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Preface

Traumatic Brain Injury and Opioid Use: Additional Evidence Supporting the "Perfect Storm" of Cascading Vulnerabilities

Rachel Sayko Adams, PhD, MPH

BY THE TIME THE US Department of Health and Human Services declared the opioid epidemic a public health emergency in 2017,[1] prescription opioid rates had been declining for several years.[2] Yet, alarmingly, despite broad, multifaceted policy changes and interventions launched to curb the epidemic, opioid-related overdose deaths have increased by almost 5% from 2018 to 2019.[3,4] Mortality associated with the opioid epidemic has been characterized by 3 waves,[5] with the first wave fueled by increasing prescription opioid medications beginning in the 1990s, the second wave characterized by overdose deaths involving heroin starting around 2010, and the third wave driven by overdose deaths involving synthetic opioids (eg, fentanyl) starting in 2013.[5]

In recent years, traumatic brain injury (TBI) researchers, rehabilitation providers, funders, family members, and persons living with TBI have directed attention to understanding how the opioid epidemic has affected persons with TBI in the United States.[6] There was speculation that persons with TBI may be at a greater risk for receiving prescription opioids due to secondary conditions common after injury (eg, pain)[6,7]; however, systematic study was lacking. Recently, Drs Corrigan, Dams-O'Connor, and I published a commentary, "Opioid Use Among Individuals With Traumatic Brain Injury: A Perfect Storm?"[8] in which we synthesized existing literature, highlighted gaps in knowledge, and posited that for some individuals with TBI, risk factors may converge to create a "perfect storm," placing them at an increased risk for opioid use and associated consequences. We developed a 3-phase model for the "perfect storm," which posits that there are cascading vulnerabilities that can make persons with TBI uniquely susceptible to devastating consequences from opioid use, with each phase increasing risk for progression to the next (see Figure 1). Briefly, phase I contends that persons with TBI have greater exposure to opioids. Phase II states that, given opioid exposure, persons with TBI have a greater risk for advancing to long-term opioid therapy (LTOT; a risk factor for overdose and development of dependence),[9,10] opioid misuse, or opioid use disorder (OUD). Finally, phase III hypothesizes that if persons with TBI do develop OUD, they may face greater barriers to successfully engage in OUD treatment.

In **phase I**, we posited that persons with TBI are at an increased risk for opioid exposure due to several risk factors, the most significant of which is acute or chronic pain (including headaches) following TBI, which drives prescription opioid receipt. Studies indicate that more than 50% of individuals living with TBI have chronic pain.[7,11,12] Other risk factors for prescription opioid receipt include reliance on opioids in the intensive care unit or during acute rehabilitation.[13] To date, evidence has been strongest for phase I of the "perfect storm." Most research focusing on prescription opioid receipt following a TBI diagnosis uses electronic medical record (EMR) data, largely with military/veteran populations.[14–16] A new article by Kumar and

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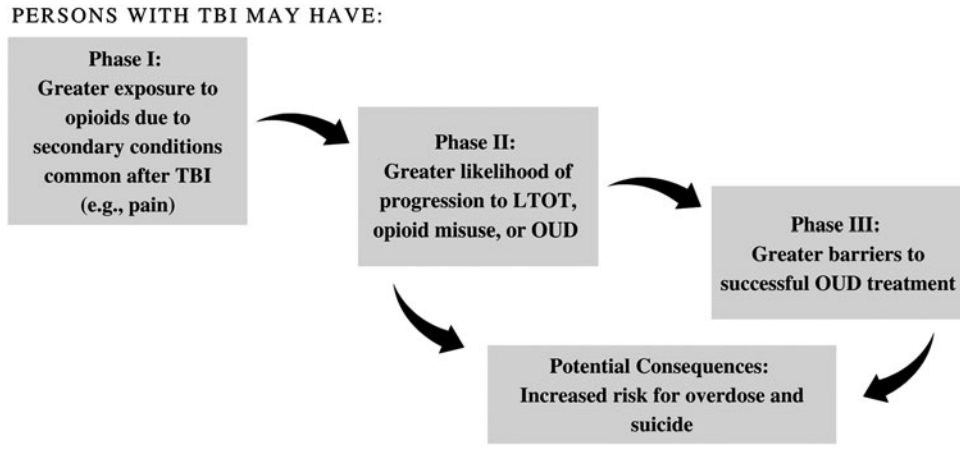

Figure 1. Cascade of vulnerabilities that create the "perfect storm." LTOT indicates long-term opioid therapy; OUD, opioid use disorder; TBI, traumatic brain injury.

colleagues[12] appears to be the first study to examine the association between lifetime history of TBI and prescription opioid receipt, using data from the nationally representative Health and Retirement Study. The authors found that older adults (aged 50+ years) with a lifetime history of TBI had a 52% increased risk for prescription opioid use in the past 3 months relative to those without a TBI history. Risk was highest among individuals with a recent TBI (1-10 years ago), first TBI after the age of 40 years, or 2+ lifetime TBIs.

There have been fewer studies directly exploring **phase II** of the "perfect storm." Some studies have found that post-9/11 military members or veterans with a TBI diagnosis were at a greater risk for LTOT than those without TBI.[14,15] Other studies examining self-reported TBI found an increased risk for prescription opioid misuse following injury; one among a small community-based sample of post-9/11 veterans reporting a deployment-related TBI,[17] and the other among a sample of adults in Ontario reporting at least one lifetime injury (ie, knocked out for 5 minutes or longer or an overnight hospitalization).[18] Lessons can be drawn from extensive literature on substance use following TBI. There is strong evidence that substance use is both a risk factor for TBI and that persons with TBI are at an elevated risk for postinjury substance use; thus, this cycle may be reinforcing.[19,20] There is also growing evidence that experiencing a TBI during childhood may increase risk for late adolescent or adult substance use.[21–23] While there has been little direct investigation into opioid misuse or OUD following childhood or lifetime TBI, there is reason to speculate that similar relationships would exist for opioids, which are uniquely addictive due to rapid development of dependence.[24] Unlike other illicit drugs, opioids are routinely prescribed to persons with TBI in the context of clinical care.[13] Damage to reward circuitry from TBI may create a biological vulnerability, while cognitive and neurobehavioral changes may serve as contributors to the development of prescription opioid misuse (eg, difficulty regulating impulsive behavior and emotions, memory problems leading to medication mismanagement, or taking extra prescription opioids to self-medicate).[8,25]

For **phase III** of the "perfect storm," we hypothesized that persons with TBI and OUD may face greater challenges accessing and successfully engaging in substance use disorder treatment due to neurobehavioral deficits or executive dysfunction following TBI.[8,24,26] To date, there are no known studies examining experiences or outcomes of persons with TBI seeking treatment specifically for OUD. However, prior studies have shown that individuals with TBI may require accommodations in substance use disorder treatment settings to address TBI-related challenges.[19] For instance, a randomized effectiveness trial within a trauma setting found that patients with TBI (vs no TBI) received less benefit from an evidence-based brief intervention for excessive alcohol use.[27]

While research is still emerging, the potential consequences of this "perfect storm" can be dire and include nonfatal overdose, fatal overdose, and suicide risk.[8,28–31] A study of post-9/11 veterans using the Veterans Health Administration (VHA) who received LTOT for treatment of chronic, noncancer pain found that veterans with TBI had a 3-fold increase in nonfatal opioid overdose compared with those without TBI.[28] Studies with both civilian[30,32] and veteran[29] populations have found that individuals with TBI were more likely to die from a drug overdose than individuals without TBI. Furthermore, while studies with both military/veteran and civilian populations have found an increased risk for death by suicide among persons with TBI,[33,34] one study of veterans using the VHA who were prescribed LTOT to treat chronic pain found that those with TBI were at an

increased risk for suicide attempt compared with those without TBI.[31]

Given the relatively nascent state of research systematically examining the relationship between TBI and opioid use and associated consequences, the current topical issue sought articles addressing this relationship broadly. This topical issue includes studies that provide further support for the "perfect storm," while informing an agenda for future research. The majority of studies included in this topical issue examine prescription opioid receipt and use data from relatively recent years, contributing new knowledge about this topic after opioid prescriptions began to decrease in the United States around 2012.[2]

Starosta and colleagues[35] conducted a scoping review to systematically characterize existing literature on prescription and nonprescription opioid use among individuals with TBI. As of their search date (ie, January, 2020), 21 articles met study inclusion criteria: English language, adults with a stable TBI, and prescription opioid receipt or use after TBI (excluding those with acquired brain injury or focusing on acute management of TBI). Four studies were review articles, and more than half of the 17 original research articles examined military/veteran populations. Most studies used EMR data, largely within the VHA, to examine prescription opioid receipt among persons with a TBI diagnosis, with fewer relying on self-report of opioids or self-report of TBI. Preliminary findings from articles included in the scoping review support phase I of the "perfect storm." Findings indicate that individuals with TBI have an increased likelihood of receiving prescription opioids and that opioid receipt is more common among those with comorbid pain and/or psychological health conditions in addition to TBI. The authors reported that few studies examined data from more recent years of the epidemic, a gap addressed by the studies in this topical issue as described as follows.

Adams and colleagues[36] examined the association of lifetime history of TBI with past year prescription opioid use and misuse among adults using data from the 2018 Ohio Behavioral Risk Factor Surveillance System survey. They found that adults with a lifetime history of TBI had 1.5 times the odds of past year prescription opioid use and 1.7 times the odds of past year prescription opioid misuse, compared with adults without TBI, controlling for sex, age, race/ethnicity, and marital status. This study was among the first to examine the relationship between lifetime history of TBI and opioid misuse. Study findings provide support for phases I and II of the "perfect storm" among an adult noninstitutionalized civilian population.

While prior studies examining opioid use following TBI have been conducted almost exclusively with adult populations, **Tham and colleagues**[37] conducted the first study of TBI and opioids among a nationally representative sample of US adolescents. Using the 2019 Youth Risk Behaviors Survey, the authors found that the odds of prescription opioid misuse were 1.5 times higher for adolescents with a past year sports-related concussion than those without a past year concussion, controlling for sex, race/ethnicity, other substance use, and depressive symptoms. These results are consistent with a previous study of Canadian adolescents,[38] which found that self-report of lifetime history of TBI (ie, injury to the head resulting in loss of consciousness for 5+ minutes or a minimum 1-night hospital stay) was associated with 2.7 higher odds of past year prescription opioid misuse, controlling for grade and sex.

A series of articles in this issue examine prescription opioid receipt and consequences among military members and veterans with TBI who received care in the Military Health System or VHA, respectively. A study by **Hoover and colleagues**[39] examined risk factors of prescription opioid receipt among individuals who received an index TBI diagnosis in the Military Health System between 2016 and 2017. They found that 29% of military members with an index TBI diagnosis received prescription opioids in the year prior to their TBI diagnosis, and importantly, 84% of these individuals continued receiving prescription opioids after their injury. On the contrary, among those who did not receive a prescription opioid in the year prior to their TBI, only 20% received postinjury prescription opioids. Thus, prior prescription opioid receipt was a strong predictor of future opioid use. Both musculoskeletal conditions and behavioral health diagnoses (eg, mental health or substance use disorder) in the year prior to the index TBI were associated with an increased risk for prescription opioid receipt postinjury, similar to other studies.[40] Women with TBI were at an increased risk for postinjury opioid receipt compared with men with TBI. Other studies with military/veteran and civilian samples have found that women are at an increased risk for prescription opioid receipt compared with males,[14,41,42] yet this appears to be the first study to examine this relationship in a population of persons with TBI.

A study by **Holmer and colleagues**[43] examined opioid and sedative-hypnotic prescription receipt and high-risk opioid outcomes among post-9/11 veterans with and without a TBI diagnosis treated in the VHA between 2012 and 2020. High-risk opioid outcomes included the following: LTOT, high-dose opioid therapy, and overlapping opioid prescriptions and benzodiazepine and/or nonbenzodiazepine sedative-hypnotic prescriptions–each of which increases risk for overdose and development of OUD.[10,44] Among veterans with TBI, more than one-fourth subsequently received a

prescription opioid in the VHA. Among veterans with TBI who received opioids, 30.1% received a concurrent benzodiazepine, 36.0% received concurrent nonbenzodiazepine sedative-hypnotic prescriptions, and 26.3% used LTOT. This study was among the first to reveal that veterans with a moderate/severe TBI (compared with a mild TBI), and those who experienced blast exposure (compared with nonblast exposure), were more likely to have high-risk opioid use. **Ashraf and colleagues**[45] were the first to integrate VHA and non-VHA prescription opioid data to examine the prevalence and predictors of concurrent opioid and sedative-hypnotic prescriptions from VHA/non-VHA systems of care among post-9/11 veterans with TBI. They found that among veterans diagnosed with TBI in the VHA between 2014 and 2019 who received an opioid in the VHA, 20% received an overlapping opioid prescription from a non-VHA provider and 5.3% received overlapping benzodiazepines. These results imply that clinicians considering prescribing opioids to veterans with TBI in the VHA or in civilian settings may not have the complete picture of total opioid and/or benzodiazepine exposure and thereby fail to recognize the full risk for overdose or OUD.

To investigate potential explanations for sleep-related disorders that are common following TBI, **Martin and colleagues**[46] examined the association between prescription opioid receipt during acute inpatient rehabilitation for moderate/severe TBI with sleep parameters (eg, quality, architecture, respiration) during 2017-2019; a quarter of the sample used a VHA facility. They found that prescription opioid receipt early after TBI was associated with impaired sleep parameters and sleep-related respiration outcomes (eg, increased frequency of central sleep apnea events during total and non-REM [rapid eye movement] sleep; higher frequency of obstructive sleep apnea events during REM sleep). This is among the first studies to consider the implications for sleep-related outcomes from opioid use during acute rehabilitation for TBI, expanding the scope of potential adverse outcomes associated with the "perfect storm."

Finally, an article by **Herrera and colleagues**[47] used EMR data from 2011-2015 to examine how prescription opioid receipt was associated with risk for TBI among community-dwelling Medicare beneficiaries aged 65+ years. Among Medicare beneficiaries who received an index TBI diagnosis during the study period, 16.2% were prescribed opioids in the 7 days preceding the TBI diagnosis. Prescription opioid use independently increased the odds of TBI by 30% compared with nonusers. This study highlights that prescription opioid use may ultimately increase risk for future TBI; thus, the pattern of risk may be cyclical once someone has either experienced a TBI or initiated opioids. These findings buttress previously recognized concerns that the opioid epidemic may be contributing to additional brain injuries, as anoxic or hypoxic brain damage can occur during a nonfatal overdose.[24] As we saw in Hoover and colleagues,[39] prescription opioid use prior to TBI increases risk for continuation of opioid use postinjury. Thus, older adults who are using prescription opioids in the months prior to a new TBI may be at a greater risk for continuing opioids after injury and advancing to LTOT, accelerating into phase II of the "perfect storm."

Together, the original research articles in this topical issue contribute new knowledge about risk for prescription opioid use, misuse, and other negative outcomes among persons with TBI. These studies rely on recently collected data, reflecting risks that endure after the reduction in opioid prescribing that started circa 2012.[2] Since then, clinical practice guidelines have been introduced to reduce high-risk opioid receipt, particularly among individuals with chronic pain,[10,48] and to caution against prescribing opioids to military members/veterans with a mild TBI[49]; yet, findings from this topical issue suggest that persons with TBI remain at an elevated risk for prescription opioid receipt and high-risk use or misuse of prescription opioids. The findings presented emanate from diverse populations of persons with TBI (ie, civilians, adolescents, military members, and veterans). These studies provide further evidence to support phases I and II of the "perfect storm"—that persons with TBI are at a greater risk for opioid exposure and, given exposure, they are at a greater risk for opioid misuse and high-risk opioid receipt (eg, LTOT, overlapping opioids and benzodiazepines) and adverse consequences (ie, adverse sleep-related outcomes).

Although the original data used in the studies in the topical issue were collected during the second and third waves of the opioid epidemic, no study investigated illicit opioid use following TBI or how prescription opioid use may be a pathway to illicit opioid use. This aspect remains a high-priority research area. More research is needed to understand patterns of prescription opioid use and associated outcomes following TBI for those with and without preinjury opioid use. In general, women are less likely to advance to LTOT or experience opioid misuse or OUD[14,42]; yet, sex differences in opioid use remain largely unexplored among persons with TBI. This is an important area for future research, as gender or sex can impact outcomes following TBI.[50,51] Given high rates of pain following TBI,[7,11,12] alternative pain management options are urgently needed. Evaluation of nonpharmacological treatments of chronic pain is underway in other populations[52] and should be examined in populations of individuals with TBI and comorbid pain to minimize adverse outcomes in this high-risk group. Clinicians considering tapering opioid prescriptions for their patients with TBI should use

caution and provide careful oversight, as reports of increased suicide risk following forced tapering have been observed in the United States.[53]

More research is needed to fully understand the association of high-risk opioid use with adverse outcomes among TBI survivors. As noted earlier, studies indicate that persons with TBI who engage in LTOT are at an increased risk for overdose (nonfatal and fatal) and suicide attempt.[8,28–31] A recent study that used machine learning to reveal sex-specific predictors of suicide among persons with substance use disorders in Denmark revealed that prior poisoning (ie, overdose) was among the most important predictors of suicide death, particularly among women, and that this risk could extend for many years after the poisoning.[54] Investigation of this dynamics among persons with TBI is warranted, as persons with TBI are at an elevated risk for suicide,[33,34,55] and prior overdose may help identify those at even a greater risk of suicide.

Phase III of the "perfect storm," which hypothesizes that persons with TBI who develop OUD may face greater challenges successfully accessing and engaging in OUD treatment, remains unstudied specific to OUD. This gap in knowledge is critical, as studies in the topical issue found additional evidence that persons with TBI are at a greater risk for opioid misuse, increasing their likelihood of developing OUD and risk for morbidity and mortality. While examination of barriers to substance use disorder treatment following TBI, and outcomes of such treatment, has been limited to date, prior studies indicate that persons with TBI face greater barriers and do not benefit as much as persons without TBI in standard substance use disorder treatments.[19,27,56] Evaluation of how individuals with TBI are able to access and benefit from evidence-based interventions and treatments of OUD is of the utmost importance.[35] Substance use disorder treatment providers should be trained to screen for lifetime history of TBI, as evidence is mounting that a large portion of persons seeking substance use disorder treatment have a history of TBI.[57] These providers should be trained to recognize and accommodate cognitive and other neurobehavioral consequences of TBI in their practice.[19]

Empirical investigation into each element of the "perfect storm" is needed to identify treatment targets and prevention opportunities. This research will require investment in longitudinal studies that allow assessment of lifetime history of TBI, exposure to prescription and nonprescription opioid use, and long-term morbidity and mortality outcomes. As research progresses to address gaps in knowledge highlighted herein, prevention strategies inclusive of nonpharmacological pain management interventions and evidence-based treatments of OUD incorporating accommodations for persons with TBI should be implemented to prevent future morbidity and mortality.

Rachel Sayko Adams, PhD, MPH
Institute for Behavioral Health
Heller School for Social Policy & Management
Brandeis University
Waltham, Massachusetts
Rocky Mountain Mental Illness Research Education and Clinical Center
Veterans Health Administration
Aurora, Colorado

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