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Traumatic brain injury and mood disorders

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Abstract

Traumatic brain injury is an increasing cause of morbidity worldwide. Neuropsychiatric impairments, such as behavioral dysregulation and depression, have significant impacts on recovery, functional outcomes, and quality of life of patients with traumatic brain injuries. Three patient cases, existing literature, and expert opinion are used to select pharmacotherapy for the treatment of target symptoms while balancing safety and tolerability.

Keywords: traumatic brain injury, aggression, impulsivity, mood disorders, depression, bipolar disorder

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Introduction

Traumatic brain injury (TBI) is an acute injury with potentially long-lasting complications. Traumatic brain injuries are classified as mild, moderate, or severe according to features denoting the extent of the injury to the brain. They can lead to neurological sequelae such as seizures and strokes. Other impairments include personality changes, emotional or behavioral dysregulations, and persistent cognitive deficits (Table 1). The nature and severity of impairments resulting from TBIs vary widely given the range of injury type, location and extent of brain tissue affected.[1,2] Complex pathophysiology resulting from primary and secondary injuries evolving over minutes to days to months can lead to temporary or permanent deficits.[3] Injuries in specific brain areas may be associated with certain symptoms or syndromes, such as temporolimbic lesions with aggressive behavior and epilepsy, subcortical brainstem injuries and reduced alertness and confusion, and frontal lobe injury with disinhibition, aggression, emotional lability, and personality change.[4] However, most head injuries, especially closed ones, which are more common than penetrating head injuries, typically cause more diffuse brain damage with varied types and severities of impairments.[1]

Post-TBI neuropsychiatric disorders can pose significant barriers to initial acute medical treatment, and to longer-term rehabilitation and recovery.[1] Evidence supporting their treatment is limited and highly variable in terms of study designs, patient populations, outcome measures, and overall quality. Time since injury is an important confounder, as spontaneous recovery in earlier phases may obscure potential benefits from medication interventions, while greater chronicity could confer more refractoriness to pharmacologic treatments. While there are no standard definitions of time periods post-injury, the following terminology has been used in review articles and guidelines: immediate for 0 to 7 days post-TBI; acute for less than 4 or 6 weeks; sub- or postacute ranging from 7 to 12 weeks or up to 6 months; and chronic for greater than 12 weeks or up to 6 months post-injury.[5,6]

Take Home Points:

1. Traumatic brain injuries are associated with an increased risk of behavioral or emotional dysregulation such as agitation, aggression, or personality changes, as well as increased risk of subsequent mood disorders, namely depression.
2. First do no harm: Medications that may interfere with neurological recovery or engagement in care should be avoided. As such, use of benzodiazepines is not recommended, while antipsychotics may be used sparingly, unless long-term use is warranted for a separate psychiatric disorder. In this case, second-generation antipsychotics are favored over first-generation antipsychotics.
3. Environmental and behavioral interventions are first-line in the management of posttraumatic brain injury behavioral disturbances. Beta-blockers can be considered to target agitation, restlessness, and aggression; mood stabilizers (particularly valproate) for impulsivity, irritability, agitation, and aggression; other agents may occasionally be considered, but data are more limited.
4. Management of depression and bipolar disorder in patients with traumatic brain injury follows usual treatment guidelines, however greater sensitivity to side effects warrant more cautious initiation and titration. Some medications are best avoided (eg, tricyclic antidepressants) or may be used cautiously (eg, bupropion, lithium).

Few guidelines exist that provide clear treatment recommendations for TBI-related neuropsychiatric complications; instead, treatment selection is based on symptom targets.[5-7] Important considerations in using medications for TBI-related symptoms include: generally avoiding medications that can lower the seizure threshold in patients at high risk of seizures (eg, penetrating injuries, cerebral contusion, intracranial hemorrhage, subdural hematoma, posttraumatic epilepsy, electroencephalogram abnormalities, focal neurologic deficits, alcohol use disorder) or those that can cause confusion; give full therapeutic trials at maximum tolerated doses before discontinuing medication; monitor closely for toxicity as patients with TBIs can be more sensitive to side effects; limit quantities of medications in patients at high risk of suicide given the higher rate of suicide in TBI populations.[6,8]

Through the use of 3 patient cases, this article will summarize and apply available evidence and clinical practice informed management in the management of the following TBI-related neuropsychiatric complications: behavioral disturbances, depression, and bipolar disorder.

TBI, Agitation, Aggression, and Behavioral Disturbances

Patient Case 1

A 48-year-old patient found unconscious was evaluated in the emergency department for a severe TBI. Medical and psychiatric histories were significant for severe alcohol use disorder. The patient was admitted to the intensive care unit for intubation, sedation, and medical stabilization, which included detoxification from alcohol, empiric treatment with intravenous thiamine for possible Wernicke encephalopathy, and prophylactic levetiracetam for 1 week post-brain injury. The patient was then transferred to the medical unit. During hospitalization, the patient became increasingly aggressive, swinging at staff, throwing objects, and pulling at intravenous lines. Restraints

TABLE 1: Common posttraumatic brain injury related symptoms[6,53]

Severity of Injury	Symptoms		
	Physical	Cognitive	Psychiatric
Mild	Headache	Memory impairment	Depression
	Dizziness	Attention and concentration impairment	Anxiety
	Fatigue	Executive function deficit	
	Visual symptoms	Processing speed	
	Light/noise sensitivity	Retrograde or anterograde amnesia	
Moderate or severe	Any of above	Any of above	Any of above
	Decreased arousal		Agitation, restlessness
	Motor deficits (acute and/or long-term)		Anger
	Neurological deficits (acute and/or long-term)		Aggression
	Seizures		Irritability
	Sleep disturbances		

were frequently needed to ensure patient safety because of impulsive attempts to ambulate without assistance and nonresponse to redirection by staff. Haloperidol 5 mg intravenously every 4 hours as needed was initiated for aggressive behaviors as well as impulsivity not responding to redirection. However, the patient developed extrapyramidal side effects (EPS), so haloperidol was discontinued in favor of olanzapine 5 mg by mouth or intramuscular every 6 hours as needed. Valproate (VPA) was initiated in the form of divalproex sodium tablets to target impulsivity and irritability, and titrated to a final dose of 1000 mg twice daily with improvement after 5 days. Residual aggression continued to interfere with care, thus propranolol was initiated at 10 mg 3 times daily, with subsequent gradual titration to a final dose of 160 mg once daily of the long-acting formulation. Patient became more engaged with care, and no longer required as needed olanzapine, thus was transferred to a rehabilitation facility.

Clinical Presentation and Treatment Considerations

Post-TBI agitation and aggression develop in up to 70% of patients, and cause significant challenges to care delivery and rehabilitation.[9] A range of medications have been tried, with various goals and rationale underlying their selection: a summary of these can be found in Tables 2 and 3. While benzodiazepines may be used to acutely target severe aggression, their use has largely been supplanted by other agents because of their negative impact on arousal, mentation, and memory.[2,5]

Beta-Blockers

Interest in beta-blockers for TBI-related behavioral disturbances stemmed from older literature supporting their benefits in reducing aggressive behaviors. Controlled studies of varied quality and methodology confirmed improvements in agitation, particularly assaultive and violent episodes, and reduced need for additional medications and restraints with scheduled daily doses of beta-blockers. Propranolol and pindolol have been most extensively studied, based on the theory that higher lipophilicity is required for central nervous system effects.[10-13] The exact mechanism of action is unclear but is theorized to involve a dampening of exaggerated adrenergic responses in patients with TBI, and perhaps additional 5-HT1A partial agonist activity in the case of pindolol. There is increasing evidence of mortality benefits with the use of various beta-blockers immediately post-TBI, though more work is needed to delineate the best timing and selection of agents. Of note, patients with compelling cardiovascular indications for alternate beta-blockers should not have their beta-blocker therapy changed solely to target TBI-related behavioral disturbances.[14]

Mood Stabilizers and Anticonvulsants

Anticonvulsants have been shown to reduce TBI-related agitation, irritability, impulsivity, disinhibition, and aggression, with minimal sedation potential. Anticonvulsants may exert their benefit via increased GABAergic-mediated inhibitory control, neuronal stabilization, and *antikindling* effects in limbic areas.[15] Anticonvulsants may be a good choice, particularly in those patients who have another separate indication such as posttraumatic epilepsy or bipolar disorder.[8] Valproate has the most evidence, albeit uncontrolled, in TBI populations supporting a rapid onset of effect on target symptoms, and overall good tolerability.[5,7,16,17]

Clinical experience and anecdotal literature with very few TBI patients support the use of carbamazepine for its antiaggressive benefits.[18,19] However, use is often limited because of its broad metabolic enzyme and p-glycoprotein inducing potential. With fewer clinically relevant drug-drug interactions, oxcarbazepine can be an alternative to carbamazepine, based on benefits observed on hostility and irritability associated with intermittent explosive disorder.[5,20] However, efficacy and tolerability in TBI populations remains to be investigated.[5]

Lastly, lithium has a history of use in TBI patients to target severe mood lability and severe, destructive, and self-injurious behaviors, usually after other agents such as anticonvulsants and antipsychotics have been insufficient.[21,22] Lithium has been found to significantly improve these behaviors with negligible sedation, thereby allowing patients to participate in rehabilitation. Concerns over higher rates of neurotoxicity have been noted, particularly with concomitant use of high potency first-generation antipsychotics (FGAs).[22] Efficacy and safety data in TBI populations remain limited, thus its use is generally reserved for severe, refractory aggression.

Antipsychotics

While antipsychotics may be effective at controlling TBI-related agitation, their use is best reserved as last alternative for the short-term management of acute or severe aggression. Cautious use of antipsychotics is generally recommended based on concerns over delay in motor and cognitive function recovery observed in animal studies, and limited efficacy and safety data in humans.[5] Other relevant adverse effects include EPS, as observed in patient case 1, as well as sedation, seizures (particularly in high-risk patients or with certain agents such as clozapine, olanzapine, and quetiapine), and possibly a higher risk of neuroleptic malignant syndrome.[5,23,24] French guidelines offer the following guidance on the use of antipsychotics

TABLE 2: First-line pharmacotherapies for behavioral disturbances associated with traumatic brain injury (TBI)[2,5,7,22,54]

Medication	Total Daily Dose (mg)	Target Symptoms	Evidence	Efficacy	Pearls/Tolerability
Beta-blockers					
Propranolol	60-520	Agitation, restlessness, aggression	Randomized controlled trials	+	Well tolerated with rare hypotension or bradycardia reported in literature despite high doses; in clinical practice, tolerance varies widely, though vitals often limit dose to 120-160 mg daily.
Pindolol	40-100	Agitation, restlessness, aggression	Randomized controlled trials	+	Very low risk of hypotension or bradycardia; increased agitation at doses >60 mg/d.
Mood stabilizers					
Valproate	750-2500	Impulsivity, irritability, agitation, aggression	Retrospective reviews, case series	+	Rapid onset of effect; usually well tolerated, with minimal cognitive impairment.
Carbamazepine	400-800	Agitation, anger, aggression, disinhibition	Open trials, case series	+	Observe for drowsiness; may negatively impact cognition (mixed data).
Lithium	Various	Mood lability, aggression	Case series	+	High lithium concentrations (0.8-1.2 mEq/L) may be required in some patients. Caution: Potential for increased risk of neurotoxicity, especially if used in combination with first-generation antipsychotics. Avoid if high risk for or recent seizures.
Antipsychotics					
First-generation antipsychotics					
Haloperidol	2-20	Agitation, aggression	Open trial	+/–	May worsen neurological recovery in acute TBI stage; potential increased sensitivity to extrapyramidal side effects.
Second-generation antipsychotics					
Clozapine	300-800	Refractory psychosis, aggression	Case series	+	Caution about seizures, especially in patients at high risk; reserved for established, refractory psychosis.
Olanzapine	10-20	Psychosis, aggression	Case report	+	Potential for worsening delirium at high doses if no underlying psychosis.
Quetiapine	25-300, up to 800	Irritability, aggression	Case series	+	Low risk of akathisia; may cause restless legs syndrome.
Ziprasidone	20-80	Agitation	Case series	+	Monitor for akathisia.

post-TBI: use second-generation antipsychotics (SGAs) at conservative doses; restrict the use of these agents to the treatment of psychosis, or as a short-term alternative for acute or severe aggression.[5] Small case series or open-label studies of quetiapine (doses ranging from 25-300 mg daily) and ziprasidone (20-80 mg daily), and a placebo-controlled study of olanzapine (doses not specified) provide evidence of benefit in the treatment of agitation, irritability, and aggression related to TBI.[25-27]

Other Agents With More Limited Role

Beyond its potential role in early recovery in the acute/subacute post-TBI period, amantadine may also have a role in the treatment of chronic TBI-related irritability, agitation, and aggression, however data are mixed as to its benefits.[2,5,28,29] While its specific role in the management of such TBI-related symptoms remains to be elucidated, considerations for its use include the presence of additional target symptoms such as reduced alertness

TABLE 3: Additional agents for traumatic brain injury (TBI) related behavioral disturbances with more limited role[2,5,7,28,29,32,33]

Medication	Total Daily Dose (mg)	Target Symptoms	Evidence	Efficacy	Pearls/Tolerability
Antidepressants					
Tricyclic antidepressants	Low to moderate	Agitation, anger	Retrospective reviews	+	Rarely used for such indication because of risk of worsening confusion and lowering of seizure threshold.
Selective serotonin reuptake inhibitors	Usual	Primarily for depression or anxiety but secondary benefits on aggression	Single-blind trials, randomized controlled trials	+	Usual side effect profile though may be more sensitive; observe for increased agitation, anxiety.
Dopamine agonist					
Amantadine	50-400	Irritability, agitation, distractibility; apathy; wakefulness	Case series, open trials, randomized controlled trials	+/–	Mixed evidence of benefit (with delayed onset of several weeks) for irritability and aggression (up to 200 mg daily) in chronic TBI; may worsen irritability in early post-TBI period. May improve apathy and wakefulness at higher doses (with potential for worsening irritability). Avoid if high risk for or recent seizures.
Serotonin agonist					
Buspirone	30-60	Agitation, aggression, particularly if anxious component	Case reports, retrospective reviews	+	Delayed onset of anxiolytic effect of 2-3 wk, though few case reports suggest improved agitation after 12-36 h. Usual side effect profile.
Stimulants					
Methylphenidate	30+	Anger, aggression; cognition	Randomized controlled trials	+/–	Can reduce anger in patients with high baseline anger in chronic TBI; may increase agitation if used in acute/subacute phase; more evidence in treatment of cognitive deficits. Not recommended if high risk for or recent seizures.

and cognitive deficits.[5] Aside from their use to target TBI-related reduced alertness or cognitive deficits, stimulants may also improve frontal lobe function and have a role in reducing dysfunctional anger resulting from TBI.[5,7,30,31] Methylphenidate was shown to improve neurobehavioral symptoms, most notably anger, in patients with high levels of anger at baseline. It is unclear whether benefits are sustained beyond the short term (eg, 6 weeks) as the only long-term study (eg, 1 year) had a high attrition rate.[32,33]

Antidepressants have some evidence of benefit on agitation and aggression, but that is most often a secondary benefit in the course of their use for the treatment of depression. Buspirone may also represent another option for agitation and aggression, particularly if anxiety is associated with agitation.[5] An ongoing trial will hopefully confirm the limited positive evidence available to date.[34]

This case illustrates the challenges associated with the management of agitation and aggression, particularly in the acute period following a severe TBI. While environmental and behavioral approaches are crucial, behavioral disturbances that jeopardize patient or staff safety require additional interventions. Physical restraints may be necessary to prevent acute harm, but are themselves associated with adverse physical and psychological harms; thus their use should be minimized. The FGAs, namely haloperidol, are still commonly used in medical settings to control agitation due to various confusional states. However, FGAs can be poorly tolerated, with particular

concern for EPS, in antipsychotic-naïve patients, especially in those with neurological injuries such as TBIs. In this case, olanzapine would have been a safer initial choice for the acute management of severe agitation while a first-line medication treatment was initiated. Clinical experience suggests that effective doses range between 10 mg and 20 mg (often administered in divided daily doses to target daytime agitation), but would generally avoid higher doses because of concerns for EPS and delirium (latter being secondary to anticholinergic properties). Valproate is a good choice for this patient to target impulsivity and irritability as it can be titrated quickly, is well tolerated, has fewer significant drug interactions (eg, vs carbamazepine), and provides rapid onset of benefit. Should the patient's mental status be concerning for excessive sedation or unclear VPA-related toxicity, a total VPA serum concentration (or free VPA concentration for albumin <3 g/dL) could be obtained, but otherwise is of little value in such cases as there is no established therapeutic range for TBI-related behavioral disturbances. Of note, levetiracetam therapy warrants close evaluation because of its high rate of psychiatric side effects including agitation.[35] In this case, it had been discontinued more than 2 weeks prior to the escalation in agitated and aggressive behaviors, thus was not felt to be a contributor. As is fairly typical of the early period following a severe head injury, combinations of medications are often necessary to attain sufficient control of target symptoms such as impulsivity, agitation, and aggression to allow for better engagement in care and progress along the continuum of rehabilitation. In this case, the use of a beta-blocker is well suited to target aggression. It could have been considered prior to a mood stabilizer given the severity of the aggression, but impulsivity and irritability were felt to be the primary underpinnings of the aggressive behaviors. The patient responded well to the addition of moderate doses of propranolol, however some patients require much higher doses (eg, as high as 400-500 mg total daily doses), yet titrating to efficacy can be limited by bradycardia or hypotension. Alternatively, pindolol can be considered given its lesser impact on blood pressure and heart rate. Despite an unestablished link, many beta-blocker product labels list depression as a possible side effect requiring ongoing monitoring; more likely, however, is fatigue, which could impact tolerability.[36,37]

Ongoing reassessment of the benefits and needs of various behavioral medications is important as recovery may take place over weeks to months. Medications that may have been needed early on may not be needed later, and other symptoms (eg, cognitive deficits, depression) may emerge or become more apparent that then need to be addressed. In this patient, should the presentation change over time, or the current regimen becomes less tolerable, then changes such as gradual taper of VPA or beta-blocker could be attempted, and alternative medications could be considered if indicated (eg, amantadine for chronic TBI-related irritability or methylphenidate for anger or cognitive deficits).

TBI and Depression

Patient Case 2

A 56-year-old presented to the clinic for evaluation of depressed mood and irritability. The spouse reported that the patient had been different since a head injury sustained at work 6 months ago. Records revealed that the patient sustained a mild TBI requiring a brief hospitalization and discharge to outpatient rehabilitation. The patient had returned to work 1 month ago after 5 months of medical leave, but was disciplined for poor performance and anger outbursts. The spouse reported that these behaviors are uncharacteristic. Additionally, these behaviors as well as reported frequent crying spells, anhedonia, difficulty concentrating, insomnia, and fatigue were uncharacteristic. Dizziness, intermittent headaches, and tinnitus also started post-TBI. Psychiatric history before the TBI was negative, and medical history was significant for hypertension under control with lisinopril. A diagnosis of depression was made, and sertraline was initiated at 25 mg daily for 1 week followed by 50 mg daily until follow-up scheduled in 1 month.

Diagnostic and Treatment Considerations

Mood disorders are frequent following TBI; depression is the most common. Most cases develop within the year following TBI, with reported rates ranging between 6% and 77%.[38,39] Onset of depression may occur earlier (within 3 months) in patients with mild TBI, whereas it may be delayed (closer to 6 to 12 months) in those with moderate to severe TBIs.[40] This case demonstrates the importance of close monitoring for the development of post-TBI depression, given its negative impact on recovery, functional outcomes, quality of life, and risk of suicide.[38,39]

Antidepressants

Despite their frequent use, there is limited evidence supporting the efficacy of antidepressants in the treatment of post-TBI depression. Older studies found very limited benefits with amitriptyline, and better effects with desipramine, but these agents have fallen out of favor because of their overall tolerability and safety profile, particularly with regard to anticholinergic burden and seizure-lowering potential (when used at therapeutic doses for depression).[41] Data with selective serotonin reuptake inhibitors (SSRIs), namely sertraline and citalopram, was more favorable in uncontrolled studies but has been more modest and conflicting in placebo-controlled

studies, primarily because of large improvements seen in placebo groups.[42-44] A signal for lower tolerability to usual antidepressant side effects that may prevent dose optimization has been noted.[42,44] Thus, patients with TBI being initiated on antidepressants can benefit from cautious dose escalations, closer monitoring, and ongoing counseling.

Stimulants

Low dose methylphenidate (eg, initiated at 2.5 mg twice daily with titration to average daily doses of 15-20 mg) may also be considered for post-TBI depression. In a small study, both methylphenidate and sertraline produced greater improvement in depressive symptoms than placebo. The effect size was numerically greater with methylphenidate (1.194) versus sertraline (0.5).[42,45] Methylphenidate was also associated with improvements in cognitive deficits and daytime sedation. Although usually well tolerated at low doses, motor restlessness may occur, and use is generally avoided in patients with a history of seizures.[45]

In this case, selection of a SSRI such as sertraline is a reasonable first-line option. Initiating at low dose followed with slow titration is recommended given tolerability concerns observed in patients with TBIs. Activating side effects such as nervousness, agitation, and restlessness may be more likely when antidepressants are used in the acute post-TBI period. Careful monitoring of the emergence of such side effects, or exacerbation of baseline post-TBI agitation, is important. In such cases, trial of an alternate antidepressant should be attempted. Mirtazapine could be considered as a less-activating agent, however it may lead to daytime sedation and negatively impact cognition, which may be of particular relevance for patients with post-TBI cognitive deficits. While this may not be applicable to this patient case, the impact of bupropion on seizure threshold deserves special attention. Immediate release bupropion should be avoided in patients with TBI, whereas the extended-release formulation may be used cautiously. Despite a lower risk of new-onset seizures that compares favorably with other antidepressants such as SSRIs or serotonin norepinephrine reuptake inhibitors, extended-release bupropion is generally avoided in the subset of patients considered at high risk for seizures.[46] Alternatively, a stimulant could have been considered in this patient case. Low dose methylphenidate can be rapidly beneficial on depressive symptoms, particularly apathy, amotivation, anhedonia, psychomotor retardation, and daytime sedation/alertness. While stimulants may be used primarily in older, medically ill patients with depression, or occasionally as adjunctive to antidepressants for residual fatigue or apathy, they can also be an interesting option for patients with a history of TBI. Their well-known benefits on concentration, working memory, and processing speed also extend to patients with TBIs.[30,31] Thus if the patient in this case had prominent concentration difficulties or daytime fatigue, low dose methylphenidate may have been a good alternative. This therapy is usually well tolerated, with minimal impact on appetite, insomnia, and vital parameters, though monitoring for such is still warranted. Increased agitation may occur, though that appears most likely if stimulants are used in the early post-TBI phase.[2]

Effective depression treatment can also improve TBI-related irritability, aggression as well as various post-concussive somatic symptoms. This patient will benefit from close evaluation of any residual *nondepressive* symptoms to assess the need for additional intervention. Whether the patient should have been offered prophylactic treatment for depression before its development is unclear. A strong history of past depression or early subthreshold depressive symptoms may have made a compelling argument to initiate a prophylactic antidepressant such as a SSRI. In most cases, however, emerging evidence supporting primary prevention of depression post-TBI is still too limited for widespread application.

TBI and Bipolar Disorder

Patient Case 3

A 35-year-old was brought to the emergency department by family members over concerns that the patient had not slept "in days" and was becoming increasingly agitated with pressured speech. The patient endorsed feeling "Great!" and being a famous artist who sells snowmen paintings for millions of dollars. Family denied the patient was an artist. The family also reported increasing verbal aggression in the past few days, particularly when they attempted to reason with the patient. Past medical history was relevant for a closed head injury sustained 13 months ago secondary to a blunt trauma to the head. Psychiatric history was otherwise negative. In the early post-TBI period, the patient exhibited disrupted behaviors including impulsive aggression that benefited from treatment with propranolol; this was recently discontinued after such behaviors had completely resolved 2 months ago. Manic symptoms had not been observed previously. Delirium workup was negative. After baseline laboratory workup and physical exam were performed, the team elected to initiate lithium to target bipolar mania. Lithium was initiated at 300 mg twice daily with gradual titration to a goal steady-state lithium serum concentrations of 0.9 mEq/L to 1.0 mEq/L.

Diagnostic and Treatment Considerations

In contrast to depression, bipolar and related disorders are infrequent complications of TBI, with rates largely

consistent with population-based rates of bipolar disorder.[40,47] However, higher rates up to 9% have been reported in smaller studies, particularly in the early post-TBI period.[39] Prominent irritability and aggression have been noted as characteristic of bipolar disorder with premorbid TBI. An accurate diagnosis of bipolar disorder may be challenging to render given the range of behavioral symptoms, sleep disturbances, and cognitive deficits that can occur post-TBI; a distinct change in mood along with other diagnostic criteria should be present for a formal bipolar diagnosis.[39] In this patient, careful diagnostic assessment was important in differentiating between a return of TBI-related disruptive behavior since the discontinuation of propranolol versus a new diagnosis of mania. Looking beyond the impulsivity, aggression, and irritability often associated with TBI to discern other symptoms more consistent with a mood episode has important treatment implications. While an argument for resuming a previously effective beta-blocker treatment could have been made, in this case the euphoric mood along with other clear symptoms of mania painted a picture more consistent with a new episode of mania.

Lithium

Very limited data exist that can inform treatment of bipolar disorder in patients with a history of TBI. Consequently, medication selection usually follows bipolar disorder treatment guidelines, with perhaps greater caution with regard to tolerability and safety.[48] Lithium is a first-line mood stabilizer in the treatment of bipolar disorder; there is more limited evidence specifically in TBI populations suggesting improvement in mood lability, impulsivity, agitation, and aggression.[48,49] Of note, lithium has been reported to be less well tolerated in patients with a history of TBI; anecdotally, some clinicians describe a greater likelihood of intolerable gastrointestinal side effects, and higher rates of neurological side effects such as ataxia, tremor, and lethargy than in neurologically intact patients.[39] While caution is warranted, the increased risk of neurotoxicity may be particularly relevant to the concomitant use of lithium with FGAs in patients with TBI, and much less likely with lithium monotherapy as in this case.[22] Its use is usually best avoided in patients at high risk of seizures. Given its narrow therapeutic index, a good lithium candidate should be able to follow usual precautions such as adequate hydration and avoidance of interacting medications. Thus, lithium may be a safe and effective option after careful consideration of risks and benefits in individual patients.

Anticonvulsants and Antipsychotics

Recommended options for the treatment of bipolar disorder include anticonvulsants and SGA.[48] As bipolar disorder with premorbid TBI has been noted for its prominent irritability and aggression, VPA may be of particular relevance to this population. Indeed, small retrospective studies suggest that patients with a history of TBI or those with *neurologic findings* may show a greater response of their elevated mood states to VPA, even after failing several other medications including lithium.[50,51] Additional indications for VPA include the treatment of comorbid post-TBI headaches. Valproate serum concentrations may be useful to confirm adherence and optimize dosing for acute mania, and to assess for toxicity in cases where the clinical presentation is unclear, for example in patients with TBI-related neurological or cognitive deficits. Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.[48] Carbamazepine is an alternative option for acute mania and may be another good option for patients with TBI, especially if prominent aggression is observed.[48] Carbamazepine serum concentrations may be obtained to confirm adherence or assess for toxicity, however they do not correlate with efficacy in bipolar disorder.[48] Anticonvulsants should be favored mood stabilizers in the setting of post-TBI epilepsy, or if there is a high risk of seizures, such as severe TBIs, or those with early seizures, intracranial hemorrhage or lesions, electroencephalogram abnormalities or penetrating head injuries, as well as patients with comorbid alcohol use disorders. Lastly, SGAs represent another important class of medications for the treatment of bipolar disorders. Standard evidence-based guideline recommendations apply to patients with a TBI history, except for heightened vigilance for the development of EPS and sedation.[48]

In this case, additional information about the TBI should be obtained before final selection of a mood stabilizer. Ultimately, lithium was selected based on the euphoric mania presentation. Initiation at a conservative dose will provide an opportunity to assess for early side effects, while gradual titration to target serum concentration of 0.9 mEq/L to 1.0 mEq/L is consistent with guideline-recommended ranges for the treatment of acute mania. Should manic symptoms respond too slowly or insufficiently to lithium monotherapy, a SGA could be added to the regimen to provide more rapid and greater benefits on mood symptoms as well as additional prophylactic efficacy. Severe agitation or aggression may benefit from short-term addition of benzodiazepines, with the caveat of close monitoring for confusion or excessive sedation in patients with a history of TBI. Alternatively, lithium should be discontinued in favor of an anticonvulsant should manic symptoms not show improvement after 1 week or so of lithium therapy at target serum concentrations, especially if additional history is revealing for a severe TBI or previous seizures. While VPA would be a usual next step, carbamazepine could be considered in refractory

mania with severe aggression or in females with polycystic ovarian syndrome.

Conclusion

At this time, clinical management of patients with TBI presenting with psychiatric or behavioral symptoms continues to focus on careful assessment and treatment of comorbid psychiatric disorders, followed by tailored treatment of residual or distinct TBI-related symptoms.[52] As discussed, beta-blockers can be used to target agitation, restlessness, and aggression; mood stabilizers (particularly VPA) for impulsivity, irritability, agitation, and aggression; however antipsychotics should generally be reserved for short-term use of severe, violent, or assaultive aggression. Close monitoring of any emergent depressive symptoms is important given the high prevalence of this disorder post-TBI, and its consequences on quality of life, functional outcome, and recovery. While bipolar disorder is an infrequent complication of TBI, many patients with bipolar disorder have a history of TBI. The overlap with TBI-related behavioral symptoms (eg, mood lability, irritability, impulsivity) and those of mania can pose a diagnostic challenge, yet accurate diagnosis has significantly treatment implications. Management of depression and bipolar disorders in patients with a history of TBI largely follows the same standard treatment recommendations as in neurologically intact patient populations, with the exception of a greater focus on tolerability and safety, and avoidance of some medications in certain patients.

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