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REVIEW

A narrative literature review of depression following traumatic brain injury: prevalence, impact, and management challenges

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Abstract: Depression is one of the most common conditions to emerge after traumatic brain injury (TBI), and despite its potentially serious consequences it remains undertreated. Treatment for post-traumatic depression (PTD) is complicated due to the multifactorial etiology of PTD, ranging from biological pathways to psychosocial adjustment. Identifying the unique, personalized factors contributing to the development of PTD could improve long-term treatment and management for individuals with TBI. The purpose of this narrative literature review was to summarize the prevalence and impact of PTD among those with moderate to severe TBI and to discuss current challenges in its management. Overall, PTD has an estimated point prevalence of 30%, with 50% of individuals with moderate to severe TBI experiencing an episode of PTD in the first year after injury alone. PTD has significant implications for health, leading to more hospitalizations and greater caregiver burden, for participation, reducing rates of return to work and affecting social relationships, and for quality of life. PTD may develop directly or indirectly as a result of biological changes after injury, most notably post-injury inflammation, or through psychological and psychosocial factors, including pre injury personal characteristics and post-injury adjustment to disability. Current evidence for effective treatments is limited, although the strongest evidence supports antidepressants and cognitive behavioral interventions. More personalized approaches to treatment and further research into unique therapy combinations may improve the management of PTD and improve the health, functioning, and quality of life for individuals with TBI.

Keywords: traumatic brain injury, depression, inflammation, antidepressants, rehabilitation

Introduction

Psychiatric disorders, including mood, anxiety, and substance-use disorders, are prevalent after traumatic brain injury (TBI), particularly when the injury is moderate to severe, and can have serious consequences for health, participation, and quality of life. Depression is the most common psychiatric condition to occur post-TBI, although comorbidity rates with other psychiatric and behavioral disorders are high.[1,2] Despite the potentially serious consequences of depression, the majority of adults with TBI who experienced depression in the first year post-TBI did not receive treatment.[3] Treatment for post-traumatic depression (PTD) is complicated, however, due to its uncertain and multifactorial etiology; that is, it can develop through multiple and multifaceted pathways that may or may not directly result from the primary brain injury.[4] Therefore, treatment development for depression must occur in well-defined subgroups having similar symptom clusters or risk factors to address the unique underlying risk factors (eg, neurobiological changes and major life stressors) and tailor treatment

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accordingly.[4] This multifactorial nature of PTD could at least partially explain why response to PTD treatment is often poor compared to the broader major depressive disorder (MDD) population and why PTD treatment studies yield such variable results. This narrative review presents the following: 1) an updated overview of the prevalence and symptom presentation of PTD after moderate to severe TBI; 2) the impact of PTD on other long-term outcomes after moderate to severe TBI; 3) an overview of the various underlying conditions and etiological elements – from neurobiology to life stressors – that contribute to depression post-TBI; and 4) a summary of the successes and challenges in clinical management of PTD.

Methods

For this narrative review,[5] defined as a well-structured synthesis of available evidence that conveys a clear message supported by existing data,[6] we selected articles through a multistep process. The first author (SBJ) has a web-based literature database that has been continuously updated from 2013 to late 2016 and reflects the author's research areas of interest, including TBI and depression. Articles included in this database were identified from several sources, including multiple PubMed searches (with weekly updates emailed to and reviewed by the first author to build the database), reference lists of relevant articles, database searches for other TBI-related publications and projects, and recommendations from other experts and collaborators. PubMed searches included the search term "brain injury" AND (alone and in combination): depression, affect, suicide, anxiety, fatigue, cytokine, biomarker, participation, treatment, systematic review. Within this database, we entered "depression" as a search term and reviewed abstracts of all resulting articles for relevance to TBI and depression and categorized articles into one or more of the following headings based on the relevant content: PTD symptoms and prevalence, PTD predictors, PTD impact, PTD treatment, mild TBI, and suicide. Articles published prior to 2000 or not published in English were excluded. Articles were then read to produce overall narrative summaries within each of the identified headings in the "Discussion" section, with priority given to previously published systematic reviews.

Discussion

Prevalence and symptom presentation

Numerous studies have reported prevalence for psychiatric disorders, and specifically, for depression after TBI. Psychiatric diagnoses, including mood, anxiety, and substance abuse disorders, were reported in 75.2% of individuals across the first 5 years post-TBI, with the majority of these (77.7%) emerging in the first year,[7] similar to another study indicating clinically significant psychiatric symptoms in 42% of adults with TBI at 6 months post-injury.[8] The majority of all psychiatric disorders (56.5%) post-TBI, and two-thirds of PTD diagnoses specifically,[9] were first-time diagnoses. Point prevalence rates of psychiatric disorders up to 20 years post-TBI ranged from 17% to 31%,[2,10–14] with a systematic review from 2011 estimating a point prevalence of 30% across multiple time points post moderate to severe TBI.[15] Cumulative prevalence rates for PTD were higher, just over 50%,[3,9,16] indicating that more than half of individuals with TBI will experience a depressive episode after injury. Most individuals will experience their first post-injury major depressive episode within the first year after TBI.[3] In addition, individuals with TBI had an elevated risk of suicide attempt (5-fold increase in risk) and completion (3–4 times more likely to die from suicide) compared to the general population.[17–19]

Depression and TBI share many common somatic symptoms, including fatigue, poor concentration, and sleep disruption. However, a study by Jorge et al[20] found that nearly all of the 66 adults with TBI in their cohort with notable depressive symptoms had depressed mood; that is, they found no evidence for "masked" depression. However, they did suggest that the symptoms that best differentiated those with and without depression also differed based on time post-injury, with symptoms related to sleep disruption and poor concentration only distinguishing between groups after 6 months post-injury. Seel et al[12] reported that the most common symptoms of depression across the first 10 years post-TBI included fatigue, distractibility, and rumination, and that rumination, self-criticism, and guilt were the symptoms that best differentiated those with depression from those without depression after TBI.[21] Furthermore, they found that depression post-TBI was characterized more by irritability, anger, and aggression than by sadness or tearfulness.[21]

The impact of depression after TBI

PTD has implications for: 1) health, including higher re-hospitalization rates, greater suicide risk, and more caregiver burden; 2) participation, including return to work or school and social relationships; and 3) quality of life, including life satisfaction and overall well-being. Emotional changes, in particular, influenced long-term functional, psychosocial, and quality of life, especially as time since injury increased.[2,3,22–28] Psychiatric conditions, such as depression, accounted for a majority of all re-hospitalizations beyond the first year post-injury,[29,30] resulting in increased medical costs, and depression was among the strongest contributors to the high suicide risk reported after TBI.[19,31] Depression was also significantly associated with poor vocational,[32,33] psychosocial,[2,32] and

functional independence outcomes.[32,34] A systematic review conducted by Garrelfs et al[33] reported a strong negative association between depression and return to work after acquired brain injury. Furthermore, depression was associated with poorer social functioning after TBI.[2,25] One potential pathway through which depression could lead to poor participation outcomes is through disrupted behavior, such as aggression, impulsivity, or poor decision making. Post-TBI depression was highly associated with disrupted behavior after TBI,[2,35] with some evidence indicating that depression preceded behavioral disruption,[36,37] and disrupted behavior was a significant predictor of poor participation outcomes.[38] Often, however, it is difficult to differentiate cause from effect with regard to the relationship between PTD and other TBI-related impairments (Unpublished Material. Kumar RG, Gao S, Juengst S, Wagner AK, Fabio A. Post-traumatic depression effects on cognitive and physical impairments after moderate to severe civilian traumatic brian injury: a thematic review). For example, Perrin et al[39] found that functional independence may be more of a cause than a consequence of PTD, though they concluded that there was likely reciprocal causation between the two. Other predictors of PTD are discussed in the "Predictors/etiology of depression" section. Finally, PTD up to and beyond 10 years post-injury was associated with lower and declining life satisfaction[40–42] and with poorer quality of life after TBI.[3,25,43–45] A study by Diaz et al[45] reported that those with depression after TBI had greater impairments in all domains of the Short Form Health Survey (SF-36), a health-related quality of life measure, compared to those without depression.

Predictors/etiology of depression

The presentation of PTD is a multifactorial response to a number of underlying factors associated with TBI rather than just the direct result of a primary pathology.[4] Therefore, one of the greatest challenges to managing PTD is identifying its unique etiology, which can differ from person to person. Strakowski et al[4] emphasized the importance of identifying underlying risk factors for PTD that should be managed first, prior to addressing depressive symptoms, to maximize the chances for a positive treatment response; this included employing focused treatments in well-defined subgroups. As an example, one subgroup may be those who experience fatigue after TBI. Recent evidence suggests that fatigue is directly caused by TBI and may lead to, rather than result from, PTD.[46] Therefore, a treatment approach to PTD among those with primary fatigue may include addressing fatigue first. The first step toward personalized treatment approaches to PTD is to understand the heterogeneity in its risk factors and its underlying causes after TBI.

Biological mechanisms of PTD: inflammatory-induced depression

There are numerous biological mechanisms through which depression can develop after TBI,[47] including through inflammation (Figure 1). Inflammatory mediators, including cytokines and inflammatory cell surface markers, are elevated with central nervous system (CNS) injury,[48,49] including TBI,[50,51] and these markers have been linked to depression in neurologically intact adults,[52–54] older adults,[55] and individuals with chronic conditions associated with inflammation,[56–61] including TBI.[62,63] Acute cerebral spinal fluid (CSF) inflammation has been shown to be associated with PTD in the first year post-TBI.[62] Specifically, higher acute CSF levels of the cell surface markers such as sVCAM-1, sICAM-1, and sFAS were associated with a significant increase in risk for depression 6 months post-TBI, and higher acute CSF levels of IL-12 were associated with PTD at 12 months.[62] These markers are known to be associated with inflammation and white matter changes among older adults with depression.[55,64] Inflammation occurring early after TBI may contribute to long-term, chronic inflammation even several years post-injury,[65] and hence, to chronic risk for depression.

Acute inflammation post-TBI may also lead to depression via maladaptive "sickness behavior" (Figure 1), which shares several symptoms (eg, lack of energy and interest and decreased appetite) with depression.[61,66–68] While sickness behavior is initially adaptive and helps the body respond to acute injury and/or infection, it becomes maladaptive if it persists for longer than 3–6 weeks.[61,69] This time frame marks a transition from acute, adaptive behavior to a chronic, maladaptive process that may develop into depression.[70,71] Cytokines such as IL-6 or tumor necrosis factor-α (TNF-α) are signaling molecules of the immune system that have been associated with MDD.[67,72] Elevated serum IL-6, which was significantly elevated up to 3 months after TBI,[73,74] is considered a reliable biomarker of MDD,[75] though whether it is a biomarker for PTD remains to be determined. While prospective studies are needed to validate this hypothesis, it is reasonable to consider that individuals whose inflammation remains high chronically after TBI may transition from an adaptive immune response (initial high inflammation with return to baseline) to a chronic, maladaptive response (sustained inflammation), leading to PTD and greater disability.

Another cytokine that has shown preliminary associations with PTD is IL-7,[62] which has been implicated in lymphoproliferative processes needed to generate an adaptive immune response.[76] This connection to generating an effective immune response may explain why low levels of CSF IL-7

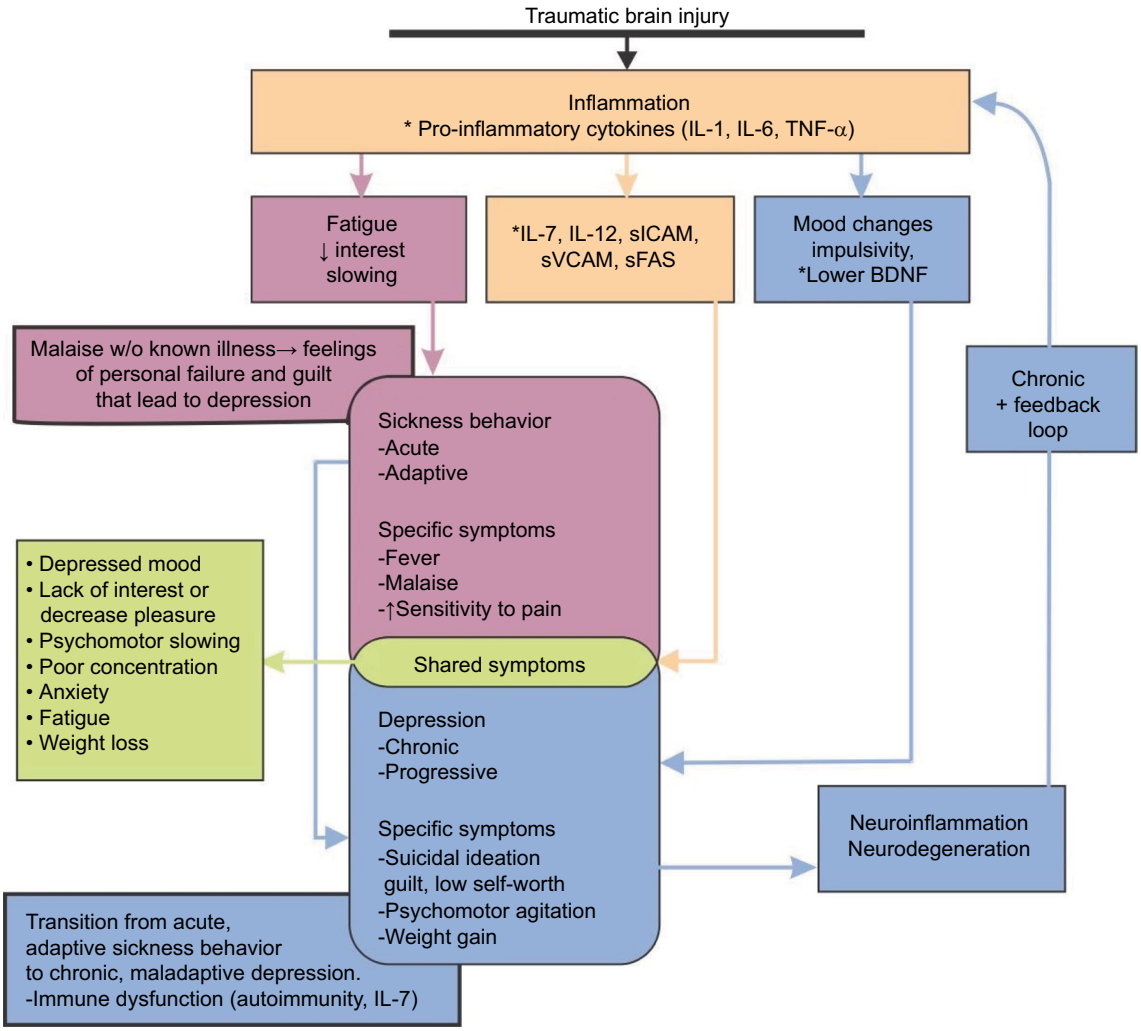

Figure 1 Conceptual diagram of inflammatory-induced PTD.
Notes: A conceptual diagram of potential pathways by which the acute inflammatory response after TBI can lead to an inflammatory-induced depression. This conceptual diagram is based on research on major depressive disorder in the general population and on early work in PTD after TBI. *Specific inflammatory markers, including IL-7, IL-12, sICAM, sVCAM, sFAS, and brain-derived neurotrophic factor, are based on preliminary studies from a population with PTD. They are not validated biomarkers for PTD, nor do they represent an exaustive list of potential biomarkers for PTD.
Abbreviations: PTD, post-traumatic depression; TBI, traumatic brain injury

in the first week post-injury were inversely related to PTD at 1 year post-injury (eg, levels "below" the 25th percentile in the sample of adults with severe TBI were associated with higher risk for PTD).[62] This finding in severe TBI was consistent with a study in MDD in which those in the lowest tertile for serum IL-7 levels had a 3.4-fold greater risk for depression,[77] supporting the hypothesis that lower levels of IL-7 among those with depression reflect disruption of T-cell homeostasis as a potential pathway for inflammation-mediated depression.[77]

IL-6 and TNF-α may also affect brain-derived neurotrophic factor (BDNF) in the setting of chronic stress. Increases in proinflammatory cytokines resulting from chronic stress could potentially lead to dampening of BDNF expression, as evidenced in preclinical models,[78] which may then contribute to depression.[79] BDNF levels were decreased in untreated depression, but increased with antidepressant treatment.[80–82] Notably, in post-stroke depression, serum BDNF levels were higher during periods with no depressive symptoms, but lower in the presence of depressive symptoms.[83] BDNF levels in serum during the first week post-TBI may be indicative of risk for the development of PTD by 1 year.[84] Overall, BDNF represents a potential biomarker for risk stratification and a potential therapeutic target for both prevention and treatment of PTD.

Psychosocial risk factors for PTD

Pre-injury and comorbid personal factors, as well as changes in functional abilities and community-based participation after injury, could contribute to an adjustment-based, rather

than biologically based, depression after TBI.[47,85] Adjustment-based depression is characterized more by low self-worth, feelings of guilt, agitation, and suicidal endorsement when compared to depression resulting from maladaptive sickness behavior,[69,70] suggesting not only distinct mechanisms for the development of PTD (Figure 1) but also potentially different subtypes of PTD. This point has implications for treatment decisions, as particular subtypes of PTD, such as inflammatory-induced versus adjustment-based, may be more or less responsive to pharmacological versus behavioral interventions.

Age,[8,15] race,[8,86] less independence in functional tasks after injury,[11,15,87–89] engaging in maladaptive coping,[90,91] and sleep disturbance or fatigue[46,92,93] were all associated with PTD. Furthermore, being unemployed or impoverished at the time of injury or substance abuse before or at the time of injury also conferred a higher likelihood of developing PTD.[8,12,13,15,94] Personality characteristics and pre-injury psychiatric conditions that increase the risk of sustaining a TBI[95,96] may also put individuals at greater risk for developing PTD.[7,85,94] In fact, one of the biggest predictors of PTD was a pre-injury history of depression or other psychiatric disorder.[7,94,97] However, the extent to which pre-injury mental health conditions contribute to PTD development through biological versus psychological pathways is unknown.

The appraisal of post-injury abilities compared to the appraisal of pre-injury abilities was another underlying factor related directly to the adjustment to disability that contributes significantly to the development of psychiatric disorders after TBI.[87,98–101] Individuals with TBI often overgeneralize the effects their injuries have on their abilities and daily lives.[102,103] These perceptions were strongly influenced by the individual's ability or failure to attain post-injury goals.[104,105] Individuals with cognitive impairment may have difficulty engaging in goal-directed, problem-solving behavior,[106–108] resulting in poor goal attainment and contributing to PTD. Individuals with TBI engaged less frequently in goal-directed problem-solving than individuals without injuries,[109] often as a result of associated impairments in executive functions.[90,110] Individuals who do engage in goal-directed problem-solving post-injury had higher self-efficacy, less perceived stress, less depression and anxiety, and overall better psychosocial functioning than those who engage in wishful thinking or avoidance behaviors after injury.[90,102,109,111] Therefore, goal-directed and problem-solving behaviors may represent one effective avenue of treatment for PTD.

Management challenges

A number of systematic reviews and meta-analyses have been conducted to examine the evidence for efficacious interventions to address PTD, with very limited evidence supporting any approach.[27,101,112–118] In addition to (and perhaps partly as a result of) the lack of clear recommendations and guidelines for treating PTD, studies have suggested that a relatively high proportion of individuals living in the community received limited or no treatment for PTD.[3,119] Given the long-term consequences of PTD, research to establish evidence-based rehabilitation interventions for depression should be a high priority in rehabilitation research.[120–122] Increasing priority should also be given to investigating personalized treatment approaches based on factors ranging from genetic variation to mental health history. Rehabilomics is a rehabilitation-centered conceptual framework that adapts the World Health Organization's International Classification of Function, Disability, and Health to outline a personalized biopsychosocial approach to rehabilitation research and care,[123–126] and it could serve as a contemporary framework from which to conduct innovative and effective research into personalized risk assessment and personalized rehabilitation interventions, where treatment assignment is delineated based on personal biology and other individual factors hypothesized to contribute to PTD.

Current evidence for effective treatment for PTD

The current literature does not support any gold standard for PTD treatment. Antidepressant treatment – specifically serotonergic drugs – and psychotherapeutic approaches – particularly cognitive behavioral approaches – have the best levels of evidence. To date, however, studies on effective treatments for PTD have not differentiated potential subgroups that may have differential responses to treatment.

Pharmacological interventions: Antidepressants have yielded mixed results in studies of depression treatment after neurological injury, such as TBI,[112,113] and there is growing evidence that some antidepressants may be less effective among individuals with TBI compared to those without TBI.[113] The reduced treatment effectiveness of selective serotonin reuptake inhibitors (SSRIs) after TBI may be due to the high levels of inflammation post-injury. An animal model of postepilepsy depression, another condition associated with high levels of inflammation, revealed that treatment with fluoxetine alone yielded no antidepressant effects, but when paired with an IL-1Ra (an IL-1 antagonist), nearly all depressive indicators were eradicated.[127] Currently, treatment with SSRIs is still one of the most evidence-based

approaches to PTD treatment,[27,113,128] and recent evidence suggested that one such antidepressant (sertraline) may be a promising preventative treatment for PTD.[129] Combination therapy with an SSRI and anti-inflammatory agent is also promising, and further study is warranted. However, it is important to note that side effects of newer-generation antidepressant drugs often overlap with and may compound symptoms after TBI.[130] Thus, careful consideration should be given to the relative benefits and risks of using these pharmacological agents, particularly where little is known about how they will interact with other TBI-related medical sequelae to cause adverse side effects.

Behavioral/psychological interventions: Cognitive behavioral interventions also have a growing body of evidence to support their efficacy for treating PTD,[131–136] though to what extent any specific approach (eg, cognitive behavioral therapy[27,134,135] and problem-solving treatments[137]) was better than another or better than traditional psychotherapy (eg, talk therapy and psychodynamic therapy) still remains to be determined.[117,131] Isolating the "active ingredients" of behavioral interventions, particularly if different components are more or less effective for specific subtypes or subgroups of individuals with PTD, will inform clinical triage, training for practitioners, and systems of care.

One meta-analysis suggested that behavioral activation approaches, specifically activity scheduling, showed promise and could be integrated into holistic treatment programs to improve mood in addition to functional and community-based outcomes.[138] Problem-solving characterized another class of behavioral intervention that has the potential to improve mood, in addition to other rehabilitation-relevant outcomes such as goal attainment and executive function.[27,114] Setting and attaining goals are critical components of the rehabilitation process and may be compromised by executive impairment after TBI.[139–141] If goal attainment after TBI is compromised, it may further contribute to the discrepancy between the appraisal of one's pre- and post-injury abilities, leading to depression. Therefore, interventions that promote goal attainment and address impairments in executive functions may prevent or improve PTD,[34,135] particularly if it has more of an adjustment-based etiology.

A review of the literature conducted by the Brain Injury Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM BI-ISIG) recommended metacognitive strategy training, a problem-solving-based approach, as a treatment guideline for executive dysfunction, which often manifests in disrupted behavior, after TBI.[142] Impairment in problem-solving mechanisms was at the core of executive dysfunction, and problem-solving was both supported and impeded by emotion after TBI.[143] The ACRM BI-ISIG recommended incorporating training in formal problem-solving strategies applied to everyday activities as a cornerstone of cognitive rehabilitation.[144] It was also recommended that treatment should be provided in a top-down manner, that is to focus on functional and activity-based goals rather than improvement of symptoms or bodily functions, to ensure generalization to non-trained goals and activities.[143] While these strategy-training, self-management approaches are a recommended guideline for treating executive impairments after TBI, the extent to which they improve PTD and its impact on other outcomes remains unclear. Huckans et al[145] conducted a pilot study examining a 6- to 8-week group-based cognitive strategy training program for veterans with a history of TBI and found increased life satisfaction and decreased depressive symptoms and cognitive complaints among those who completed the intervention. However, despite evidence that combining cognitive and emotional interventions yielded more positive outcomes than addressing cognition and emotion in isolation,[146,147] there is little research assessing the direct effect of problem-solving approaches on PTD.

Other potential pharmacological and non-pharmacological approaches to effectively treat PTD have shown some promise, but require further study. As mentioned earlier, targeting inflammation and/or BDNF levels may help to improve depressive symptoms or prevent the transition from adaptive to maladaptive sickness behavior. There is emerging evidence for agents that selectively enhance BDNF improving depressive symptoms in MDD.[115] Exercise-based interventions[148,149] may also improve depressive symptoms partially by enhancing BDNF. Targeting inflammation through transcranial photobiomodulation[150] was found to improve mood in MDD and through an anti-inflammatory diet[58] was found to improve mood in spinal cord injury. Other potential avenues for research that may reveal effective treatments for PTD include methylphenidate[118,151] and mindfulness-based interventions.[152,153] Recommendations for non-pharmacological treatments of PTD, based on evidence from a systematic review conducted by the French Society of Physical Medicine and Rehabilitation, included structured holistic approaches and family and systemic therapies, though the authors note that this was based on low levels of evidence.[136] Finally, further research is required to assess the efficacy of interventions employed in clinical practice that demonstrate anecdotal success for treating PTD, but lack a sufficient evidence base.

Challenges and considerations

In addition to a lack of clear PTD treatment guidelines, there are other challenges and considerations when managing PTD. During the initial hospitalization after TBI, 95% of patients were prescribed a psychotropic medication, with over half of the medications classified as antidepressants.[154] Many of these antidepressants, however, were used more for sedation (eg, mirtazapine and trazodone) than for depression.[155] Often reasons for prescribing antidepressants in the hospital are not well documented, and patients with TBI may continue to take these antidepressants after discharge from the hospital without a clear indication as to the reason for continued use. Further, while an antidepressant may be effective in addressing other symptoms, the drug class and/or dose may not be effective in reducing depressive symptoms. Polypharmacy is also a significant concern, as individuals with TBI are prescribed multiple medications for several conditions or symptoms. In a large study of adults admitted to inpatient rehabilitation after TBI, 31.8% of patients were receiving ≥6 psychotropic medications. Similarly, a study on polypharmacy in veterans indicated that those with comorbid TBI, anxiety, and mood disorders had the highest odds (adjusted odds ratios [AOR] 15.30) of psychotropic polypharmacy (≥5 medications), and after controlling for these comorbid conditions, polypharmacy was associated with greater risk of overdose and suicidality.[156] Polypharmacy is also a problem when combining psychotropic medications with medications for other active medical conditions, such as preexisting chronic disease or other secondary conditions post-TBI (eg, seizures and migraine). Particular consideration should be given to drug interactions that may increase the risk of intracranial bleeds, such as that associated with combined use of antidepressants and nonsteroid anti-inflammatory drugs in the general population,[157] though no studies have investigated this interaction after TBI specifically. Physicians may be reluctant to prescribe antidepressants in these cases due to risk for unwanted side effects, especially if an individual had previously not responded to an initial depression treatment.

Individuals with TBI experience many barriers to care, which may be particularly compounded when seeking care for PTD. A study by Matarazzo et al[158] that solicited feedback from clinical providers treating veterans with a history of TBI and comorbid mental health conditions presented an illustrative example of these compounded barriers. The clinician-perceived barriers preventing veterans with TBI from seeking care included a lack of knowledge of where to go for treatment, cost of treatment, embarrassment or concern about how they would be perceived by others, and fear of it having a negative impact on their careers. Traditional mental health practitioners may not understand or know how to manage behaviors or unique emotional regulation difficulties of individuals with TBI; similarly, community-based physicians and other medical providers may not feel equipped to treat PTD or may not be aware of the unique considerations (eg, polypharmacy, contraindicated medications after TBI, and differential response to antidepressants) required when considering how to treat adults with TBI. In addition, some interventions may require modifications,[132,135] such as pacing or presenting information in different formats, and clinicians may not know how to appropriately adapt these interventions for adults with TBI.[158]

Other clinical considerations for PTD management include: 1) cultural values, both with regard to how they contribute to depression and how they impact perceptions about treatment;[159] 2) pain, which co-occurs frequently with depression[160] and should be managed as part of prevention and treatment of mental health conditions;[114] 3) personalized risk and treatment response, based on personal biology and/or personal genetics,[161,162] an emerging field that requires further study.

The evidence to support PTD treatment continues to grow, with multiple avenues to explore further. However, even the most evidence-based treatments are only effective for certain individuals. Overall, no single PTD treatment is likely to be universally effective and, therefore, personalized approaches to the research and management of PTD are necessary. The Rehabilomics framework is one tool to operationalize the multifactorial nature of PTD and provides the necessary theoretical groundwork to advance our understanding and management of PTD in the emerging practice of personalized medicine.

Disclosure

The authors report no conflicts of interest in this work.

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