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Title: The Intersection of Lifetime History of Traumatic Brain Injury and the Opioid Epidemic

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It is estimated that 20% of non-institutionalized adults have experienced at least one traumatic brain injury (TBI) with a loss of consciousness during their lifetime (Corrigan, Yang, Singichetti, Manchester, & Bogner, 2017; Whiteneck, Cuthbert, Corrigan, & Bogner, 2016). It is well established that a TBI of sufficient force will damage the frontal lobes, ventral medial prefrontal cortex, and orbital frontal cortex regardless the location of the impact to the head (Bigler & Maxwell, 2012). Neural networks connecting these areas of the prefrontal cortex to the basal ganglia and midbrain constitute the reward circuit, which have been implicated in substance abuse (Casement, Shaw, Sitnick, Musselman, & Forbes, 2014; Forbes, Rodriguez, Musselman, & Narendran, 2014). Specifically, damage to the orbital frontal cortex has been associated with reduced ability to control impulsive behavior (Sellitto, Ciaramelli, & di Pellegrino, 2010), which may influence self-regulation of substance use (Adams, Corrigan, Mohr, Williams, & Larson, 2017). We propose that TBI can have unrecognized consequences that may increase the risk for opioid use disorders (OUD).

People who incur TBIs frequently experience headaches (Aldag et al., 2017; Stacey et al., 2017), and pain from orthopedic and other injuries (Bertenthal et al., 2018; Grandhi, Tavakoli, Ortega, & Simmonds, 2017). One multi-center study found that over 70% of people receiving acute rehabilitation after TBI were prescribed opioids during their hospital stay (Hammond et al., 2015). Persons with persistent post-concussive symptoms after TBI are also more likely to be prescribed opioids (Mehalick & Glueck, 2018; Seal et al., 2018). In addition to the known addictive properties of long-term opioid therapy (Chou et al., 2015; Dowell, Haegerich, & Chou, 2016), individuals with TBI may be more susceptible to OUD compared to those without a history of brain injury. It has been demonstrated that survivors of TBI are at risk for problem substance use, and in particular alcohol misuse, post-injury (Adams, Larson, Corrigan, Horgan,

& Williams, 2012b; Corrigan & Cole, 2008; Weil, Corrigan, & Karelina, 2016). Alcohol misuse after TBI is a risk factor for poor rehabilitation outcomes, mood and anxiety disorders, negative drinking-related consequences, and future TBIs (Adams, Corrigan, & Larson, 2012a; Adams, Larson, Corrigan, Ritter, & Williams, 2013; Dams-O'Connor et al., 2013; Ilie et al., 2015; Weil et al., 2016). Increased alcohol use following TBI may further impair judgement and increase impulsivity (Stuss, 2011), perhaps increasing susceptibility to developing an OUD once opioids are initiated.

There is also growing evidence suggesting that experiencing a childhood TBI increases the likelihood of behavioral health problems, including substance misuse during adolescence and adulthood, and that this relationship is more pronounced the younger the age of injury (Corrigan, Bogner, & Holloman, 2012; Corrigan et al., 2013a; Corrigan & Hammond, 2013b; Dams-O'Connor et al., 2013; Karver et al., 2012; McKinlay, Corrigan, Horwood, & Fergusson, 2014). A study of persons who required rehabilitation for a TBI in adulthood found that those with a prior TBI before age 6 were more likely than those without a prior TBI to be misusing alcohol (54% and 31%, respectively), and illicit drugs (36% and 20%, respectively) at the time of their adult TBI (Corrigan et al., 2013). It is worth noting that the vast majority of the injuries identified in the above studies are mild TBIs. Animal studies have also found a relationship between juvenile TBI and adult preference for alcohol (Weil, Karelina, Gaier, Corrigan, & Corrigan, 2015). While most research has focused on increased vulnerability for alcohol and illicit drug use following TBI, similar relationships can be expected for OUD due to the highly addictive nature of opioids.

Notably, there have not been systematic studies examining the prevalence of opioid use or OUD among individuals with a history of TBI, and much of what is known has been informed by

research with military service members and Veterans. While the Veterans Administration/Department of Defense (VA/DoD) clinical practice guidelines for management of opioid therapy and mild TBI both recommend against prescribing opioids to individuals with a history of TBI (Department of Veterans Affairs - Department of Defense, 2017; The Management of Concussion/mTBI Working Group, 2016), a study of VA-utilizing Afghanistan and Iraq Veterans with a TBI diagnosis in 2010-2012, revealed that 21% initiated opioids and 25% of these individuals went on to use opioids long-term (Hudson et al., 2018). By comparison, 58% of soldiers returning from an Afghanistan or Iraq deployment in fiscal years 2008-2014 who had a TBI diagnosis were prescribed an opioid during the post-deployment year in the DoD, and these soldiers were at increased risk to use opioids long-term (Adams et al., 2018 In press).

Another concern is that OUD is likely a risk factor for future brain injury. For example, overdosing on opioids suppresses or stops respiration, which in turn denies oxygen to the brain leading to anoxic brain damage if completely denied, or hypoxic brain damage if reduced (Schirmer & Seale, 2018). Hypoxic damage commonly leads to cognitive impairment (e.g., memory, attention, mental processing speed, executive functioning) and emotional dysregulation in the form of lability, impulsivity, irritability and apathy (Anderson & Arciniegas, 2010). The impact on executive functions, particularly self-regulation, is similar to TBI. Data is limited about the scope of hypoxia with OUD overdoses. By definition some hypoxia occurs with every overdose that results in a loss of consciousness, yet the residual effects have not been studied. There has been substantial research from trauma care showing additional damage when TBI and hypoxia co-occur (Rubenson Wahlin et al., 2018). Further, TBI could occur during opioid overdose events due to losing consciousness and falling.

Given the urgency of the opioid epidemic, clinical practitioners can proactively mitigate potential opioid use problems by identifying high-risk populations, which we argue, includes individuals with a lifetime history of TBI. Clinicians considering initiation of opioids for pain should complete an evaluation of a patient's lifetime history of TBI and follow existing clinical guidelines described above to use caution when prescribing opioids to individuals with TBI. Educational interventions and OUD treatment should accommodate inhibited cognitive abilities and executive function weaknesses in patient interactions and treatment planning. More study is needed to identify non-pharmacological approaches to treating pain among people with TBI. More research is warranted to examine whether a history of TBI increases risk for OUD, including among individuals with mild TBI in which symptoms appear to have resolved, and to determine if additional barriers exist for people with TBI and OUD to access evidence-based treatments. We contend that clinicians can implement these screening and prescribing practices now, as we await stronger research evidence, which we fully expect to substantiate the relationship between lifetime history of TBI and OUD.

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