. *Journal of Neuroscience Nursing*, *Publish Ahead of Print*. https://doi.org/10.1097/JNN.0000000000000570

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., Wallin, D., Pendse, G., McDonald, L., Griffin, M., Anderson, J., Nutile, L., Renshaw, P., Weiss, R., Becerra, L., & Borsook, D. (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain*, *133*(7), 2098–2114. https://doi.org/10.1093/brain/awq138

U.S. Administration for Strategic Preparedness and Respons. (2017). *List of Public Health Emergency Declarations*. https://aspr.hhs.gov:443/legal/PHE/Pages/default.aspx

Vakil, E., Greenstein, Y., Weiss, I., & Shtein, S. (2019). The effects of moderate-to-severe traumatic brain injury on episodic memory: A meta-analysis. *Neuropsychology Review*, *29*(3), 270–287. https://doi.org/10.1007/s11065-019-09413-8

Venkatesan, U. M., Rabinowitz, A. R., Wolfert, S. P., & Hillary, F. G. (2021). Duration of post-traumatic amnesia is uniquely associated with memory functioning in chronic moderate-to-severe traumatic brain injury. *NeuroRehabilitation*, *49*(2), 221–233. https://doi.org/10.3233/NRE-218022

Verdejo, A., Toribio, I., Orozco, C., Puente, K. L., & Pérez-García, M. (2005). Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug and Alcohol Dependence*, *78*(3), 283–288. https://doi.org/10.1016/j.drugalcdep.2004.11.006

Verellen, R. M., & Cavazos, J. E. (2010). Post-traumatic epilepsy: An overview. *Therapy*, *7*(5), 527–531.

Villesen, H. H., Foster, D. J. R., Upton, R. N., Somogyi, A. A., Martinez, A., & Grant, C. (2006). Cerebral kinetics of oxycodone in conscious sheep. *Journal of Pharmaceutical Sciences*, *95*(8), 1666–1676. https://doi.org/10.1002/jps.20632

Von Korff, M., Kolodny, A., Deyo, R. A., & Chou, R. (2011). Long-term opioid therapy reconsidered. *Annals of Internal Medicine*, *155*(5), 325. https://doi.org/10.7326/0003-4819-155-5-201109060-00011

Vonder Haar, C., Martens, K. M., Riparip, L.-K., Rosi, S., Wellington, C. L., & Winstanley, C. A. (2017). Frontal traumatic brain injury increases impulsive decision making in rats: A potential role for the inflammatory cytokine interleukin-12. *Journal of Neurotrauma*, *34*(19), 2790–2800. https://doi.org/10.1089/neu.2016.4813

Vos, P. E. (2011). Biomarkers of focal and diffuse traumatic brain injury. *Critical Care*, *15*(4), 183. https://doi.org/10.1186/cc10290

Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & Van Der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*, *156*(4), 569–576. https://doi.org/10.1097/01.j.pain.0000460357.01998.f1

Wang, K. K. W., Moghieb, A., Yang, Z., & Zhang, Z. (2013). *Systems biomarkers as acute diagnostics and chronic monitoring tools for traumatic brain injury* (Š. O. Southern, Ed.; p. 87230O). https://doi.org/10.1117/12.2020030

Ware, J. B., & Jha, S. (2015). Balancing underdiagnosis and overdiagnosis. *Academic Radiology*, *22*(8), 1038–1039. https://doi.org/10.1016/j.acra.2015.05.004

Weil, Z. M., Corrigan, J. D., & Karelina, K. (2018). Alcohol use disorder and traumatic brain injury. *Alcohol Research: Current Reviews*, *39*(2), 171–180.

Wollman, S. C., Hauson, A. O., Hall, M. G., Connors, E. J., Allen, K. E., Stern, M. J., Stephan, R. A., Kimmel, C. L., Sarkissians, S., Barlet, B. D., & Flora-Tostado, C. (2019). Neuropsychological functioning in opioid use disorder: A research synthesis and meta-analysis. *The American Journal of Drug and Alcohol Abuse*, *45*(1), 11–25. https://doi.org/10.1080/00952990.2018.1517262

Yehene, E., Lichtenstern, G., Harel, Y., Druckman, E., & Sacher, Y. (2020). Self-efficacy and acceptance of disability following mild traumatic brain injury: A pilot study. *Applied Neuropsychology: Adult*, *27*(5), 468–477. https://doi.org/10.1080/23279095.2019.1569523

Zieman, G., Bridwell, A., & Cárdenas, J. F. (2017). Traumatic brain injury in domestic violence victims: A retrospective study at the barrow neurological institute. *Journal of Neurotrauma*, *34*(4), 876–880. https://doi.org/10.1089/neu.2016.4579

Zuckerman, S. L., Morgan, C. D., Burks, S., Forbes, J. A., Chambless, L. B., Solomon, G. S., & Sills, A. K. (2015). Functional and structural traumatic brain injury in equestrian sports: A review of the literature. *World Neurosurgery*, *83*(6), 1098–1113. https://doi.org/10.1016/j.wneu.2014.12.030

VITA

HANNAH G. MITCHELL

Education:	Ph.D., Psychology, East Tennessee State University, August 2024
	Master of Arts, Clinical Psychology, Western Carolina University May 2019
	Bachelor of Arts, Psychology, The University of Tennessee, Knoxville, May 2017
Professional Experience:	Graduate Research Assistant, Department of Psychology, East Tennessee State University, August 2019 – May 2023
	Neuropsychometrician, Tennessee Neuropsychology, May 2022 – May 2023
	Behavioral Health Consultant, Quillen College of Medicine, July 2020 – June 2022
Publications:	Mitchell, H. G., Ginley, M. K. Foster, K. N., Sevak, R. J., & Hagemeier, N. E. (In Press). Nonmedical use of prescription stimulants and nicotine among community college students. Community College Review.
	Mitchell, H. G., King, S. A., Ginley, M. K., Hagemeier, N. E., Foster, K. N., & Sevak, R. (In Press). Motives for nonmedical use of prescription stimulants in a sample of community college students. Journal of American College Health.

Flatt, R. E., Thornton, L. M., Smith, T., Mitchell, H. G., Argue, S., Baucom, B., Deboeck, P. R., Adamo, C., Kilshaw, R. E., Shi, Q., Tregarthen, J., Butner, J. E., & Bulik, C. M. (2022). Retention, engagement, and binge-eating outcomes: Evaluating feasibility of the Binge-Eating Genetics Initiative study. The International Journal of Eating Disorders, 55(8), 1031–1041. https://doi.org/10.1002/eat.23726

Mitchell, H. G., Kromash, R., Holt, L. J., & Ginley, M. K. (2021). Concurrent gaming disorder/internet gaming disorder and electronic nicotine delivery systems dependency in emerging adults. The International Journal of Mental Health and Addiction. https://doi.org/10.1007/s11469-021-00643-7

Mitchell, H. G., Frayne, D., Wyatt, B., Goller, H., & McCord, D. M. (2019). Comparing the PHQ-9 to the Multidimensional Behavioral Health Screen in predicting depression-related symptomatology in a primary medical care sample. Journal of Personality Assessment, 2(2), 175-182. https://doi.org/10.1080/00223891.2019.1693388