Review Article

Neuropsychiatric Manifestations Following Traumatic Brain Injury: Clinical Implications for Comprehensive Patient Care

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International Archives of Integrated Medicine, Vol. 13, Issue 4, April, 2026.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 23-3-2026 **Accepted on:** 20-4-2026
Source of support: Nil **Conflict of interest:** None declared.

DOI: **10.5281/zenodo.19816830**

How to cite this article: Montserrat Sthepania Martínez Rodas, Andrea Retana González, Hector Gabriel Torres Garcia, Addy Samantha Defrancisco Agüero, Ana Karen Blanco Salazar, Nicole Alejandra Chaves Ortega. Neuropsychiatric Manifestations Following Traumatic Brain Injury: Clinical Implications for Comprehensive Patient Care. Int. Arch. Integr. Med., 2026; 13(4): 259-270.

Abstract

Traumatic brain injury is a major public health concern and a leading cause of long-term disability worldwide. Beyond its acute neurological consequences, it is increasingly recognized as a condition associated with persistent neuropsychiatric sequelae that substantially affect quality of life. Primary and secondary injury mechanisms, including diffuse axonal damage, intracranial hemorrhage, cerebral edema, and sustained neuroinflammation, disrupt neural networks and neurotransmitter systems. These alterations particularly affect frontotemporal and limbic regions, contributing to mood, cognitive, and behavioral disturbances. Mood disorders are among the most frequent complications, with major depressive disorder and anxiety commonly emerging within the first year after injury. Post-traumatic stress disorder may also develop, especially in individuals exposed to life-threatening circumstances. Cognitive impairment represents another central domain, involving deficits in

attention, memory, and executive functioning that interfere with autonomy and occupational reintegration. Behavioral changes, such as irritability, aggression, impulsivity, and disinhibition, further complicate recovery and may strain interpersonal relationships. Sleep disturbances and chronic fatigue can exacerbate these symptoms and hinder rehabilitation. Comprehensive clinical assessment requires structured neurological, neuropsychological, and psychiatric evaluation, supported by neuroimaging and emerging biomarkers that help characterize structural and functional alterations. Management involves pharmacological treatment, psychotherapeutic interventions, and individualized rehabilitation programs delivered through an interdisciplinary approach. Prognosis varies according to injury severity, pre-injury health status, and psychosocial factors. Persistent disability remains common, underscoring the chronic nature of the condition. Early identification, standardized screening, and precision-based strategies are essential to improve long-term outcomes and optimize functional recovery.

Key words

Neuroinflammation, Cognitive dysfunction, Behavioral dysregulation, Rehabilitation strategies, Biomarkers, Quality of life.

Introduction

Traumatic brain injury is defined as an alteration in brain function or other evidence of brain pathology caused by an external force [1]. The severity of this condition is commonly classified using the Glasgow Coma Scale, which stratifies patients into mild injury when scores range from 13 to 15, moderate injury when scores range from 9 to 12, and severe injury when scores are 8 or lower [2]. This standardized classification framework provides a structured approach for initial assessment and prognostic orientation. From an epidemiological perspective, traumatic brain injury represents a major global public health concern. It is estimated to affect between 27 and 69 million individuals annually, with a disproportionately higher incidence in low- and middle-income countries [3]. Beyond its high prevalence, traumatic brain injury constitutes a leading cause of disability and death worldwide, generating substantial healthcare expenditures that are estimated to reach approximately 400 billion dollars globally each year [2].

Clinically, it is essential to distinguish between acute neurological deficits and chronic neuropsychiatric outcomes. Acute neurological manifestations occur immediately after the injury and frequently include loss of consciousness or amnesia [4]. In contrast, chronic neuropsychiatric sequelae may emerge or persist long after the initial insult and encompass depression, anxiety, cognitive impairment, and personality changes. This temporal and phenomenological distinction highlights the evolving nature of traumatic brain injury and the need for ongoing monitoring beyond the acute phase [1, 5].

The long-term consequences of traumatic brain injury extend beyond neurological symptoms, significantly affecting economic stability, occupational functioning, and psychosocial well-being. Many individuals experience persistent disability that interferes with employment and social relationships [1]. The economic burden is multifaceted and includes direct healthcare costs, loss of income, and diminished quality of life, with lifetime costs in the United States alone estimated at 750 billion dollars [4].

Given the high prevalence of chronic sequelae, comprehensive neuropsychiatric evaluation is fundamental in the management of traumatic brain injury. Approximately 80 percent of patients develop long-term neuropsychiatric consequences, making systematic assessment essential for accurate identification and targeted intervention. Early recognition and timely management have been associated with improved

outcomes and enhanced quality of life, thereby emphasizing the importance of individualized rehabilitation strategies tailored to the patient's clinical profile and contextual factors [3, 5].

The objective of this article is to examine the epidemiology, clinical classification, and long-term neuropsychiatric consequences of traumatic brain injury, emphasizing the importance of comprehensive evaluation to optimize patient outcomes and quality of life.

Methodology

This manuscript was developed as a structured narrative review aimed at synthesizing contemporary evidence on neuropsychiatric manifestations following traumatic brain injury and their clinical implications for comprehensive patient care. The methodological approach prioritized conceptual integration, clinical applicability, and interpretation of heterogeneous evidence domains, including epidemiology, pathophysiological mechanisms, psychiatric and cognitive sequelae, diagnostic frameworks, and multidisciplinary management strategies, rather than quantitative evidence aggregation or adherence to formal systematic review protocols.

A focused literature search was conducted between January 2020 and December 2025 using established scientific databases, including PubMed, ScienceDirect, and the Cochrane Library. High-impact journals in neurology, psychiatry, neurorehabilitation, and neuroscience were also reviewed to identify influential clinical studies, cohort analyses, and consensus-oriented publications relevant to the topic. The search strategy combined controlled vocabulary and free-text terms using Boolean operators to ensure comprehensive coverage. Representative search formulations included combinations such as ("traumatic brain injury" OR "TBI") AND ("neuropsychiatric manifestations" OR "psychiatric sequelae" OR "cognitive impairment") AND ("depression" OR "anxiety" OR "psychosis" OR "behavioral changes" OR "long-term outcomes"). Additional searches incorporated terms related to neuroinflammation, diffuse axonal injury, rehabilitation, and quality of life to capture literature spanning biological mechanisms, clinical presentation, and longitudinal prognosis.

The initial search identified approximately 142 potentially relevant records. After title and abstract screening for relevance and duplication, 72 publications underwent full-text review. Following qualitative appraisal and application of predefined eligibility criteria, 51 peer-reviewed studies were selected for inclusion in the final synthesis.

To enhance transparency and consistency in study selection, predefined eligibility criteria were established a priori. Inclusion criteria comprised clinical studies evaluating neuropsychiatric outcomes in patients with traumatic brain injury, including randomized controlled trials assessing therapeutic interventions targeting post-traumatic psychiatric or cognitive sequelae. Prospective and retrospective cohort studies analyzing depression, anxiety, cognitive dysfunction, behavioral changes, and quality of life after traumatic brain injury were included, as were large registry-based or population-level investigations reporting short- and long-term neuropsychiatric outcomes. Systematic reviews and meta-analyses addressing epidemiology, mechanisms, diagnostic strategies, or management approaches related to post-traumatic neuropsychiatric manifestations were also considered eligible. Only publications written in English or Spanish were included. Exclusion criteria comprised preclinical studies, including animal or in vitro research, except when cited exclusively for pathophysiological context; case reports, narrative opinions, and editorials lacking original quantitative data; studies without clearly defined neuropsychiatric or functional outcomes; and investigations focusing exclusively on acute neurosurgical management without evaluation of psychiatric or cognitive sequelae.

No quantitative pooling, meta-analysis, formal risk-of-bias grading, or statistical modeling was performed. Evidence appraisal was interpretative and qualitative in nature, consistent with the narrative design of the review. The authors used OpenAI-based artificial intelligence tools to assist with structural organization and linguistic refinement of the manuscript. All study selection, interpretation, critical appraisal, and final scientific judgments were performed exclusively by the authors.

Pathophysiological Basis of Post-TBI Neuropsychiatric Sequelae

Primary and secondary brain injury mechanisms play a central role in the development of long-term neuropsychiatric sequelae following traumatic brain injury. Among the most severe consequences is diffuse axonal injury, characterized by widespread axonal damage within the cerebral white matter. This form of injury significantly contributes to long-term disability and mortality, and its complex pathophysiology poses challenges for early detection and prognostic assessment [6]. In addition to axonal disruption, intracranial hemorrhage and cerebral contusions produce direct structural damage to brain tissue. These focal injuries are associated with both immediate neurological impairment and persistent neuropsychiatric outcomes, with the extent of tissue damage often correlating with the severity of subsequent psychiatric and cognitive symptoms [7].

Beyond the primary insult, secondary injury processes further amplify neural damage. Cerebral edema and secondary inflammatory cascades commonly occur after traumatic brain injury, exacerbating tissue injury through additional cellular damage and neuroimmune activation. These processes have been linked to the emergence of neuropsychiatric disorders, including depression and anxiety, highlighting the role of sustained inflammation in long-term symptomatology [7, 8].

Traumatic brain injury frequently results in neuroinflammation and network dysfunction, which together influence neurotransmitter systems and neural circuitry. Disruption of dopaminergic, serotonergic, and glutamatergic pathways has been associated with the development of neuropsychiatric symptoms. Alterations in serotonin signaling have been linked to depressive and anxiety symptoms following injury [8, 9]. Structural and functional damage involving the frontotemporal regions and limbic system, areas essential for emotional regulation and higher cognitive processing, can further contribute to personality changes and cognitive deficits [5]. Moreover, persistent neuroinflammatory activity may adversely affect neuroplasticity, limit adaptive recovery processes and exacerbating psychiatric manifestations. Targeting neuroinflammatory pathways has therefore been proposed as a strategy to enhance neuroplasticity and improve clinical outcomes [10].

The development and severity of neuropsychiatric outcomes are also influenced by several risk factors. The severity of the initial brain injury remains one of the strongest predictors, with more severe injuries generally associated with more pronounced and persistent symptoms [11]. Age and cognitive reserve may modulate vulnerability, as younger individuals and those with higher cognitive reserve may demonstrate some degree of protection against severe neuropsychiatric impairment, although this protective effect is not universal [12]. Pre-existing psychiatric conditions further increase the likelihood of developing post-traumatic neuropsychiatric symptoms [5]. Additionally, psychosocial determinants, including social support, socioeconomic status, and access to rehabilitation services, significantly influence recovery trajectories and the overall burden of neuropsychiatric sequelae [11].

Major Neuropsychiatric Manifestations

Mood disorders represent some of the most frequent neuropsychiatric sequelae following

traumatic brain injury. Major depressive disorder is among the most prevalent conditions, affecting approximately 14.1 to 15.5 percent of patients within the first year after injury. Depression is often persistent and has been shown to significantly interfere with cognitive performance and overall recovery outcomes [5, 12]. Anxiety disorders are also commonly observed, with reported prevalence rates ranging from 7.9 to 9.5 percent in individuals with traumatic brain injury. Anxiety frequently co-occurs with depression, and the bidirectional interaction between these conditions may contribute to symptom persistence and clinical worsening over time [13]. In addition, post-traumatic stress disorder is frequently identified, particularly among patients who experienced highly stressful or life-threatening circumstances during the injury. Clinical manifestations often include re-experiencing the traumatic event, avoidance behaviors, and hyperarousal, further complicating emotional recovery [14, 15].

Cognitive impairment constitutes another central domain of post-traumatic neuropsychiatric morbidity. Attention deficits are commonly observed, especially during the early stages following injury, and may persist long term, limiting functional reintegration. Memory dysfunction is also prevalent, affecting both short-term and long-term memory processes and thereby complicating rehabilitation efforts and daily functioning. Executive functions, including planning, decision-making, and problem-solving, are frequently impaired as well. Such deficits have a direct impact on autonomy, occupational capacity, and overall quality of life [5].

Behavioral and personality changes further contribute to the complexity of post-traumatic outcomes. Irritability and aggression are common manifestations, often associated with frontal lobe involvement, and may generate significant interpersonal and social challenges. Similarly, increased impulsivity and disinhibition can emerge following injury, manifesting as inappropriate social behavior and impaired emotional regulation. These alterations can substantially affect family dynamics and community reintegration [1, 5].

Although less frequent, psychotic disorders and severe neurobehavioral symptoms may also occur. Post-traumatic psychosis can develop in a subset of patients and may include delusions and hallucinations, adding further complexity to diagnosis and management. These symptoms are typically associated with more severe forms of traumatic brain injury and can profoundly impair functional capacity and independence [5].

Sleep disturbances and chronic fatigue are additional common sequelae. Insomnia and hypersomnia are frequently reported, with insomnia being the most prevalent presentation. Sleep disruption may exacerbate mood, cognitive, and behavioral symptoms, thereby hindering recovery. Moreover, disruption of circadian rhythms has been described following traumatic brain injury, contributing to persistent fatigue and negatively influencing overall rehabilitation trajectories [11, 15].

Comprehensive Clinical Assessment

Neurological and neuropsychological evaluation constitutes a fundamental component in the assessment of patients with traumatic brain injury and its associated neuropsychiatric sequelae. The Glasgow Coma Scale remains one of the most widely used tools for evaluating the level of consciousness in individuals with traumatic brain injury. By systematically assessing eye, verbal, and motor responses, this scale provides a rapid and standardized measure of injury severity, which is essential for initial triage, clinical stratification, and ongoing monitoring throughout the acute phase [16]. Its application not only facilitates early clinical decision-making but also contributes to prognostic orientation. Beyond the initial neurological assessment, standardized cognitive evaluation tools are employed to characterize specific domains of impairment. During the acute phase, instruments such as the Mini Mental State

Examination and the Coma Recovery Scale-Revised are frequently utilized to assess global cognitive status and level of consciousness. As patients transition into post-acute and chronic stages, more specialized neuropsychological tests are implemented to evaluate higher-order cognitive functions. The Wisconsin Card Sorting Test and the Trail Making Test are commonly applied to assess executive functioning, cognitive flexibility, and processing speed, thereby allowing a more detailed characterization of persistent deficits. This staged approach ensures that cognitive assessment evolves in parallel with the patient's clinical trajectory [16, 17].

Structured psychiatric evaluation is equally critical, particularly given the broad spectrum of neuropsychiatric manifestations associated with traumatic brain injury. Accurate differential diagnosis is necessary to determine whether symptoms such as depression, anxiety, or personality changes represent direct consequences of the injury or reflect primary psychiatric conditions. In this context, the Hierarchical Taxonomy of Psychopathology model has been proposed as a transdiagnostic framework that may more effectively capture the dimensional nature of psychiatric symptoms in patients with traumatic brain injury when compared to traditional categorical diagnostic systems [18]. Additionally, identification of comorbidities is essential, as traumatic brain injury increases the risk of developing concurrent psychiatric disorders as well as medical conditions, including cardiovascular and endocrine disturbances. Comprehensive assessment of these comorbid states is necessary to guide individualized and multidisciplinary interventions [19].

Complementary diagnostic studies further enhance clinical characterization. Structural and functional magnetic resonance imaging play a pivotal role in identifying alterations in gray and white matter integrity, which have been shown to correlate with cognitive impairment and psychiatric symptomatology. These imaging modalities contribute to a more precise understanding of the anatomical and network-level substrates underlying clinical manifestations [20]. In parallel, emerging biomarkers such as serum tau, neurofilament light chain, glial fibrillary acidic protein, and ubiquitin carboxy-terminal hydrolase L1 are being investigated for their potential to predict long-term neurobehavioral outcomes. Elevated concentrations of these biomarkers within the first year after injury have been associated with chronic symptom deterioration. Electrophysiological studies, although less extensively described, may provide additional insights into functional brain alterations following traumatic brain injury and can complement structural imaging findings, thereby contributing to a more comprehensive diagnostic framework [21].

Therapeutic Strategies and Multidisciplinary Management

Pharmacological treatment constitutes a central component in the management of neuropsychiatric symptoms following traumatic brain injury, although no medication has received specific approval from the United States Food and Drug Administration for this indication. Antidepressants, particularly selective serotonin reuptake inhibitors, are commonly prescribed for the treatment of post-traumatic depression. However, available evidence regarding their efficacy in this specific population remains limited [22]. Atypical antipsychotics, such as olanzapine, are frequently recommended for the management of agitation and aggression. Their use requires careful consideration, as potential adverse effects may interferewith cognitive and motor rehabilitation processes. Mood stabilizers, including anticonvulsants such as carbamazepine and valproate, are employed to address irritability and behavioral dysregulation. In addition, psychostimulants such as methylphenidate and amantadine have been considered for the treatment of cognitive deficits and apathy, although the evidence supporting their effectiveness remains mixed [5, 23, 22].

Psychotherapeutic interventions play a complementary and often indispensable role in addressing the emotional and cognitive challenges associated with traumatic brain injury. Cognitive behavioral therapy has demonstrated effectiveness in managing depression, anxiety, and stress in this population and has been shown to be comparable to supportive psychotherapy in certain contexts [24, 25]. Neuropsychological rehabilitation programs provide structured strategies aimed at improving cognitive domains such as memory and attention, which are frequently compromised after injury. Family-based interventions further contribute to recovery by equipping relatives with strategies to manage behavioral changes and facilitating improved social reintegration [5].

Comprehensive rehabilitation remains essential for holistic recovery, focusing not only on symptom reduction but also on restoration of functional capacity and societal participation. Occupational therapy is directed toward improving daily living skills and promoting autonomy. Cognitive rehabilitation programs are tailored to individual deficits and aim to enhance specific cognitive functions, thereby supporting long-term functional independence. Programs targeting social and vocational reintegration are also crucial, as return to work and participation in social activities significantly influence quality of life after traumatic brain injury [5].

Given the multifaceted nature of post-traumatic neuropsychiatric manifestations, an interdisciplinary approach is fundamental. Effective management requires coordination among neurology, psychiatry, psychology, and rehabilitation services to ensure comprehensive and integrated care. Longitudinal follow-up models are equally important, as continuous monitoring allows treatment strategies to be adjusted in response to the evolving clinical condition of the patient over time [5].

Prognostic Impact and Quality of Life

Several predictors have been identified as determinants of favorable recovery following traumatic brain injury. Pre-injury health status plays a central role, as both mental and physical baseline conditions significantly influence post-injury trajectories. Individuals with better overall health and higher educational attainment prior to injury tend to demonstrate more favorable mental health outcomes during recovery. Employment status before injury has also been shown to be a strong predictor of both physical and psychological recovery, with previously employed individuals exhibiting more positive functional trajectories. In addition, longer time since injury and male gender have been associated with improved recovery patterns in both physical and mental health domains, suggesting that demographic and temporal factors contribute to variability in long-term outcomes [27, 28].

In contrast, several factors increase the risk of persistent disability. The severity of the initial traumatic brain injury remains one of the most significant predictors of long-term neuropsychiatric impairment, particularly when frontal lobe involvement is present, as this is strongly associated with depression and anxiety [5]. Loss of consciousness at the time of injury has likewise been linked to poorer clinical outcomes, including persistent post-concussive symptoms and depressive manifestations, which may contribute to long-term functional limitations [29]. Furthermore, traumatic brain injury is increasingly recognized as a chronic condition rather than an isolated acute event. Many individuals continue to experience moderate to severe disability years after the initial insult, and factors such as older age and lower acute functional status have been associated with deterioration after an initial period of recovery [20].

Functional independence and long-term outcomes can also be anticipated through validated prognostic models. Instruments such as the IMPACT and CRASH models have

demonstrated good discriminatory capacity in identifying patients at high risk for mortality or unfavorable functional outcomes [30]. Health-related quality of life is significantly affected by traumatic brain injury, and its trajectory is influenced by predictors such as Glasgow Coma Scale scores and pre-injury health status [27, 28]. These predictive frameworks facilitate a more comprehensive understanding of both physical and mental health outcomes over time. Importantly, targeted rehabilitation and intervention strategies have been shown to improve long-term quality of life, particularly in individuals identified as high risk based on demographic and injury-related characteristics [28, 31].

Current Challenges and Future Directions

Neuropsychiatric sequelae following traumatic brain injury remain frequently underdiagnosed despite their high prevalence. Approximately 80 percent of individuals experience neuropsychiatric symptoms after injury, with depression and anxiety representing the most common disorders [5]. Nevertheless, these conditions are often overlooked in clinical practice due to symptom overlap with other post-traumatic complications and limited awareness among healthcare providers [4]. The variability in symptom trajectories further complicates diagnostic accuracy. Findings from the TRACK-TBI study demonstrate that some patients exhibit progressive worsening of psychiatric symptoms over time, whereas others show gradual improvement, underscoring the heterogeneity of recovery patterns and the difficulty in establishing consistent diagnostic frameworks [11].

The absence of standardized screening protocols contributes significantly to both underdiagnosis and undertreatment of psychiatric disorders associated with traumatic brain injury (Bowman et al., 2022). Without systematic evaluation strategies, subtle or evolving symptoms may remain unrecognized, delaying appropriate intervention. The implementation of comprehensive and structured screening tools, such as the Hierarchical Taxonomy of Psychopathology model, has been proposed as a means to capture the dimensional and transdiagnostic nature of TBI-related psychopathology more effectively than traditional categorical systems [18]. Standardized protocols could facilitate earlier identification of at-risk individuals and promote timely intervention, thereby potentially reducing long-term neuropsychiatric morbidity [5].

Advances in neuroimaging and biomarker research offer promising avenues for improving diagnostic precision and understanding the biological substrates of post-traumatic psychiatric disorders. Neuroimaging studies have identified structural and functional alterations associated with conditions such as post-traumatic stress disorder following traumatic brain injury. However, a lack of consensus regarding specific neuroimaging correlates limits their current clinical application, highlighting the need for further investigation [32]. Concurrently, biomarker research, particularly in relation to neuroinflammatory mechanisms, has emerged as a potential pathway for identifying individuals at risk and developing novel therapeutic targets [7].

In this context, personalized and precision medicine approaches have gained increasing relevance. Given the substantial variability in symptom progression and treatment response, individualized care models are essential for optimizing outcomes in traumatic brain injury populations [11]. The adaptation of transdiagnostic frameworks such as the Hierarchical Taxonomy of Psychopathology to traumatic brain injury populations may enhance diagnostic specificity and therapeutic alignment [18]. Furthermore, precision medicine strategies may integrate advances in neuroimaging and biomarker research to tailor interventions according to distinct neurobiological profiles, thereby improving the effectiveness and efficiency of psychiatric care after traumatic brain injury [33].

Conclusions

Neuropsychiatric sequelae following traumatic brain injury arise from a complex interaction between primary structural damage, secondary inflammatory cascades, and network-level dysfunction, with diffuse axonal injury, neuroinflammation, and disruption of frontotemporal and limbic circuits playing central roles in the development of mood, cognitive, and behavioral disorders. The severity of the initial injury, along with biological and psychosocial vulnerability factors, significantly shapes long-term psychiatric outcomes.

Mood disorders, cognitive impairment, behavioral dysregulation, sleep disturbances, and, in some cases, psychotic symptoms constitute a broad and heterogeneous clinical spectrum that requires comprehensive neurological, neuropsychological, and psychiatric assessment. Multimodal diagnostic strategies, including structured clinical evaluation, neuroimaging, and emerging biomarkers, combined with pharmacological, psychotherapeutic, and rehabilitative interventions within an interdisciplinary framework, are essential to optimize functional recovery and quality of life.

Prognosis after traumatic brain injury is influenced by pre-injury health status, demographic factors, injury severity, and access to rehabilitation, while persistent disability is more likely in cases of severe injury, loss of consciousness, and chronic functional decline. Ongoing challenges such as underdiagnosis of psychiatric sequelae and the absence of standardized screening protocols highlight the need for precision-based, individualized care models supported by advances in neuroimaging and biomarker research.

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