Published in final edited form as:
Psychiatr Clin North Am. 2014 March ; 37(1): 13–29. doi:10.1016/j.psc.2013.11.005.

Mood Disorders after TBI

Ricardo E. Jorge[1,2] and **David B. Arciniegas**[2,3]

[1]Mental Health Care Line, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA

[2]Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA

[3]Brain Injury Research Center, TIRR Memorial Hermann, Houston TX, USA

Synopsis

In this article, we will examine the epidemiology and risk factors for the development of the most common mood disorders observed in the aftermath of TBI: depressive disorders and bipolar spectrum disorders. We will describe the classification approach and diagnostic criteria proposed in the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-V). We will also examine the differential diagnosis of post-TBI mood disorders and describe the mainstay of the evaluation process. Finally, we will place a special emphasis on the analysis of the different therapeutic options and provide guidelines for the appropriate management of these conditions.

Introduction

Disorders of mood are common consequences of traumatic brain injury (TBI). The pathophysiology of mood disorders involves the interaction of factors that precede trauma (e.g., genetic vulnerability and previous psychiatric history), factors that pertain to the traumatic injury itself (e.g., type, extent and location of brain damage) and factors that influence the recovery process (e.g., family and social support). In some cases, especially in the early period following TBI, mood disturbance may reflect the effects of neurotrauma on the distributed neural networks that generate and regulate emotion.[1] In some cases, especially those in which depressive disorders develop in the late post-injury period, psychological and social factors appear to be etiologically important.[1, 2]

Mood disorders occur in the context of significant deficits in cognitive and emotional processing that may result from TBI. Individuals are challenged by deficits of which, in some cases, they are only partially aware. Consequently, life stressors increase and, in many cases, social support is reduced. These changes may lead to a disturbed and poorly integrated self-representation as well as to dysfunctional interpersonal relationships that increase the subjects' vulnerability to develop an affective episode. The high frequency and functional importance of disorders of mood among persons with TBI makes this an important topic for clinicians to understand.

Corresponding Author: Ricardo Jorge, MD, One Baylor Plaza, BCM350, Houston, TX, 77030, jorge@bcm.edu.

Depressive Disorders

Epidemiology

Depressive disorders develop commonly among persons with TBI, with estimated frequencies ranging from 6-77%.[3] Within this range, most experts on this subject accept an estimated first-year post-TBI depression frequency in the range of 25-50%[3, 4] and lifetime rates of 26-64%.[5, 6] The variability in the reported frequency of depressive disorders is related to the heterogeneity of the study groups as well as to the instruments used to ascertain a diagnosis of depression. In fact, many of the aforementioned studies have used arbitrary cut-offs in depression scales rather than conducting structured interviews and using accepted diagnostic criteria. We have studied the frequency and clinical correlates of depressive disorders occurring during the first year after TBI in two independent samples of TBI patients recruited from an urban population in Maryland and a mostly rural population in Iowa. Depression diagnosis was made using a semi-structured interview and the DSM nomenclature. In our studies, the frequency of major depression was 42% and 32%, respectively. Of note, depressive disorders were significantly more frequent among TBI patients than in a control group of patients with orthopedic injuries. This suggests that the pathological processes associated with TBI constitute an important contributing factor to the development of mood disorders.[7, 8]

In our experience, depressive disorders following TBI were significantly associated with the presence of anxiety disorders. Approximately three quarters of patients with depression had a coexistent anxiety disorder[8]; this finding that was replicated in a recent prospective study that used a similar methodology.[9] In addition, major depression was associated with the occurrence of aggressive behavior[10] that, as expected, contributed to the deleterious effects of depression on community reintegration.

More recently, a study of 559 adults with complicated mild to severe TBI found that approximately half of patients (53.1%) developed major depression during the first year after TBI. Consistent with previous studies, major depression was frequently associated with significant anxiety, a history of affective illness, and a history of substance misuse.[11]

Although the risk of developing depression is generally regarded as being highest in the first post-injury year, the risk of this condition remains increased even decades after TBI. Hart et al. (2012)[12] analyzed the course of depressive disorders in the second year after TBI in a large sample (n=1089) of subjects enrolled in the Traumatic Brain Injury Model Systems database. Approximately a fourth of patients who were not depressed during the first year following TBI developed depressive disorders during the second year. In addition, approximately two-thirds of subjects who were depressed during the first year after TBI continued to show significant depressive symptoms during the second year of follow-up.[12] Consistent with these observations in the early years after TBI, Koponen et al.[5] reported that major depression had a lifetime prevalence of 26.7% in a group of 60 TBI patients followed for an average of 30 years.

Risk Factors

Genetic, demographic, developmental and psychosocial factors, as well as their complex interactions, influence the risk of depression following TBI. There is no consistent data regarding the effect of age on the onset of mood disorders, particularly depression. While some studies suggest that the frequency of psychiatric disorders and depression is greater among younger patients,[13, 14] other investigators reported that depression is significantly more common in elderly patients.[15] A recent study reported a higher frequency of depressive symptoms in women than in men during the first 6 months after TBI.[16] However, there were no persistent gender differences in this study group at 1 year post-injury, and the

mechanisms of early differences were not identified in this work. The issue of whether there are gender differences in depression following TBI remains unresolved, with a more recent study by our group finding no such effect.[8, 17]

The literature investigating the effect of genetic factors for the development of depressive disorders after TBI is relatively scarce. A recent study examined the association between APOE-epsilon4 genotype and psychiatric disorders among 60 patients assessed an average of 30 years after severe TBI.[18] Cognitive disorders were significantly more common with the presence of APOE-epsilon4. The frequency of mood disorders, however, did not differ between patients with or without APOE-epsilon4 allele.

Polymorphisms in genes coding for proteins involved in the regulation of monoaminergic systems and of the hypothalamus-pituitary-adrenal axis (e.g., 5HTT-P, tryptophan hydroxylase, MAO, COMT, FKBP5) and the interactions between genetic polymorphisms and environmental influences[19] might play a role on the likelihood of developing mood disorders.[20-29] Unfortunately, the effect of these factors on the psychiatric consequences of TBI has not been extensively studied and the effect sizes of those that have been identified are modest. Genetic polymorphisms modulating central dopaminergic pathways can affect prefrontal function following traumatic brain injury.[30, 31] However, it is not known if they have an effect on depressive disorders. Although a recent study failed to demonstrate an association between 5HTT polymorphisms and depression following TBI,[32] response to citalopram in this population is influenced by genotype, with adverse treatment effects occurring more frequently among persons with specific 5HTT polymorphisms and favorable treatment response predicted by the C-(677) T polymorphism of the methylene tetrahydrofolate reductase (MTHFR) gene and the val66met polymorphism of the brain-derived neurotrophic factor (BDNF) gene.[33]

Early psychosocial adversity (e.g., history of physical or sexual abuse), life stress and limited social support are also well recognized risk factors for the development of psychiatric illness.[34, 35] These factors have not been extensively studied among TBI populations. We found, however, that personal history of mood and anxiety disorders and previous poor social functioning are associated with the occurrence of major depression in the aftermath of TBI.[8, 36] Furthermore, Fann et al. (2004)[37] observed that, the risk of psychiatric illness is highest shortly following injury in persons with no psychiatric history, was unrelated to the severity of TBI, and appeared to increase in subsequent years in persons with previous psychiatric disorders.[37] This suggests that the effect of different risk factors vary over time and that psychosocial factors might be more relevant in the chronic stages of TBI.

It is well known that alcohol misuse is a significant risk factor for TBI, particularly when the latter occurs as a consequence of motor vehicle accidents or assault. We have recently examined the relationship between alcohol misuse and the frequency of mood disorders among a group of 158 patients followed for a year after TBI. Of the 55 TBI patients with a history of alcohol misuse, 33 (60%) developed a mood disorder during the first year of follow-up compared with 38 (36.9%) of 103 patients without a history of alcohol misuse.[38] Furthermore, three quarters of patients who abused alcohol in the year after their TBI had a coexistent mood disorder.[38]

Diagnostic Assessment

Depressive disorders imply a pervasive and sustained alteration of emotion and affect that fundamentally alters one's way of being-in-the-world. As such, it impacts function in a wide variety of areas ranging from cognition to occupational performance and quality of life. The pervasive and, for many patients, recurrent nature of this alteration is essential for current

classification schemes and helps to differentiate these disorders from other common emotional disorders among persons with TBI – especially the transient (i.e., moment-to-moment) disturbances of emotional expression and experience that occur in this population, including emotional (or affective) lability and pathological laughter and crying (or pseudobulbar affect).

During the past two decades, investigators strived to categorize psychiatric disturbances occurring after TBI within a common and reliable framework established by the DSM nomenclature. Standard diagnostic criteria for depression are appropriately applied to the diagnosis of depression among persons with TBI.[1] Overall, following the recently introduced DSM-V revision, depressive disorders associated with TBI are categorized as Mood Disorder Due to Another Medical Condition (TBI) with the following subtypes: 1) with major depressive-like episode (if the full criteria for a major depressive episode are met); 2) with depressive features (prominent depressed mood but full criteria for a major depressive episode are not met); and 3) with mixed features (when the predominant depressed mood coexist why manic-like symptoms).

Among patients with a preexisting mood disorder or whose depression develops in the late post-injury period, it may be more difficult to establish confidently that the depressive episode is a direct physiologic consequence of TBI. In such circumstances, a conservative approach is to indicate a diagnosis of depressive disorder not otherwise specified (NOS) and to regard TBI as important and a possible treatment-informing comorbidity rather than as a critical etiological factor.

Structured or semi-structured psychiatric interviews are useful to elicit a diagnosis of depression (and other psychiatric disorders) after TBI.[39, 40] After establishing a categorical diagnosis of depression, symptom severity may be assessed using scales that are valid and reliable in this population. Particularly useful scales include the Beck Depression Inventory (BDI),[41] Hamilton Depression Scale (HAM-D),[7] Neurobehavioral Functioning Inventory Depression Scale,[42] or the Center for Epidemiologic Scales for Depression.[39] Clinician-administered scales offer advantages over self-report instruments, particularly among persons with limited insight due to TBI. Administration at the initial assessment and serially during the course of treatment provides information regarding the efficacy of interventions and may serve as an educational tool during psychotherapy.

Differential Diagnosis

The differential diagnosis of post-TBI depressive disorders includes, but is not limited to, delirium-associated mood disturbances, substance-related mood disturbances (including those related to substance intoxications, withdrawals or medication induced), adjustment disorder with depressed and or anxious mood, pathological laughter and crying, posttraumatic stress disorder (PTSD), posttraumatic apathy, personality change due to a general medical condition (especially labile type), and pre-TBI depressive disorders.

Pre-TBI mood (and especially depressive) disorders are common among persons with TBI[6, 43] and must be included in the differential of any post-TBI depressive disorder. When such disorders are part of the pre-TBI history, it may not be possible to assert the role of TBI in the development and maintenance of post-injury depressive disorders. In these cases, it is important to observe is there have been a significant change in the clinical presentation of the current episode compared to the ones that occurred in the past (e.g., the occurrence of prominent aggression or significant cognitive alterations) that might point to the relevance of the incident structural or functional brain damage.

Depressive symptoms may develop during post-traumatic delirium or along a substance withdrawal syndrome. These symptoms are usually evident as such rather than forming part of a depressive syndrome by virtue of the co-occurrence of other symptoms (e.g., deficits in attention, fluctuating course or autonomic instability) related to the pathophysiology of delirium. They tend to be labile and resolve in concert with the medical conditions underlying them. Medication-induced depressive symptoms are often more challenging to identify as such and, when suspected, tapering or discontinuing potentially causative medication is appropriate.

Adjustment disorders are related to the occurrence of a life stressor (e.g., a motor vehicle accident), develop within 3 months of that stressor, and comprise a host of depressive and anxiety symptoms that are more transient and less severe than those observed in depressive disorders. In addition, they have significantly less impact on occupational and social functioning.

Apathy is frequently observed among TBI patients, particularly those with more severe injuries, and may be mistaken for, or comorbid with, depression.[3, 44] Apathy is a syndrome of diminished goal-directed behavior (as manifested by lack of effort, initiative and productivity), cognition (as manifested by decreased interests, lack of plans and goals, and lack of concern about one's own health or functional status), and emotion (as manifested by flat affect, emotional indifference, and restricted responses to important life events).[45] Apathy is distinguished from depression by virtue of the absence of the core psychological symptoms of depression (i.e., the apathetic patient is better described as “emotionally neutral” or “emotionally absent” than as one experiencing persistent and excessive sadness that negatively valences and distorts appraisal of the self, world, and future).

PTSD is also within the differential diagnosis for depression after TBI, and often these conditions coexist in the same individual. The presence of PTSD is suggested by re-experiences of the trauma through flashbacks or vivid nightmares, avoidance of circumstances related to the trauma, and emotional withdrawal or blunting. As the treatment for comorbid PTSD and depression differs from the treatment of depression alone, identification of this comorbidity is essential.

Pathological laughter and crying, also called pseudobulbar affect, is in the differential diagnosis for depression among persons with TBI. It is characterized by the presence of stereotyped, sudden and uncontrollable affective outbursts (e.g., crying or laughing). These emotional displays may occur spontaneously or may be triggered by minor stimuli. This condition lacks the pervasive alteration of mood, as well as the specific vegetative symptoms associated with a depressive episode.

Ancillary Studies

Physical examination, including a complete neurological exam, is a requisite element of the initial evaluation along with conventional radiological procedures such as brain CT scans or, in certain cases, a brain MRI. Other neuroimaging techniques such as quantitative MRI, diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (^{1}HMRS), functional MRI (fMRI) and positron emission tomography (PET) are increasing our understanding of the neurobiological bases of behavioral disorders among persons with TBI. However, these sophisticated research based techniques require further validation before they can be routinely used in clinical and forensic settings. Quantitative EEG and more complex electrophysiological responses may be relevant to the study of depression among persons with TBI[46, 47] but have not been incorporated to clinical practice. If the history or examination suggests endocrine or diagnostically relevant physical conditions, then performing problem-focused laboratory studies are appropriate.[48] In light of the relatively

high frequency of neuroendocrine abnormalities in this population,[49] screening for thyroid and growth hormone dysfunction is encouraged as part of the pre-treatment depression evaluation. The American Psychiatric Association also suggests that physicians consider screening persons with depression for human immunodeficiency virus infections,[48] and encourages pre-treatment urine and/or serum toxicology screening for alcohol and other substances of abuse.

Psychotherapy

Education regarding TBI and recovery expectations, reassurance, and frequent support is recommended as a part of all treatment plans for persons with these disorders.[50, 51] Cognitive behavioral therapy (CBT) may decrease depressive, anxious, and anger symptoms as well as improve problem-solving skills, self-esteem, and psychosocial functioning following TBI.[52, 53] Behavioral interventions such as the Differential Reinforcement of Other Behavior (DRO) may successfully reduce the frequency of problematic behavior.[54] In addition, psychotherapy groups implemented in post-acute rehabilitation settings may focus on treatment of substance abuse and anger management through education, social support, and development of interpersonal skills.[55] More recently, Bell et al. (2004)[56] demonstrated the feasibility of using the telephone as a means of providing education and psychotherapeutic support during the first year after moderate to severe traumatic brain injury.[56] Furthermore, in a recent study of 132 children with TBI, a web-based counselor-assisted problem-solving intervention was shown to be efficacious to improve behavioral outcomes, including emotional wellbeing as rated by their primary caregivers.[57]

Peer support programs for persons with TBI and their families increase their knowledge about TBI, enhance coping with depression, and improve quality of life.[58] Attending to the psychological needs of spouses, families, and caregivers of persons with TBI is also important – post-TBI depression is strongly associated with significant family dysfunction[59] and depression is common among caregivers of persons with TBI.[60] Helping family members develop problem-solving and behavioral coping strategies also appears to decrease the severity of depression in the family member with TBI.[61] Engaging both the patient and also their family members therefore is essential in the treatment of depression following TBI.

Pharmacotherapy

In general, the medications used to treat idiopathic depressive disorders are useful for the treatment of depression among persons with TBI. As with any medication intervention, clinicians are encouraged to refer to the product information sheet provided by the drug manufacturer for warnings and special considerations relevant to TBI as well as for information on side effects, drug-drug interactions, treatment risks, and treatment contraindications before prescribing these or any other medications.

The selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) may improve depression following TBI.[62] Effective treatment of post-TBI depression with SSRIs also reduces comorbid irritability and aggression[63] as well as the number and perceived severity of co-occurring somatic and cognitive symptoms.[64, 65]

Concerns about both the tolerability and effectiveness of TCAs in this population lead most experts to regard them as second-line pharmacotherapies for depression after TBI and to recommend SSRIs as the first-line agents for this purpose. Among the SSRIs, sertraline and citalopram are favored in light of their beneficial effects, relatively limited side effects, and short half-lives. The use of other SSRIs, especially fluoxetine and paroxetine, is limited by their relatively greater potential for adverse effects and drug-drug interactions. For example,

fluoxetine is a robust inhibitor of cytochrome P450 (CYP450) enzymes 2D6, 2C19, and 3A and is associated with problematic drug-drug interactions when co-administered with a substrate, inhibitor, or inducer of these enzymes. Paroxetine also is potent inhibitor of CYP450 2D6 and 2C19 and its significant anticholinergic effects increase the risk of treatment-related cognitive dysfunction even among healthy adults.[66] These issues limit enthusiasm for the use of fluoxetine or paroxetine to treat depression among persons with TBI.

Methylphenidate also has been compared to sertraline and placebo in a small double-blind, parallel-group study.[67] Both agents improved depression and methylphenidate – but not sertraline – also improved neuropsychological performance. Gualtieri and Evans (1988)[68] also observed similar methylphenidate-induced benefits on depression after TBI. Although methylphenidate would be an uncommon first-line intervention for depression after TBI in an outpatient setting, it may be useful for this purpose in an inpatient (including acute rehabilitation) setting or when a rapid therapeutic response is required. Early positive responses to methylphenidate in such circumstances are generally followed by a transition to maintenance therapy with an SSRI. Methylphenidate and other stimulants, including dextroamphetamine, are also used commonly to augment partial responses to SSRIs, especially when cognitive impairments and/or fatigue are residual symptoms during treatment with conventional antidepressants.

The efficacy and tolerability of other antidepressants, including the serotonin-norepinephrine reuptake inhibitors, bupropion, and the monoamine oxidase inhibitors (MAOIs), for the treatment of depression among persons with TBI are not well established. Many of these agents are used commonly in clinical practice and, in general, they appear to be similar to the SSRIs with respect to their benefits and adverse effects. However, using of MAOIs is discouraged among persons with cognitive or other neurobehavioral impairments likely to reduced adherence to their dietary restrictions. Bupropion also is of concern in light of it propensity for lowering seizure threshold. This risk is greatest with the immediate-release form of bupropion.[69] Accordingly, using the sustained-release form of bupropion is prudent in this population and maintaining heightened vigilance for treatment-related seizures during treatment initiation and dose escalation is essential.

Amantadine, a drug with complex pharmacologic effects on glutamatergic, dopaminergic, cholinergic systems might be of some use for the treatment of motivational deficits[70, 71] and has shown beneficial to hasten recovery of patients with severe TBI and post-traumatic disorders of consciousness.[72] However, there are no data demonstrating a specific beneficial effect of amantadine on depression among persons with TBI.

Electroconvulsive Therapy and Brain Stimulation Techniques

Electroconvulsive therapy (ECT) may be used to treatment of depression among persons with TBI who fail to respond to other interventions. When ECT is used for the treatment of posttraumatic depression, we recommend treatment with the lowest possible energy levels that will generate a seizure of adequate duration (greater than 20 seconds), using pulsatile currents, increased spacing of treatments (two to five days between treatments), and fewer treatments in an entire course (i.e., four to six). If the patient also suffers from significant cognitive (especially memory) impairments due to TBI, non-dominant unilateral ECT is the preferred technique.

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have not been rigorously studied in TBI populations. However, given that TBI patients are more vulnerable to develop seizures in both the acute and chronic

stages of their illness, tDCS and, alternatively, low frequency rTMS, appear to be more suitable options to treat depressive disorders due to TBI.[73]

Vagal nerve stimulation (VNS) and even deep brain stimulation (DBS) of the ventral cingulate cortex might also be considered as a therapeutic option in an individual with unusually severe, treatment refractory and disabling symptoms. However, the use of this intervention among persons with depression following TBI also has not been studied specifically.

Manic, hypomanic and mixed disorders

Epidemiology

Bipolar and related disorders are relatively uncommon consequences of TBI.[74] Estimated frequencies of secondary mania (i.e., an early post-TBI manic, hypomanic, or mixed episode that is unequivocally related to neurotrauma, usually involving right ventral frontal and/or basotemporal injury) range from 1.7-9%.[74, 75] Clinical experience among rehabilitation specialists working in non-psychiatric settings suggests that this condition occurs at a low frequency. In our studies, the frequency of bipolar and related mood episodes among the TBI patients was 9%[76] and 6.5%[76] in Maryland and Iowa; these frequencies are based on relatively small samples (66 and 91 patients, respectively, in these studies). The episodes were short-lasting (i.e., average duration of approximately two months), often involved mixed mood states, and associated with other externalizing features such as aggression and substance misuse.[76] In these patients, mood symptoms not infrequently persisted for as long as six months despite resolution of other cognitive, behavioral, and vegetative manic symptoms.

The estimated lifetime relative risk for bipolar and related disorders after TBI ranges from 1.1 (in a sample of more than 5,000 community-dwelling individuals interviewed in the Epidemiologic Catchment Area study)[74] – a level of risk not statistically different than that of the general population – to five (in a review of five studies comprising 354 clinical subjects).[75] These estimates are influenced strongly by sample sizes, selection biases, and diagnostic ascertainment issues. Unfortunately, there are no studies that had followed patients with bipolar spectrum episodes for an extended period of time (i.e., beyond the first year following TBI). Thus, uncertainty remains with regard to the prognosis and clinical course of persons with such episodes as well as the relationship of their symptoms to primary (idiopathic) bipolar disorder.

Risk Factors

The limited evidence and variable methods used to define and study bipolar and related mood disorders among persons with TBI preclude drawing definitive conclusions about risk factors for these conditions. In our study of early post-TBI mania, we observed no clear relationship between mixed episodes and TBI severity, posttraumatic epilepsy, post-TBI physical or cognitive impairments, level of social functioning, or the presence of family or personal history of psychiatric disorders.[76] Shukla et al. (1987)[77] also observed no relationship between posttraumatic mania and family history of bipolar disorder, but did note associations between post-TBI mania and injury severity (as estimated by duration of posttraumatic amnesia) as well as posttraumatic epilepsy. Complicating matters, the frequency of TBI may be elevated among unaffected family members of persons with bipolar disorder,[78] suggesting the possibility that heritable components of the bipolar phenotype (e.g., increased novelty seeking, reduced harm avoidance and impaired decision making) may increase the risk for TBI. Comorbid alcohol use disorders also affect the apparent, but not actual, risk for bipolar disorder among persons with TBI.[74]

Diagnostic Assessment

The DSM-V categorizes these disorders as bipolar and related disorders due to another medical condition (TBI) with: 1) manic or hypomanic-like episode; 2) with manic features; and 3) with mixed features. Their diagnosis requires the unequivocal presence of: a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least four days for hypomanic episodes or one week for manic episodes. Any other cognitive, vegetative, or behavioral disturbance counted toward that diagnosis must either be clearly related to the pervasive mood disturbance(s) or, if otherwise present, clearly exacerbated during the mood disturbance(s).

Over-diagnosis of mania and mixed states in this population is common in many clinical settings. This problem appears to derive most often from misattribution of TBI-related disturbances in affect regulation (e.g., frequent brief episodes of irritability or laughing), impulsive/disinhibited behaviors, alterations in sleep and appetitive behaviors, and cognitive disturbances to manic-like features despite the absence of the cardinal (mood) disturbance that the diagnosis requires. This distinction is not a matter of semantics: the treatment of paroxysmal disturbances of affect and disinhibited behaviors differ from those offered to persons with bipolar spectrum episodes. In particular, unopposed selective serotonin reuptake inhibitors are prescribed routinely and appropriately for the treatment of posttraumatic disturbances of affect and behavioral dyscontrol syndromes, a practice that is generally inadvisable among persons with secondary mania or mixed states.[79]

The methods used to diagnose manic or mixed episodes among persons with TBI are the same as those use to make primary (idiopathic) diagnoses of these types.[80] Using structured or semi-structured psychiatric interviews to diagnose these conditions is encouraged, and the Young Mania Rating Scale[81] is useful as a measure of symptom severity and treatment response in this population.[82, 83]

Differential Diagnosis

The differential diagnosis of mood disorders with manic, hypomanic or mixed features among persons with TBI is broad and overlaps substantially with that of post-TBI depressive disorders. Several additional conditions merit consideration in this context, including: emotional disturbances associated with delirium; mood disorders due to the effect of drugs, including intoxication and/or withdrawal states; posttraumatic epilepsy; and personality change due to TBI.

Transient euphoric and irritable symptoms may develop during the posttraumatic confusional state, during a post-TBI substance intoxication or withdrawal syndrome, or as a result of some medications, all of which preclude diagnosis of post-TBI mood disorder with manic, hypomanic or mixed features. These symptoms rarely take on the appearance of true mania given their transience, lability, and co-occurrence with other symptoms of an acute confusional state. Such symptoms generally resolve in concert with the conditions in which they arise. When medication-induced manic-like or mixed-mood symptoms are suspected, medication taper and/or discontinuation are appropriate.

Posttraumatic epilepsy and its treatments are associated with the development of emotional disturbances, including manic-like symptoms and/or mixed mood states. Similarly, psychosis associated with epilepsy also may entail the concurrent development of emotional disturbances. Manic or mixed mood episodes that develop in this context may be temporally linked to seizures (or post-ictal psychosis) or may have a more prolonged course.

Finally, personality change due to traumatic brain injury may include mood instability, disinhibited or impulsive behavior and hyperactivity. These patients lack, however, the pervasive and sustained alteration of mood that characterizes manic or mixed syndromes.

Ancillary Studies

The evaluation of persons with TBI and suspected bipolar spectrum disorders follows the general principles and components of a complete psychiatric evaluation as outlined in the American Psychiatric Association's Practice Guideline for Psychiatric Evaluation of Adults.[84] Physical examination, including vital signs and a complete neurological exam, is a requisite element of the initial evaluation.

As aforementioned, structural neuroimaging is a useful component of the evaluation of persons with TBI generally. However, more recent and refined neuroimaging techniques should be reserved for research at the present time. Video-EEG monitoring and 24-hour ambulatory recordings may be useful in the differential diagnosis of patients presenting with paroxysmal behavioral disturbances of unclear etiology or those that are associated with intra- or post-episode alterations of consciousness. This is particularly relevant to the evaluation of persons with TBI and mixed affective episodes in light of the possible associations between such disorders and posttraumatic epilepsy. Otherwise, neurophysiologic studies are not presently regarded as useful elements of the clinical evaluation in this context.

If the clinical history or examination suggest other endocrine or concurrent physical conditions, then performing problem-focused laboratory studies is appropriate.[48, 85] In light of the relatively high frequency of neuroendocrine abnormalities in this population,[49] screening for thyroid dysfunction is encouraged as part of the initial evaluation. As with the evaluation of persons with depression, screening for human immunodeficiency virus infection as well as performing urine and/or serum toxicology screening for alcohol and other substances of abuse is encouraged.

Pharmacotherapy

The literature describing pharmacotherapy of bipolar spectrum disorders among persons with TBI is insufficient to permit the development of formal treatment guidelines.[62] Agents used to treat idiopathic manic and mixed mood states are used to treat bipolar spectrum disorders among persons with TBI. Clinicians are encouraged to refer to each medication's product information sheet as well as other reference materials for complete reviews of dosing, side effects, drug-drug interactions, treatment risks, and treatment contraindications before prescribing these or any other medications. The literature and common clinical experience suggests that most of these medications treat TBI-related manic and/or mixed mood states effectively. Their use in clinical practice therefore is informed by their side effect profile.

Valproate may exacerbate cognitive impairments in some persons with TBI, but it appears less likely to do so than either carbamazepine or lithium.[86-88] Nonetheless, use of any of these agents necessitates careful and continuous assessment for the development of treatment-related motor (e.g., tremor, ataxia, gait disturbances) and cognitive impairments as well as other adverse side effects (e.g., weight gain, gastrointestinal problems, hematologic abnormalities, hepatotoxicity, alopecia, etc.). Additionally, the risk of polycystic ovarian syndrome requires consideration of alternate treatments in females.

Given that lithium carbonate is used often as a first-line treatment among persons with idiopathic bipolar disorder, it merits special comment as a treatment of mixed states among persons with TBI. Intolerance of doses necessary to effect mood stabilization appears to be

more common among persons with TBI than with primary mania or mixed mood episodes. This intolerance is often attributable to the adverse cognitive and motor effects of lithium carbonate, which appears more likely to produce nausea, tremor, ataxia, and lethargy in persons with neurological disorders than in the general psychiatric population. Additionally, lithium carbonate lowers seizure threshold; in light of the risk for posttraumatic epilepsy as well as the potential comorbidity between posttraumatic epilepsy and mania, this effect is concerning with respect to lithium's use in this population. As such, partial response, relapse of symptoms, or need for a second mood-stabilizing medication are common limitations of the use of this agent among TBI patients.

Several of the newer anticonvulsants (e.g., lamotrigine, oxcarbazepine) and the atypical antipsychotics (e.g., risperidone, olanzapine, ziprasidone, aripiprazole, etc.) may be useful in the treatment of posttraumatic manic, hypomanic and mixed states, but there are few published reports of their use. Clinicians interested in using these agents for this purpose are advised to undertake such treatments cautiously and with careful monitoring for adverse cognitive, motor, cardiac, and metabolic side effects.

In the absence of evidence demonstrating the superiority of one of these agents over the others, we generally recommend either valproate or quetiapine as first-line treatments given their effectiveness for acute mania, rapid-cycling bipolar disorder, and anti-manic prophylaxis as well as their reasonable tolerability in persons with TBI. When these agents, alone or in combination, prove ineffective, then the use of one or more of the other agents may be required.

Psychotherapy

The TBI literature provides no clear guidance regarding the psychotherapeutic approach to persons with mania or mixed mood states after TBI. Education and supportive interventions regarding both TBI and also the mood disturbance with which the patient presents are reasonable and common sense interventions. Additional psychotherapeutic interventions are modeled after those used in the management of persons with idiopathic bipolar disorders, as described in the American Psychiatric Association's practice guidelines for the treatment of patients with bipolar disorder.[85, 89]

Electroconvulsive Therapy and Brain Stimulation Techniques

Electroconvulsive therapy (ECT) appears to be effective for treatment-resistant or life-threatening manic or mixed mood episodes among persons with TBI. When ECT is selected as a treatment alternative, we recommend treatment with the lowest possible energy levels that will generate a seizure of adequate duration (greater than 20 seconds), using pulsatile currents, increased spacing of treatments (two to five days between treatments), and fewer treatments in an entire course (i.e., four to six). In addition, if the patient also suffers from significant cognitive impairment due to TBI, unilateral ECT is the preferred technique. The role of other brain stimulation techniques as treatment of these infrequent post-TBI disorders is uncertain at the present time and the available evidence does not support its use.

Summary and Future Directions

Mood disorders are frequent psychiatric complications of TBI that overlap with prominent anxiety, substance misuse, impulsivity and aggression. Furthermore, in a significant number of cases, they become chronic and resistant to treatment with the consequent deleterious impact on community reintegration and quality of life. Although the diagnosis of post-TBI mood disorders is still based on the DSM nomenclature, future nosology should incorporate the advances in neuroscience that are gradually allowing to parse the neural circuits whose disruption constitute the biological substrate of the behavioral alterations associated with

these conditions. Current therapeutic strategies are based on current standards of practice rather that empirically-based controlled treatment trials. Randomized, double blind, placebo controlled trials to establish the most effective treatments for the variety of mood disorders associated with TBI are needed.

Acknowledgments

Support for this work was provided by the Veterans Health Administration's Traumatic Brain Injury Center of Excellence at the Michael E. DeBakey Veterans Affairs Medical Center, the National Institute of Health grants RO1MH53592 and RO1 MH65134 01 (REJ) and the National Institute on Disability and Rehabilitation Research (NIDRR) grants H133A120020 and H133A130047 (DBA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs or NIDRR. The authors also gratefully acknowledge the assistance of Ms. Ashley Devereaux in the preparation of this manuscript.

References

1. Jorge RE, Robinson RG, Arndt SV, et al. Comparison between acute- and delayed-onset depression following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 1993; 5(1):43–9. [PubMed: 8428134]
2. Whelan-Goodinson R, Ponsford JL, Schonberger M, et al. Predictors of psychiatric disorders following traumatic brain injury. J Head Trauma Rehabil. 2009
3. Seel RT, Macciocchi S, Kreutzer JS. Clinical considerations for the diagnosis of major depression after moderate to severe TBI. J Head Trauma Rehabil. 2010; 25(2):99–112. [PubMed: 20134332]
4. Kim E, Lauterbach EC, Reeve A, et al. Neuropsychiatric complications of traumatic brain injury: a critical review of the literature (a report by the ANPA Committee on Research). J Neuropsychiatry Clin Neurosci. 2007; 19(2):106–27. [PubMed: 17431056]
5. Koponen S, Taiminen T, Portin R, et al. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. Am J Psychiatry. 2002; 159(8):1315–21. [PubMed: 12153823]
6. Hibbard MR, Uysal S, Kepler K, et al. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil. 1998; 13(4):24–39. [PubMed: 9651237]
7. Fedoroff JP, Starkstein SE, Forrester AW, et al. Depression in patients with acute traumatic brain injury. Am J Psychiatry. 1992; 149(7):918–23. [PubMed: 1609872]
8. Jorge RE, Robinson RG, Moser D, et al. Major depression following traumatic brain injury. Arch Gen Psychiatry. 2004; 61(1):42–50. [PubMed: 14706943]
9. Gould KR, Ponsford JL, Johnston L, et al. The nature, frequency and course of psychiatric disorders in the first year after traumatic brain injury: a prospective study. Psychol Med. 2011; 41(10):2099–109. [PubMed: 21477420]
10. Tateno A, Jorge RE, Robinson RG. Clinical correlates of aggressive behavior after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2003; 15(2):155–60. [PubMed: 12724455]
11. Bombardier CH, Fann JR, Temkin NR, et al. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA. 2010; 303(19):1938–45. [PubMed: 20483970]
12. Hart T, Hoffman JM, Pretz C, et al. A longitudinal study of major and minor depression following traumatic brain injury. Arch Phys Med Rehabil. 2012; 93(8):1343–9. [PubMed: 22840833]
13. Deb S, Burns J. Neuropsychiatric consequences of traumatic brain injury: a comparison between two age groups. Brain Inj. 2007; 21(3):301–7. [PubMed: 17453758]
14. Whelan-Goodinson R, Ponsford JL, Schonberger M, et al. Predictors of psychiatric disorders following traumatic brain injury. J Head Trauma Rehabil. 2010; 25(5):320–9. [PubMed: 20042983]
15. Rapoport MJ, McCullagh S, Streiner D, et al. Age and major depression after mild traumatic brain injury. Am J Geriatr Psychiatry. 2003; 11(3):365–9. [PubMed: 12724117]
16. Bay E, Sikorskii A, Saint-Arnault D. Sex differences in depressive symptoms and their correlates after mild-to-moderate traumatic brain injury. J Neurosci Nurs. 2009; 41(6):298–309. quiz 310-1. [PubMed: 19998681]
17. Demakis GJ, Hammond FM, Knotts A. Prediction of depression and anxiety 1 year after moderate-severe traumatic brain injury. Appl Neuropsychol. 2010; 17(3):183–9. [PubMed: 20799109]

18. Koponen S, Taiminen T, Kairisto V, et al. APOE-epsilon4 predicts dementia but not other psychiatric disorders after traumatic brain injury. Neurology. 2004; 63(4):749–50. [PubMed: 15326261]
19. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003; 301(5631):386–9. [PubMed: 12869766]
20. Arango V, Huang YY, Underwood MD, et al. Genetics of the serotonergic system in suicidal behavior. J Psychiatr Res. 2003; 37(5):375–86. [PubMed: 12849930]
21. Binder EB, Salyakina D, Lichtner P, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet. 2004; 36(12):1319–25. [PubMed: 15565110]
22. Lotrich FE, Pollock BG. Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Genet. 2004; 14(3):121–9. [PubMed: 15318024]
23. Patkar AA, Berrettini WH, Hoehe M, et al. Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. Psychiatry Res. 2002; 110(2):103–15. [PubMed: 12057823]
24. Sen S, Villafuerte S, Nesse R, et al. Serotonin transporter and GABAA alpha 6 receptor variants are associated with neuroticism. Biol Psychiatry. 2004; 55(3):244–9. [PubMed: 14744464]
25. Tunbridge E, Burnet PW, Sodhi MS, et al. Catechol-o-methyltransferase (COMT) and proline dehydrogenase (PRODH) mRNAs in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. Synapse. 2004; 51(2):112–8. [PubMed: 14618678]
26. Zubenko GS, Maher B, Hughes HB 3rd, et al. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. Am J Med Genet B Neuropsychiatr Genet. 2003; 123(1):1–18. [PubMed: 14582139]
27. Lasky-Su JA, Faraone SV, Glatt SJ, et al. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. Am J Med Genet B Neuropsychiatr Genet. 2005; 133B(1):110–5. [PubMed: 15578606]
28. Sun HS, Tsai HW, Ko HC, et al. Association of tryptophan hydroxylase gene polymorphism with depression, anxiety and comorbid depression and anxiety in a population-based sample of postpartum Taiwanese women. Genes Brain Behav. 2004; 3(6):328–36. [PubMed: 15544576]
29. Smith GS, Lotrich FE, Malhotra AK, et al. Effects of serotonin transporter promoter polymorphisms on serotonin function. Neuropsychopharmacology. 2004; 29(12):2226–34. [PubMed: 15354180]
30. McAllister TW, Flashman LA, Harker Rhodes C, et al. Single nucleotide polymorphisms in ANKK1 and the dopamine D2 receptor gene affect cognitive outcome shortly after traumatic brain injury: a replication and extension study. Brain Inj. 2008; 22(9):705–14. [PubMed: 18698520]
31. Lipsky RH, Sparling MB, Ryan LM, et al. Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2005; 17(4):465–71. [PubMed: 16387984]
32. Chan F, Lanctot KL, Feinstein A, et al. The serotonin transporter polymorphisms and major depression following traumatic brain injury. Brain Inj. 2008; 22(6):471–9. [PubMed: 18465388]
33. Lanctot KL, Rapoport MJ, Chan F, et al. Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury. Brain Inj. 2010; 24(7-8):959–69. [PubMed: 20515362]
34. Heim C, Newport DJ, Bonsall R, et al. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry. 2001; 158(4):575–81. [PubMed: 11282691]
35. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000; 284(5):592–7. [PubMed: 10918705]
36. Jorge RE, Robinson RG, Arndt SV, et al. Depression following traumatic brain injury: a 1 year longitudinal study. J Affect Disord. 1993; 27(4):233–43. [PubMed: 8509524]
37. Fann JR, Burington B, Leonetti A, et al. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry. 2004; 61(1):53–61. [PubMed: 14706944]

38. Jorge RE, Starkstein SE, Arndt S, et al. Alcohol misuse and mood disorders following traumatic brain injury. Arch Gen Psychiatry. 2005; 62(7):742–9. [PubMed: 15997015]
39. Starkstein SE, Lischinsky A. The phenomenology of depression after brain injury. NeuroRehabilitation. 2002; 17(2):105–13. [PubMed: 12082237]
40. Fann JR, Bombardier CH, Dikmen S, et al. Validity of the Patient Health Questionnaire-9 in assessing depression following traumatic brain injury. J Head Trauma Rehabil. 2005; 20(6):501–11. [PubMed: 16304487]
41. Green A, Felmingham K, Baguley IJ, et al. The clinical utility of the Beck Depression Inventory after traumatic brain injury. Brain Inj. 2001; 15(12):1021–8. [PubMed: 11712948]
42. Seel RT, Kreutzer JS. Depression assessment after traumatic brain injury: an empirically based classification method. Arch Phys Med Rehabil. 2003; 84(11):1621–8. [PubMed: 14639561]
43. Whelan-Goodinson R, Ponsford J, Johnston L, et al. Psychiatric disorders following traumatic brain injury: their nature and frequency. J Head Trauma Rehabil. 2009; 24(5):324–32. [PubMed: 19858966]
44. Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. Brain Inj. 1998; 12(1):87–92. [PubMed: 9483342]
45. Marin RS, Fogel BS, Hawkins J, et al. Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci. 1995; 7(1):23–30. [PubMed: 7711487]
46. Larson MJ, Kaufman DA, Kellison IL, et al. Double jeopardy! The additive consequences of negative affect on performance-monitoring decrements following traumatic brain injury. Neuropsychology. 2009; 23(4):433–44. [PubMed: 19586208]
47. Reza MF, Ikoma K, Ito T, et al. N200 latency and P300 amplitude in depressed mood post-traumatic brain injury patients. Neuropsychol Rehabil. 2007; 17(6):723–34. [PubMed: 18030646]
48. American Psychiatric Association. Treatment of Patients with Major Depressive Disorder, in APA Practice Guidelines, Major Depressive Disorder. American Psychiatric Association; 2010.
49. Rothman MS, Arciniegas DB, Filley CM, et al. The neuroendocrine effects of traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2007; 19(4):363–72. [PubMed: 18070838]
50. Bell KR, Hoffman JM, Temkin NR, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. J Neurol Neurosurg Psychiatry. 2008; 79(11):1275–81. [PubMed: 18469027]
51. Snell DL, Surgenor LJ, Hay-Smith EJ, et al. A systematic review of psychological treatments for mild traumatic brain injury: an update on the evidence. J Clin Exp Neuropsychol. 2009; 31(1):20–38. [PubMed: 18608646]
52. Anson K, Ponsford J. Evaluation of a coping skills group following traumatic brain injury. Brain Inj. 2006; 20(2):167–78. [PubMed: 16421066]
53. Anson K, Ponsford J. Who benefits? Outcome following a coping skills group intervention for traumatically brain injured individuals. Brain Inj. 2006; 20(1):1–13. [PubMed: 16403695]
54. Hegel MT, Ferguson RJ. Differential reinforcement of other behavior (DRO) to reduce aggressive behavior following traumatic brain injury. Behav Modif. 2000; 24(1):94–101. [PubMed: 10641369]
55. Delmonico RL, Hanley-Peterson P, Englander J. Group psychotherapy for persons with traumatic brain injury: management of frustration and substance abuse. J Head Trauma Rehabil. 1998; 13(6): 10–22. [PubMed: 9885315]
56. Bell KR, Hoffman JM, Doctor JN, et al. Development of a telephone follow-up program for individuals following traumatic brain injury. J Head Trauma Rehabil. 2004; 19(6):502–12. [PubMed: 15602312]
57. Kurowski BG, Wade SL, Kirkwood MW, et al. Online problem-solving therapy for executive dysfunction after child traumatic brain injury. Pediatrics. 2013; 132(1):e158–66. [PubMed: 23753094]
58. Hibbard MR, Cantor J, Charatz H, et al. Peer support in the community: initial findings of a mentoring program for individuals with traumatic brain injury and their families. J Head Trauma Rehabil. 2002; 17(2):112–31. [PubMed: 11909510]

59. Groom KN, Shaw TG, O'Connor ME, et al. Neurobehavioral symptoms and family functioning in traumatically brain-injured adults. Arch Clin Neuropsychol. 1998; 13(8):695–711. [PubMed: 14590629]
60. Harris JK, Godfrey HP, Partridge FM, et al. Caregiver depression following traumatic brain injury (TBI): a consequence of adverse effects on family members? Brain Inj. 2001; 15(3):223–38. [PubMed: 11260771]
61. Leach LR, Frank RG, Bouman DE, et al. Family functioning, social support and depression after traumatic brain injury. Brain Inj. 1994; 8(7):599–606. [PubMed: 7804296]
62. Warden DL, Gordon B, McAllister TW, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma. 2006; 23(10):1468–501. [PubMed: 17020483]
63. Kant R, Smith-Seemiller L, Zeiler D. Treatment of aggression and irritability after head injury. Brain Inj. 1998; 12(8):661–6. [PubMed: 9724837]
64. Fann JR, Uomoto JM, Katon WJ. Sertraline in the treatment of major depression following mild traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2000; 12(2):226–32. [PubMed: 11001601]
65. Fann JR, Uomoto JM, Katon WJ. Cognitive improvement with treatment of depression following mild traumatic brain injury. Psychosomatics. 2001; 42(1):48–54. [PubMed: 11161121]
66. Schmitt JA, Kruizinga MJ, Riedel WJ. Non-serotonergic pharmacological profiles and associated cognitive effects of serotonin reuptake inhibitors. J Psychopharmacol. 2001; 15(3):173–9. [PubMed: 11565624]
67. Lee H, Kim SW, Kim JM, et al. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Hum Psychopharmacol. 2005; 20(2):97–104. [PubMed: 15641125]
68. Gualtieri CT, Evans RW. Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. Brain Inj. 1988; 2(4):273–90. [PubMed: 3060211]
69. Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry. 2007; 62(4):345–54. [PubMed: 17223086]
70. Kraus MF, Maki PM. Effect of amantadine hydrochloride on symptoms of frontal lobe dysfunction in brain injury: case studies and review. J Neuropsychiatry Clin Neurosci. 1997; 9(2):222–30. [PubMed: 9144101]
71. Meythaler JM, Brunner RC, Johnson A, et al. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. J Head Trauma Rehabil. 2002; 17(4):300–13. [PubMed: 12105999]
72. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012; 366(9):819–26. [PubMed: 22375973]
73. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Bernabeu M, et al. Noninvasive brain stimulation in traumatic brain injury. J Head Trauma Rehabil. 2012; 27(4):274–92. [PubMed: 21691215]
74. Silver JM, Kramer R, Greenwald S, et al. The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. Brain Inj. 2001; 15(11):935–45. [PubMed: 11689092]
75. van Reekum R, Cohen T, Wong J. Can traumatic brain injury cause psychiatric disorders? J Neuropsychiatry Clin Neurosci. 2000; 12(3):316–27. [PubMed: 10956565]
76. Jorge RE, Robinson RG, Starkstein SE, et al. Secondary mania following traumatic brain injury. Am J Psychiatry. 1993; 150(6):916–21. [PubMed: 8494069]
77. Shukla S, Cook BL, Mukherjee S, et al. Mania following head trauma. Am J Psychiatry. 1987; 144(1):93–6. [PubMed: 3799847]
78. Malaspina D, Goetz RR, Friedman JH, et al. Traumatic brain injury and schizophrenia in members of schizophrenia and bipolar disorder pedigrees. Am J Psychiatry. 2001; 158(3):440–6. [PubMed: 11229986]
79. Dealberto MJ, Marino J, Bourgon L. Homicidal ideation with intent during a manic episode triggered by antidepressant medication in a man with brain injury. Bipolar Disord. 2008; 10(1): 111–3. [PubMed: 18199249]

80. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. Int Rev Psychiatry. 2003; 15(4):317–27. [PubMed: 15276953]

81. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978; 133:429–35. [PubMed: 728692]

82. Oster TJ, Anderson CA, Filley CM, et al. Quetiapine for mania due to traumatic brain injury. CNS Spectr. 2007; 12(10):764–9. [PubMed: 17934381]

83. Daniels JP, Felde A. Quetiapine treatment for mania secondary to brain injury in 2 patients. J Clin Psychiatry. 2008; 69(3):497–8. [PubMed: 18402501]

84. American Psychiatric Association. Practice guideline for psychiatric evaluation of adults. Am J Psychiatry. 1995; 152(11 Suppl):63–80. [PubMed: 9565542]

85. Hirschfeld RMA. Guideline Watch: Practice Guideline for the Treatment of Patients with Bipolar Disorder. APA Practice Guidelines. 200210.1176/appi.books.9780890423363.148430

86. Dikmen SS, Machamer JE, Winn HR, et al. Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. Neurology. 2000; 54(4):895–902. [PubMed: 10690983]

87. Massagli TL. Neurobehavioral effects of phenytoin, carbamazepine, and valproic acid: implications for use in traumatic brain injury. Arch Phys Med Rehabil. 1991; 72(3):219–26. [PubMed: 1998458]

88. Hornstein A, Seliger G. Cognitive side effects of lithium in closed head injury. J Neuropsychiatry Clin Neurosci. 1989; 1(4):446–7. [PubMed: 2521097]

89. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry. 2002; 159(4 Suppl):1–50.

Acronyms

TBI	traumatic brain injury
MTHFR	methylene tetrahydrofolate reductase
BDNF	brain-derived neurotrophic factor
NOS	Not otherwise specified
BDI	Beck Depression Inventory
HAM-D	Hamilton Depression Scale
PTSD	Post-traumatic stress disorder
DTI	diffusion tensor imaging
HMRS	proton magnetic resonance spectroscopy
fMRI	functional MRI
PET	positron emission tomography
CBT	Cognitive behavioral therapy
DRO	Differential Reinforcement of Other Behavior
SSRIs	Selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
CYP450	cytochrome P450
MAOIs	monoamine oxidase inhibitors
ECT	Electroconvulsive therapy
rTMS	Repetitive transcranial magnetic stimulation
tDCS	transcranial direct current stimulation

VNS	Vagal nerve stimulation
DBS	Deep brain stimulation

Key Clinical Points

- Depressive disorders are the most common neuropsychiatric sequels of TBI. Mania, hypomania, and mixed mood states are less frequent but serious complications of TBI. In many respects, the evaluation and management of these conditions is similar to that provided to persons with primary (idiopathic) mood disorders.
- Mood disorders are highly comorbid with anxiety, substance misuse and other behavioral alterations like impulsivity and aggression. Furthermore, once developed, they may have a chronic and refractory course.
- The functional repercussion of these disorders is huge, affecting the rehabilitation process as well as the long term outcome of TBI patients.
- Currently treatment options are, in a great part, dictated by expert opinion rather by rigorous, adequately designed, and sufficiently large studies.