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Case Conference

A Case Study on the Management of the Behavioral Sequelae of Traumatic Brain Injury

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We present the case of a 46-year-old male with a history of post-traumatic stress disorder and opioid use disorder who sustained a severe traumatic brain injury secondary to motor vehicle accident and was brought to the attention of our psychiatry consultation-liaison team owing to significant physical and verbal aggression. This article will detail the specific behavioral and pharmacological management for this patient's symptoms. Additionally, experts in the field of consultation and liaison psychiatry will provide guidance based on their experience and a review of the available literature. Key teaching topics include the pathophysiology and cognitive evaluation of traumatic brain injury, conducting a behavioral analysis and developing a behavioral management plan and finally how to utilize appropriate symptom-based pharmacology while taking into account evidence-based treatment. Neuropsychiatric symptoms in traumatic brain injury are often challenging to manage owing to the varied symptom profile. Thus, treatment requires continued re-evaluation and a mixture of behavioral therapy and psychopharmacologic approaches.

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PRESENTATION OF CASE

Mr. D was a 46-year-old male with a psychiatric history of opioid use disorder and post-traumatic stress disorder. In June 2020, he was involved in a motor vehicle accident that resulted in a severe traumatic brain injury (TBI). Computed tomography scan of the head showed a right-sided subarachnoid hemorrhage with concern for uncal herniation. He was placed on mechanical ventilation. He required percutaneous endoscopic gastrostomy tube placement due to dysphagia. After medical stabilization, he was transferred to a long-term care facility in September 2020. He would frequently try to exit this facility and when redirected would yell, hit, and push staff. For management of aggression at this long-term care facility, he was being prescribed ziprasidone 40 mg twice daily, quetiapine 100 mg daily, and haloperidol decanoate 300 mg intramuscularly monthly. He was also prescribed valproic acid 500 mg 3 times daily, alprazolam 1 mg scheduled every 6 hours, and sertraline 50 mg daily. Benztropine 0.5 mg twice daily was also prescribed for tremor and methadone for treatment of opioid use disorder. In November 2020, he was transferred to the Veteran's Affairs Medical

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Centers from this long-term care facility. Psychiatry at the Veteran's Affairs Medical Centers was consulted for management of aggressive behaviors.

At the first encounter, he was noted to be anxious with low frustration tolerance. He was disoriented to time, place, and situation and was difficult to reorient. A 1:1 sitter was ordered for safety. Valproic acid was increased to 500 mg at breakfast and lunch and 1000 mg at bedtime. Haloperidol decanoate was discontinued as it was felt to be contributing to akathisia. Alprazolam was changed to lorazepam 1 mg every 8 hours owing to concerns about its contribution to daytime sedation, thus affecting sleep at night. There was suspicion that continuous percutaneous endoscopic gastrostomy feedings might be contributing to agitation, so a change to bolus feedings was recommended. This appeared to decrease restlessness and frustration as he was now able to move around more freely. Discussions with nursing staff occurred about minimizing noise and extraneous activity around his room and about having simple activities to occupy him, such as folding towels and playing with a stress ball.

During the second week of admission, lorazepam was decreased to 0.5 mg every 8 hours owing to less agitation. Valproic acid was also decreased to 500 mg twice daily owing to decreased platelet count from 162,000 to 101,000. Platelet count returned to within normal range, and no increase in aggression was noted. Benztropine was decreased to 0.5 mg at bedtime to see if a decreased amount of anticholinergic medication burden would improve cognition, as Mr. D no longer exhibited tremor.

At 3 weeks, discussions occurred with the internal medicine team about addressing pain, as it was observed that pain appeared to increase irritability for this patient. A printed list of as-needed pain medications was created for Mr. D so that he would have more autonomy and awareness of his options for pain management. Physical therapy was consulted to teach Mr. D daily stretching exercises to help with pain. As he was less agitated, a Montreal Cognitive Assessment could be completed. Deficits were noted in the visuospatial/executive functioning, sustained attention, language fluency, delayed recall, and orientation subsets of this examination.

By the fifth week of admission, Mr. D's 1:1 sitter was removed as he had no aggressive behaviors and demonstrated better emotional regulation. Persistent hyponatremia was noted, so sertraline was discontinued in favor of mirtazapine as it was also felt this medication may help with sleep as well as anxiety. No increase in agitation or anxiety was noted, and sleep improved. He was able to engage in more activities that he enjoyed. He was able to look through books/magazines, attempt puzzles, and play a donated guitar. He requested and was given the opportunity for regular meetings with the hospital chaplain.

After 6 weeks, he was temporarily discharged to a long-term care facility where he would reside pending bed availability at a Neurorestorative TBI program where he had been accepted. Psychiatric medications at discharge were as follows: quetiapine 100 mg at bedtime, ziprasidone 40 mg twice daily, mirtazapine 15 mg at bedtime, benztropine 0.5 mg QHS, lorazepam 0.5 mg every 8 hours, and valproic acid 500 mg twice daily. Mr. D successfully was transferred to a neurorestorative TBI program where he resided until his death this past fall.

THE PATHOPHYSIOLOGY AND EVALUATION OF TBI

For the purposes of this overview, TBI refers to moderate to severe TBI. The neuropathology of TBI may be broadly classified as either metabolic or anatomical. The effects of these forces may occur either immediately following the injury (primary injury) or days/weeks following the injury (secondary injury).[1] Primary injuries generally result from rotational and/or linear forces (e.g., skull fracture, subarachnoid hemorrhage). The anatomical structure of the head places the highest susceptibility for direct injury upon the frontal and temporal lobes. Diffuse axonal injury (DAI) can also occur and is most common at the gray-white matter junctions. The presence of DAI is often correlated with higher injury severity, often has a protracted recovery, and is often correlated with higher mortality.[2,3] DAI is typically caused by the stretching of myelinated axons connecting differing brain tissues. DAI is not observable on typical magnetic resonance imaging or computed tomography, but advanced magnetic resonance imaging techniques show some promise (e.g., weighted susceptibility and diffusion tensor imaging). There are some findings on standard neuroimaging that can increase the probability of DAI such as hemorrhages in the corpus callosum and gliding contusions at gray-white matter junctions.

Secondary injuries typically result from a series of events after the brain tissue has been injured (e.g., hypoxia, edema, poor cerebral perfusion pressure) or from secondary injuries sustained during the accident (e.g., bone fractures that can produce thrombi).[4] Secondary injuries also often involve a complex metabolic cascade (e.g., neuronal excitotoxicity and neuronal inflammation through cytokines and chemokines).[5]

In this patient, cognitive testing revealed deficits in encoding and retrieval of new memories and tasks involving sustained attention and executive functioning. Owing to the heterogeneity of TBI, there is no single neurobehavioral profile; however, there are several commonalities. Overlearned skills (e.g., vocabulary) are typically unaffected. Tests that require psychomotor/mental processing speed and attention are often negatively impacted. Given the prominence of frontal and temporal injuries, resulting reductions in declarative memory, encoding, and retrieval and organization strategies when encoding are typical. Executive dysfunction (e.g., difficulties with planning, organization, mental flexibility) is also common.[6] Table 1 summarizes bedside screening examinations that can be used to estimate various aspects of cognitive dysfunction.[6,7] Individuals who sustain TBIs may also display deficits in awareness, reduced self-control, apathy, impulsivity, fatigue, and deficient social skills.[8]

As seen in this patient, depression and anxiety following TBI are often observed. Of note, damage to the frontal lobes may mimic conditions such as depression, bipolar disorder, and obsessive compulsive disorder. Depending on the mechanism of injury, posttraumatic or adjustment disorders can develop. Even milder injuries (e.g., concussion) may be susceptible to developing postconcussive syndrome, which from a neuropsychological perspective is driven by psychological processes.[9] Therapies focused on dismantling cognitive biases surrounding their injuries and helping to prevent misattribution biases may help circumvent the processes that lead to postconcussive syndrome.[10,11]

THE BEHAVIORAL MANAGEMENT OF TBI

As seen in this case, when patients are hospitalized on a nonrehabilitation or neurotrauma floor, behavioral analysis and management plans are imperative for patient and staff safety. Owing to the cognitive and affective disturbances discussed previously, these types of patients have a higher prevalence of sleep disruption, emotional lability, difficulty articulating needs, exit seeking, and aggressive behaviors.[12] In these situations, it is important to educate staff that behaviors such as exit seeking, noncompliance with bedtime norms, and emotional outbursts are not intentional acts of aggression but by-products of their injury.[13] A multistep process as outlined in the following can assist in education and implementation of a management plan.

The first step is to identify risk factors associated with behavioral disturbances. These factors can be sorted into 5 general categories: environment, staff, medications/drugs, mental health, and physical health. A simple way to begin this step is to ask, "What is likely to disrupt this patient's daily routine or make them feel discomfort?" Most common offenders are related to abnormal levels of stimulation, unfamiliar environment with rotating staff, underlying psychiatric conditions, increased risk of delirium due to polypharmacy, and decreased nutritional intake.[14] It is important to take into account that this patient population can have trouble adjusting to increased levels of stimulation and can have misperceptions owing to memory loss and cognitive impairment. Additionally, patients with cognitive/speech deficits may have difficulty articulating basic drives, such as hunger, and this discomfort may manifest as irritability or agitation. If the mode of nutritional consumption is a new change as it was in this patient's case with placement of a percutaneous endoscopic gastrostomy tube, patients may miss the act and satisfaction of taste that is only achieved through oral consumption. Additionally, some percutaneous endoscopic gastrostomy tube feedings are continuous, which then decreases ability to use meal times as a means to orient the patient. In this case, bolus feedings improved the patient's mobility and increased his self-sufficiency by allowing him to assist with administering his own nutrition.

The second step requires observing the patient, staff, and flow of the unit with specific attention paid to the aforementioned risk factors. Consultants need to identify dynamic factors and their related intervention and provide adaptations for static factors. Mr. D resided for weeks on a busy and dynamic medical floor. The staff was asked to consider limiting noise and activity around the patient room to decrease overstimulation. To address the discrepancy between his limited availability for activity and the overactivity on the floor, the staff kept tasks available for the patient while remaining cognizant of his physical and cognitive

TABLE 1. Recommended Bedside Screening exams

Cognitive domain(s)	Test name
Global screening of cognitive deficits	Montreal Cognitive Assessment (MoCA)
Visuospatial planning/executive functioning (specifically organization and planning subsets of executive functioning)	Clock Drawing Test, can be used for serial re-evaluation
Executive functioning	Luria-Nebraska Neuropsychological Battery (various subtests that can test specific aspects of executive functioning)
Cognitive inhibition	"Go-no-go" tasks (e.g., asking the patient to hold up 2 fingers when you hold up one and vice versa)
Multiple fontal systems functions	Frontal System Battery (e.g., asking similarities between items, testing verbal fluency [S word generation in 60 s], testing rapid alternating movements, cognitive inhibition [go-no-go task] and testing prehension behaviors [patient unable to inhibit grasp reflex when asked])

limitations. Initial activities included simple tasks, but as mentation improved, activities were adjusted to include more complex ones.

The third step involves creating the behavioral plan, implementing interventions, and adjusting techniques as needed. Table 2 provides a summary of techniques that can be used to target specific behavioral problems. It is best to consult with nursing and medical teams to get their input on the logistics of the recommended changes. Further consultation with a psychologist knowledgeable of functional behavioral assessments would be a good resource. Patient participation in the creation of the behavioral plan will depend on his/her level of functioning and ability to understand situation. It would be wise to have an identified person re-evaluate the patient regularly for any additional adjustments for continuity. The plan should be listed in the medical record with mental health maintaining ownership/authorship.

THE PSYCHOPHARMACOLOGICAL MANAGEMENT OF TBI

As noted in this case, agitation and aggression are issues that can impair the care of patients with TBI. Agitation can occur at any point in a patient with TBI, but approximately 40% of cases occur during the acute phase (within weeks to a month) of recovery rather than after emergence from the post-traumatic confusional state and are associated with the severity of cognitive impairment, particularly disorientation and environmental stimuli.[15–17] Agitation in this acute phase has historically been observed in the setting of post-traumatic delirium, characterized by fluctuation in mental status and in attention, presenting either as disorganized thinking or as an altered level of consciousness, slurred speech, and acute-onset motor signs which likely result from a combination of structural damage and functional disturbances.[18] The recommendations on management of agitation in TBI are guided by targeting a symptom-focused approach to specific behavioral disturbances, and many of these guidelines come from studies conducted in the acute/subacute rehabilitation settings.[19] Guidelines in the pharmacologic management of agitation after TBI are often conservative in approach given the patients' vulnerabilities to side effects and exacerbation of confused states. General pharmacologic practice in managing acute agitation in TBI is summarized in Table 3.

There are studies that have broadly looked at agitation after TBI in inpatient and rehab settings. Based on the evidence that has been provided in the literature as well as expert consensus guidelines for management of acute agitation, it is prudent to algorithmically start with beta-blockers, then mood stabilizers for rapid abatement of agitation, followed by a lower-potency second-generation antipsychotic (quetiapine or olanzapine), which should be considered second line.[12]

Beta-blockers and mood-regulating antiepileptics that target GABA and glutamate have shown the most robust evidence in the management of acute agitation in TBI.[12] Brooke et al.[16] found that propranolol at doses ranging from 60 to 420 mg daily was effective in reducing the intensity of agitation and number of physical restraints, but not in the number of agitated episodes or use of medications for agitation in 21 patients at a Level 1 trauma rehabilitation center. Based on the severity of agitation and hemodynamic parameters of a patient, propranolol can be initiated at a standing dose of 10 mg 3 times daily and titrated to a range of 60 mg–100 mg, with very close monitoring.

TABLE 2. Example Techniques to Mitigate Risks for Behavioral Disturbances

Specific behavior	General principle	Technique execution
Refusing hygiene care/lab draws Hitting/swatting towards staff	Using time and distance	Allowing more physical distance during social interactions Informing patient beforehand that close proximity will be needed for certain monitoring activities (i.e., vitals, labs)
Hyperactivity during the night Restlessness contributing to irritability Increased confusion at nighttime as they are awake in lowlight conditions	Addressing sleep disturbance	Minimize overnight interruptions Reduce occurrence of daytime naps by turning on lights and opening blinds Review any medications that may be reducing nighttime sleepiness and increasing daytime fatigue Initiate physical therapy or activities to stimulate patient during the day
Misunderstanding of instructions Noncompliance with requests Seeming overwhelmed or not listening	Improving communication through clarity of speech	Be specific in language and reduce use of sarcasm, idioms, and medical jargon Adjust speech content to estimated intelligence of patient Do not lie or intentionally deceive
Tearfulness or watery eyes when talking with staff Fidgeting/restlessness or pacing Raised voices/yelling	Assessing for emotional lability	Monitor the patient's emotions while interacting with staff as staff may need to adjust communication attempt or modality Consider pharmacotherapy to address mood Review whether the patient could be experiencing withdrawal from caffeine, nicotine, or other medications/drugs
Watching the door/hallway intensely Irritability in speech/demeanor when interacting with staff	Reducing stimulation	Be selective in room position on unit, especially if near an active nursing station At teaching hospital, limit the number of residents/students visiting during rounds Review necessity of lab draws/vitals checks and tailor a unique schedule to complete these activities for the patient
Standing in doorway to room, wandering to nurses station Explicit speech of intent to leave Gathering items or asking for shoes/clothes	Be aware of precipitants to exit seeking	Selecting a room, i.e., not located near a stairwell or elevator where people will be coming and going Consider wanderguard or monitoring device on open units Pay attention if patients misperceive conversations with others as applying to them (e.g., telling another patient his ride is on the way)
Restlessness, purposeless behaviors with hands Pulling at tubes, cords, or other items in the room	Providing tasks/activities	Facilitate access to activities to assist in preserving motor skills/dexterity while also providing relief/distraction from stress of hospitalization Work with physical and occupational therapy on appropriate activities to provide physical activity as well as potential outlet of energy or anxiety; be aware of pain/discomfort onset with increased activity
Not recognizing presence in a hospital, not recognizing staff as health care staff Explicit reference to being home or at another location	Reorient frequently	Repeatedly introduce yourself, even if patient has met you multiple times across multiple days Provide written information on reason for hospitalization, medications and treatments as this can be referenced by patient as much as they need

The most compelling evidence in the literature is that of oxcarbazepine, which has been shown in a randomized, double-blinded study to significantly decrease aggression (assessed by the Global Overt Aggression Scale) compared with placebo.[20] This is a very effective agent in the management of acute agitation in TBI, particularly in those with mood lability and irritability. It is generally well tolerated and safe, although close monitoring of liver function tests and sodium must ensure that transaminitis and hyponatremia do not develop. A starting dose of 150 mg twice daily can be titrated to a target dosing of 600 mg twice daily. Valproic acid at a mean dose of 1250 mg has also been shown to reduce agitated behavior in one retrospective chart review examining 29 inpatients; however, this was a sample of participants with all types of acquired brain injuries.[21] The benefit of valproic acid in the inpatient settings is that it is available in oral and intravenous forms. It may be used to manage agitation in TBI on an "as-needed"

TABLE 3. General Pharmacologic Practice in Managing Acute Agitation in TBI

1. Start at lower doses with slow, gradual titration
2. Complete therapeutic trial of all medications
3. Continuously reassess the clinical condition
4. Monitor drug-drug interactions
5. Avoid polypharmacy
6. Consider coexisting medical conditions

TBI = traumatic brain injury.

basis (125 mg every 6 h as needed or agitated) in addition to low starting standing doses of 125 mg twice daily titrated to a maximum of 1250 mg daily. Close monitoring of liver function tests, lipase, ammonia levels, and platelet counts should be routinely monitored, as transaminitis, pancreatitis hyperammonemic encephalopathy, and thrombocytopenia are all side effects that can occur with valproic acid treatment.

Methylphenidate has been shown to reduce anger in 39 rehabilitation outpatients,[22] and typically a starting dose of 2.5 mg slowly titrated to a daily dose of 20–30 mg might improve irritability in younger, healthy patients without comorbid cardiac conditions. Furthermore, methylphenidate might be of particular use in managing aggression in patients with cognitive impairment from moderate to severe TBI.[23] Studies examining amantadine and sertraline have shown no overall improvement in reduction of agitation when compared with placebo in acute settings, and amantadine has in fact been shown to exacerbate agitation.[24–29] Finally, clonidine has been used in acute rehabilitation settings to manage agitation that might come from hyperarousal due to nightmares and post-traumatic stress, although it does not have evidence for management of agitation.[30]

Several observational studies have reported a reduction in agitation with the use of antipsychotics to manage agitation in TBI; however, to date, only olanzapine has been studied in a randomized controlled trial. Waidele et al.[31] found significant reduction in irritability and insomnia in patients treated with olanzapine. Olanzapine may be used in those with imminent aggression and combative behaviors as it can be delivered in an intramuscular and orally dissolving form. Quetiapine may be used at lower doses to manage agitation in TBI and typically is a first-line oral agent in clinical practice to manage acute agitation, with initial studies showing some potential protective effects on the blood-brain barrier and in delaying neurodegeneration. Further studies will be needed to explore these potential benefits further.[32,33] High-potency neuroleptics (possibly due to higher D2 receptor–binding affinity) should be avoided because these can impair neuronal growth and have increased propensity to cause extrapyramidal side effects in patients with TBI.[34,35]

Agents that worsen confusion such as medications with anticholinergic properties and benzodiazepines should be avoided. No high-quality human studies have been conducted in the use of benzodiazepines in TBI, whereas animal models reveal that they may impair neuronal recovery.[36,37] In patients with TBI, the use of benzodiazepines must take into account the risk of exacerbating aggravating distress, eliciting a paradoxical effect on agitation, hindering brain plasticity capacities, and dependence and/or addiction potential.[12]

"As-needed" or prn medications should serve the purpose of managing breakthrough agitation in between scheduled doses of medication administration and to alert the clinician that a patient may require or tolerate up to a certain dosing. Scheduled medications should be strongly considered when it is anticipated that the patient will require frequent prn's within a 24-hour period. Very slow titration of low dosing should be prescribed.

As discussed previously, environmental approaches to managing agitation in TBI in acute settings should generally aim to maintain a calm, peaceful environment while minimizing forceful interventions such as restraints and intramuscular administration of meds unless there is imminent risk of aggression.

CONCLUSION

The behavioral presentation of TBI is multifactorial. A patient's unique cognitive deficits as well as psychiatric changes such as mood dysregulation and anxiety contribute to behavioral disturbances. Environmental stressors, medication side effects, physical limitations, and pain are also important factors affecting behavior. A multidisciplinary approach to create a targeted behavioral plan and selection of appropriate evidence-based pharmacology to address specific symptoms is paramount in regards to management of these patients. Additionally, factors affecting behavior in patients with

TBI are dynamic so recurrent psychoeducation and reevaluation of behavioral interventions and medications are essential in providing adequate care for these patients.

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