Opioid Use among Individuals with Traumatic Brain Injury: A Perfect Storm?

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THE CENTERS FOR DISEASE CONTROL AND PREVENTION reported that the number of opioid deaths in 2016 was five times that in 1999,¹ prompting the United States Department of Health and Human Services to declare the opioid crisis a public health emergency. Long-term opioid use is associated with risk for opioid use disorder (OUD), overdose, and death.² In 2017, > 40% of suicide and overdose deaths involved known opioid use, which is likely an underestimate.³ The economic cost of the opioid crisis is estimated at \$504 billion or 2.8% of the gross domestic product.⁴ OUD most commonly starts with a prescription written by a trusted physician,^{5,6} and the uniquely addictive properties of opioid medications have led to disastrous consequences for people of all ages, races, ethnic groups, and income classes, and from all geographic areas.^{7–9} Considerable investments have been made by federal agencies to investigate risk factors, develop prevention programs, and promote evidence-based treatments for OUD, but relatively little work has been done to identify subgroups at heightened risk for OUD. Injury prevention requires a detailed understanding of risk factors, contributing factors, and treatment needs.

Individuals with traumatic brain injury (TBI) are disproportionately represented in marginalized groups including those who are homeless, incarcerated, and struggling with substance use disorders (SUD),^{10–14} and are 10 times more likely to die of an accidental poisoning than the general population.¹⁵ Growing evidence suggests that individuals with TBI may be uniquely susceptible to opioid misuse and the consequences of OUD.¹⁶ Multiple independent risk factors (e.g., high rates of chronic pain,^{17–19} pre- and post-injury substance misuse,^{20–22} injury-related neurobehavioral changes,^{23,24} overprescribing of opioids,^{25,26} and barriers in access to care²⁷) converge for some individuals with TBI, creating a perfect storm of risk for OUD. Each of these factors is independently associated with OUD risk and adverse outcomes, but their convergence in this population makes people who have had a TBI uniquely vulnerable to opioid misuse and its devastating consequences.

Acute and chronic pain are prevalent among individuals with TBI,^{17–19} and poorly managed pain is a common pathway to long-term opioid utilization and OUD.^{6,28} Individuals with disabilities in general tend to have high rates of poorly managed or intractable pain,^{29–32} and evidence suggests that persons with TBI are no exception. Data from the TBI Model Systems National Database (TBIMS NDB), the largest longitudinal study in the world fol-

lowing individuals with TBI who receive inpatient rehabilitation, showed that pain was the most common medical condition reported by people who have had a TBI.³³ Estimates vary across studies depending on case definitions, injury severity, and time since injury, but chronic pain prevalence was >51% across 20 studies representing 3289 civilians with TBI.¹⁸ Chronic pain is associated with functional disability and mood disorders following TBI.³⁴ As part of a larger study on long-term health following TBI, we recruited adults who were at least 1 year post-TBI who required medical care from the community and compared rates of self-reported chronic pain with those of adults without TBI from a nationwide Mid-life in the United States (MIDUS) study sample³⁵ (See Table 1). Data from this (unpublished) comparison indicate that more than twice the proportion of men with TBI in the 40–49 year age range reported chronic pain as their same-age uninjured peers, suggesting an overlap in the TBI population within the demographic (young-middle aged men) at greatest risk for OUD and opioid overdose death.^{36,37} TBIMS data has shown that 72% of patients with moderate-severe TBI were given scheduled or p.r.n. narcotic analgesics during inpatient rehabilitation, and that 45% were prescribed these medications during the last 2 days of their hospital stay.³⁸ Some evidence suggests that rates of prescription opioid use are particularly high among individuals with disabilities.^{26,39} Among the general population, chronic pain is a common pathway to long-term opioid use and OUD as prescription opioid medication dosage is escalated (either independently or by a physician) when adequate pain relief is not achieved at lower doses.^{6,28,40}

Pre-injury substance use is another factor that puts individuals with TBI at risk for post-injury substance misuse or SUD. Substance use itself is a strong risk factor for TBI, and pre-injury substance use is associated with prolonged recovery and worse outcomes.⁴¹ Those with a pre-injury history of substance misuse are considerably more likely to engage in substance misuse after injury compared with prior non-users of drugs.^{20–22} However, it is estimated that 10–20% of people with TBI develop new-onset SUD after injury.⁴² A survey of health plan participants found that people with TBI who had no evidence of SUD in the year prior to injury had more than four times the odds of substance abuse within a year post-injury; odds of substance abuse were 1.8 and 1.4 by years 2 and 3 post-injury, respectively.⁴³ Decades of literature suggest high rates of SUD among individuals with TBI^{44,45} and many studies

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confirm that these rates exceed those seen in the general population.^{46,47} Several studies have found that military members who experienced a TBI during a recent deployment to Afghanistan or Iraq were at increased risk for post-deployment alcohol misuse.^{48,49} Moreover, individuals with TBI are well represented among those seeking SUD services; for example, among 845 individuals seeking SUD services from state-funded programs (including inpatient detoxification programs, transitional living facilities, and outpatient treatment programs), 54% had persistent symptoms of TBI and most had sustained multiple blows to the head.¹³ Although the elevated risks and high prevalence of SUD among individuals with TBI are well known, very few studies^{50,51} have investigated opioid use in this population.

Many of the cognitive, behavioral, and neurological consequences of TBI may serve to increase one's risk for medication mismanagement, addictive behaviors, and substance misuse. For example, many people who have had a moderate-severe TBI experience lifelong cognitive deficits such as memory problems and executive dysfunction;⁵² these impairments contribute to medication mismanagement and poor adherence to prescribed dosing schedules.²⁷ When a highly addictive opioid medication is prescribed for acute or chronic pain, accidental misuse can lead to physiological dependence of the drug. Mood disorders including major depression and anxiety disorders are also common after TBI,^{53–55} and psychopathology is a well-known risk and perpetuating factor for substance abuse.⁵⁶ A qualitative study that sought to characterize common pathways to OUD found that individuals with mood disorders were pleasantly surprised when opioid pain medications also made them happier or less anxious.⁶ These individuals prolonged or escalated their use of opioids because of the mood-boosting effects, even after pain symptoms abated.⁶ Further, it is worth noting that brain regions and circuitry that are commonly impacted by TBI, such as the prefrontal cortex, orbitofrontal cortex,⁵⁷ and dopaminergic neurocircuitry^{58,59} overlap with those that play important roles in reward behavior and risk/consequence aversion.^{60,61} Several additional health conditions that are prevalent after TBI are associated with substance abuse risk, such as traumatic stress,⁶² multiple comorbid health conditions,⁶³ and sleep disturbance.⁶⁴ Individually and collectively, these neurobehavioral sequelae of TBI may serve to predispose individuals with TBI to OUD when opioid pain medications are prescribed or obtained.

Barriers to accessing medical and mental health care, both for pain management and for substance misuse, may place individuals with TBI at elevated risk for OUD and relapse. Simultaneous management of multiple comorbid conditions, including TBI-related physical and neurobehavioral symptoms, affective disorders, trauma symptoms, and pain, can be quite challenging.^{65,66} Effective care often requires coordinated care among multiple clinicians with expertise in each of these conditions, and many persons with TBI and their caregivers report limited or no access to specialists.²⁷ Policies that withhold prescriptions for opioid pain medications without offering alternative approaches for pain management alternatives^{67–69} may be particularly harmful for individuals who lack the skills and resources needed to self-advocate and seek care. All of these factors may impede successful pain management and increase OUD risk after TBI, as discussed. Very little is known about access to OUD treatment for people who have incurred a TBI, but research conducted among individuals with other disabilities may apply to this population. Individuals with disabilities face barriers such as inaccessibility to opioid treatment centers⁷⁰ and limited insurance coverage for SUD services.^{57,70} There is strong evidence supporting the use of medication assisted treatments (MAT) to treat OUD (i.e., methadone, buprenorphine, and extended-release naltrexone), but the numerous barriers that reduce access to these treatments for the general population⁷¹ are likely further compounded by injury-related factors among those with TBI. Analysis of Medicaid data indicate that beneficiaries with disabilities with a diagnosed OUD were significantly less likely to have a prescription for an approved treatment medication than people without disabilities (11% vs. 32%).⁷² Although data specific to persons with TBI and their caregivers are sparse, many report treatment barriers such as physical inaccessibility, financial burden, and cognitive or behavioral TBI symptoms that impact medication compliance and overall health self-management.²⁷

Even when treatment is available, evidence suggests that SUD treatments that are not tailored to address the cognitive and neurobehavioral sequelae of TBI tend to be less effective for individuals with TBI than for those without,⁷³ and it is well recognized that cognitive behavioral therapies⁷⁴ and SUD-specific treatment practices may require modification for individuals with TBI.^{73,74} The Brain Injury Association of America asserts that integrated treatment of TBI and SUD is “essential,”⁷⁵ and to our knowledge, no studies have evaluated the implementation or effectiveness of treatment programs for individuals with co-occurring TBI and OUD. Common sequelae of TBI that are well-known risk factors for OUDs such as mental health disorders, prior substance abuse, and barriers to healthcare access^{76–78} are also associated with poor SUD treatment outcomes.^{79–81}

This perfect storm of converging risks and vulnerabilities may place individuals with TBI at risk not just for OUD, but for its most devastating outcomes. A TBIMS study indicated that individuals with TBI were 10 times more likely to die from accidental poisoning (identified by cause of death reported on death certificates) than the general population.¹⁵ Ninety percent of accidental overdose deaths were drug related; 67% of these deaths were from narcotic drugs, 14% from psychostimulants, and 8% were from alcohol.⁸² Those who survived a moderate-severe TBI and later died because of an accidental overdose were functioning more independently, but had compromised social and economic circumstances, compared with those who died of other causes. Even non-lethal overdose can result in anoxic brain injury secondary to respiratory arrest,^{83, 84} the results of which would further compound the cognitive and neurobehavioral deficits already experienced by

TABLE 1. PERCENTAGE OF INDIVIDUALS WITH CHRONIC PAIN STRATIFIED BY AGE, SEX, AND TBI EXPOSURE

Age (years)	Total (%)	TBI (n = 205)		Total (%)	Control ^a (n = 5576)	
		Male (n = 119) (%)	Female (n = 86) (%)		Male (n = 2521) (%)	Female (n = 3055) (%)
< 40 ^b	25	50	–	25.5	25.9	25.2
40–49	52.4	60.0	45.5	28.2	28.4	28.0
50–59	42.6	48.6	31.6	39.5	37.1	41.3
60–69	39.0	34.4	44.4	40.3	34.1	45.7
70–79	30.6	31.8	28.6	43.3	37.9	48.1
≥ 80	32.3	16.7	53.9	39.1	40.0	38.5

^aCommunity cohort data come from the Mid-life in the United States (MIDUS) study.³⁹

^bSample size <40 was insufficient to estimate stable rates. TBI, traumatic brain injury.

many people who have had a TBI. Data from military populations also suggest that veterans with a history of TBI who have been chronically taking short- and long-acting prescription opioid medications were three times more likely than those without TBI to attempt suicide.⁸⁵ Finally, it is worth noting that chronic use of opioid drugs, even in the absence of OUD or overdose, can have particularly negative consequences for individuals with TBI who may already be struggling with the very health problems that can be caused or exacerbated by chronic opioid use. Long-term prescription or non-prescription opioid use has been associated with sleep-disordered breathing⁸⁶ and central sleep apnea,⁸⁷ adrenal and metabolic disorders,⁸⁸ cognitive dysfunction, and neurodegenerative disease;⁸⁹ each of these conditions is prevalent among persons with TBI.^{90–94}

There is an urgent need to investigate the prevalence of short-term and long-term opioid medication use among persons with TBI, and to understand the pathways to and prevalence of OUD in this population. To our knowledge, no prior study has quantified the rates of OUD among individuals with a history of TBI, and, therefore, the hypothesized risk factors and pathways to OUD for individuals with TBI are unknown. Identifying contextual precipitants of opioid use is critical for identifying clear targets for prevention and treatment,^{8,9,95,96} and can inform the timing and content of interventions tailored for individuals with TBI.

Considerable knowledge gaps remain with respect to clinical care for individuals with TBI who are at risk for OUD, as well as for those with TBI and co-occurring OUD. Although it is somewhat reassuring that the self-evident risks of prescribing opiate medications to individuals with TBI have already been translated into clinical practice guidelines that caution against opioid use after TBI,⁹⁷ these recommendations are based on scarce empirical research, and evidence suggests that these guidelines are not being followed.⁹⁸ There is an urgent need to investigate effective treatment options for individuals with comorbid TBI and OUD. Clinical experience has suggested that persons with histories of TBI who are in any SUD treatment may require accommodations for neurobehavioral deficits to allow traditional insight-oriented interventions to be cognitively accessible.⁹⁹ However, attaining insight about misuse and becoming motivated to change behavior may be necessary but not sufficient conditions of successful recovery. Because of the neurobehavioral effects of TBI, it is essential to fortify positive intentions with additional supports that do not rely on insight, including: (1) structured and systematic engagement of natural supports, (2) avoidance of environments that can cue relapse, (3) prolonged maintenance of supports (i.e., keeping supports in place for a longer time), and (4) expanded use of MAT. These precepts require investigation. In general, there is a paucity of research on whether SUD treatment interventions that are effective for the general population show comparable efficacy for persons with TBI.¹⁰⁰ This question would seem to be particularly important with regard to MAT.

The public health consequences of TBI and OUD alone are staggering, and can include lost productivity, unemployment, divorce, social isolation, homelessness, violence, incarceration, infectious disease transmission, medical and mental health morbidity, trauma recidivism, and death.^{14,16,101–106} We need to learn more about this dually marginalized subpopulation of a large and growing population of people striving toward recovery. When a person with a history of TBI who has any or all of the elements of a “perfect storm” risk profile experiences chronic pain and is prescribed opioids, numerous factors converge to confer elevated risk for the development of an OUD. Although a TBI survivor may also be vulnerable to alcohol and other drug use, opioids are uniquely

addictive and are often introduced in the context of medical care after TBI. It is imperative to better understand the associations between TBI and opioid use in the United States. The co-occurring epidemics of TBI and OUD may impact the same individuals, and their consequences can be mutually exacerbating. The importance and timeliness of elucidating unique risk factors, barriers to treatment, prevention opportunities, and treatment accommodations for those with TBI at risk for OUD cannot be understated.

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