Agitated and depressed with a traumatic brain injury

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Mr. N, age 46, has a history of alcohol use disorder, insomnia, anxiety, and depression. He is brought to the ED with a TBI after repeatedly beating his head into a table. How can you help him?

CASE TBI as a result of self-harm

Mr. N, age 46, presents to the emergency department (ED) after his neighbors report hearing "loud banging sounds" coming from his apartment for approximately 3 days. Emergency medical services found him repeatedly beating his head into a table. Upon admission to the ED, his injuries include a right temporal lobe contusion, right temporal subdural hematoma, facial fractures, bilateral foot fractures, and prevertebral swelling at the C4 vertebrate.

Mr. N is admitted to the surgical intensive care unit for hourly neurology checks. Neurosurgery recommends nonoperative management and for Mr. N to wear a cervical collar for 1 month. He is sedated after he experiences auditory hallucinations and becomes agitated toward the staff, which is later determined to be delirium. The Psychiatry team recommends inpatient psychiatric hospitalization because Mr. N's self-harming behavior resulted in severe and dangerous injuries.

HISTORY Alcohol use disorder, insomnia, anxiety, and depression

As Mr. N becomes alert and oriented, he reports a history of alcohol use disorder (AUD), insomnia, anxiety, and major depressive disorder (MDD), but no personal or family history of bipolar disorder (BD). He says he has had insomnia and anxiety since age 18, for which he received diazepam and zolpidem for 16 years. He stopped diazepam soon after a recent change in psychiatrists and subsequently had difficulty sleeping. Mr. N started taking mirtazapine, but found minimal relief and stopped it several months ago.

Can a patient with elevated mood symptoms receive a diagnosis of MDD?

a) Yes; a patient does not need to have depressed mood to meet MDD criteria, as long as anhedonia is present
b) No; the patient must have depressed mood to meet MDD criteria
c) Yes; elevated mood and MDD symptoms do not have to occur simultaneously, but rather can occur in alternating periods
d) None of the above

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The authors' observations

The term "agitated depression" refers to a mixed state that includes symptoms of depression plus marked anxiety, restlessness, and delusions. Agitated depression is not a distinct diagnosis in DSM-5, but is classified as depression with mixed features.[1] To meet the criteria for the mixed features specifier, a patient who meets the criteria for a major depressive episode needs to have ≥3 of the following manic/hypomanic symptoms[1]:

- Elevated, expansive mood
- Inflated self-esteem or grandiosity
- More talkative than usual
- Flight of ideas or racing thoughts
- Increase in energy or goal-directed activity
- Increased involvement in activities that have a high potential for painful consequences
- Decreased need for sleep.

The diagnosis for individuals who meet the full criteria for mania or hypomania would be BD I or BD II.[1] Additionally, mixed features associated with a major depressive episode are a significant risk factor for BD.[1]

EVALUATION Agitation and hallucinations

Mr. N recalls multiple falls at home in the weeks prior to hospitalization, but says he does not remember repeatedly hitting his head against a table. He reports sleeping for approximately 2 hours per night since his father's death 2 months ago, an acute stressor that likely precipitated this depressive episode. Mr. N says he had been experiencing visual hallucinations of his father and a younger version of himself for weeks before presenting to the ED. It is not clear if Mr. N does not recall beating his head on the table due to his traumatic brain injury (TBI) or because it occurred during an acute manic or psychotic episode with hallucinations.

The treatment team assigns Mr. N a working diagnosis of agitated depression with a risk for BD, mixed episode. He meets the criteria for agitated depression (major depressive episode, motor agitation, and psychic agitation), but also has many features of BD; a manic episode may have led to hospitalization. The treating clinicians continue to monitor the progression of Mr. N's symptoms to clarify his diagnoses. During the course of his hospitalization, Mr. N's psychiatric diagnoses include delirium (resolved), alcohol withdrawal, catatonia, substance-induced mood disorder, and agitated depression. Mixed episode BD is ruled out.

The authors' observations

There is significant symptomatic overlap between agitated depression and BD. It can be difficult to differentiate the diagnoses, as psychomotor agitation can be seen in MDD and agitated depression can be seen in BD. Serra et al[2] investigated the prevalence of agitated depression in patients with BD and found that agitation accompanied bipolar depression in at least one-third of cases and was associated with concurrent somatic depressive symptoms, which are common features of mixed manic states. Psychomotor agitation was also associated with lifetime experience of mixed mania, comorbid panic disorder, and increased suicidal behavior.[2]

Though antidepressants are considered a first-line treatment for depression, they should not be used to treat agitated depression because they may increase insomnia, agitation, and suicide risk, and may trigger the onset of psychotic symptoms. In a similar vein, antidepressant monotherapy is contraindicated in BD because it may induce mania or hypomania states.[2]

TREATMENT Neuroprotective psychotropics

Due to Mr. N's medical complexity (particularly cervical collar and physical therapy

Clinical Point

Antidepressants should not be used to treat agitated depression because they may increase insomnia, agitation, and suicide risk

Table

Psychotropic medications for treating traumatic brain injury

Neuroprotective	Equivocal	Not neuroprotective
Sedative agents: dexmedetomidine **Antipsychotics**: aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, asenapine, lurasidone, brexpiprazole, cariprazine **Cognitive enhancers**: memantine, donepezil **Antiepileptics**: valproic acid, levetiracetam, lacosamide, zonisamide, lamotrigine, phenobarbital **Others:** ketamine, lithium, pramipexole, amantadine, trazodone, buspirone, immediate use of benzodiazepines after ischemia	Gabapentin	**Sedative agents**: propofol **Antipsychotics**: haloperidol, clozapine **Antiepileptics**: carbamazepine, oxcarbazepine, pregabalin, phenytoin **Others**: methylphenidate, chronic use of benzodiazepines

Source: References 3-6

Clinical Point

Neuroprotection is the priority when treating agitated depression in a patient with a traumatic brain injury

needs), he is not transferred to a psychiatric facility. Instead, the consultation-liaison psychiatry team follows him and provides psychiatric care in the hospital.

Due to concerns for continued self-harm, Mr. N is observed by continuous video monitoring. After initial stabilization, the care team starts valproic acid 250 mg twice daily and titrates it to 500 mg/d in the morning and 1,000 mg/d in the evening for mood stabilization, gabapentin 300 mg 3 times daily, melatonin 3 mg/d at bedtime for insomnia, and lorazepam 1 mg/d at bedtime to rule out catatonia and 1 mg/d as needed for agitation. After starting valproic acid, the care team routinely checks Mr. N's ammonia levels throughout his hospitalization.

Which of the following may offer the most neuroprotection in a patient with an acute TBI?

a) Olanzapine
b) Haloperidol
c) Gabapentin
d) Methylphenidate
e) Carbamazepine

The authors' observations

Treatment of agitated depression both in isolation and in the context of BD presents a clinical challenge because antidepressants are contraindicated for both agitated depression and BD. In the context of TBI, treatment of agitated depression becomes more complicated because neuroprotection is the priority. Neuroprotection refers to a medication's ability to prevent neuronal cell death or further injury or damage through neurochemical modulation.

To treat agitation associated with MDD, second-generation antipsychotics and valproic acid have shown significant neuroprotective effects. The proposed mechanisms for neuroprotection include not only antioxidant effects but 5HT1A agonist properties, with the latter thought to protect against excitotoxic injury that may exacerbate agitation due to brain trauma.[3]

There is no consensus on which antipsychotics are most efficacious for treating agitation in the setting of an acute TBI. Williamson et al[4] reviewed various medications that may treat agitation in the setting of acute TBI with fewer adverse effects.

Though haloperidol is often prescribed to treat agitation in patients with TBI, animal studies have shown it is inferior to second-generation antipsychotics in protecting against excitotoxic/oxidative injury, and haloperidol has been associated with neuronal loss. Haloperidol has been linked to adverse clinical outcomes for patients with aggression after TBI, including prolonged amnesia, which is thought to be linked to haloperidol's

strong and selective dopamine-2 receptor antagonism and the mesocortical and nigrostriatal pathways involved.[4]

Carbamazepine, phenytoin, and methylphenidate cause oxidative stress and/or apoptosis, and therefore offer no neuroprotection. Data on gabapentin are mixed; a few studies suggest it may block synapse formation or decrease quantities of antioxidant enzymes in the brain, though it's known to protect against glutamate-induced neuronal injury.[3]

Additional research is needed to assess which second-generation antipsychotics offer the most neuroprotection. However, based on existing literature, olanzapine and aripiprazole may offer the most benefit because they have the greatest antioxidant—and thus, neuroprotective—activity. Cognitive enhancers such as memantine and donepezil exhibit neuroprotection, particularly in Alzheimer disease. Anticonvulsants such as levetiracetam, lacosamide, and lamotrigine offer neuroprotection and may be considered for seizure prevention.[3] The ***Table***[3-6] (***page 46***) lists psychotropic medications used to treat TBI.

Valproic acid stands out among anticonvulsants because its superior antioxidant effects, in combination with its antiepileptic effect in patients with TBI, offer more neuroprotection than other medications.[5] It is important to regularly monitor ammonia levels in patients receiving valproic acid because elevated levels can cause hyperammonemic encephalopathy.

A 2005 study by DeBattista et al[5] investigated the impact of valproic acid on agitation in 12 adults with MDD who were being treated with antidepressants. Participants were given a low dose of valproic acid for 4 weeks and their agitation, anxiety, and depressed mood were independently assessed by separate rating scales. There was a modest decrease in scores for mood symptoms but a particularly sharp decrease in agitation scores.[5]

Valproic acid has been shown to be a potentially safe and efficacious treatment for alcohol withdrawal. A clinical trial examining patients with moderate alcohol withdrawal found a faster and more consistent resolution of symptoms in patients given valproic acid detoxification compared to a control group that received the

Related Resources

- Ramaswamy S, Driscoll D, Rodriguez A, et al. Nutraceuticals for traumatic brain injury: should you recommend their use? Current Psychiatry. 2017;16(7):34-38,40,41-45.
- Sampogna G, Del Vecchio V, Giallonardo V, et al. Diagnosis, clinical features, and therapeutic implications of agitated depression. Psychiatr Clin North Am. 2020;43(1):47-57. doi: 10.1016/j.psc.2019.10.011

Drug Brand Names

Amantadine • Gocovri
Aripiprazole • Abilify
Asenapine • Saphris
Brexpiprazole • Rexulti
Buspirone • BuSpar
Carbamazepine • Tegretol
Cariprazine • Vraylar
Clozapine • Clozaril
Dexmedetomidine • Igalmi
Diazepam • Valium
Donepezil • Aricept
Gabapentin • Neurontin
Haloperidol • Haldol
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Olanzapine • Zyprexa
Oxcarbazepine • Trileptal
Paliperidone • Invega
Phenytoin • Dilantin
Pramipexole • Mirapex
Pregabalin • Lyrica
Quetiapine • Seroquel
Risperidone • Risperdal
Trazodone • Oleptro
Valproic acid • Depakene
Ziprasidone • Geodon
Zolpidem • Ambien
Zonisamide • Zonegran

Clinical Point

Second-generation antipsychotics have significant neuroprotective effects

Bottom Line

Agitated depression is a mixed state that includes features of depression and manic/hypomanic symptoms. Diagnosis and treatment can be challenging because symptoms of agitated depression overlap with bipolar disorder and antidepressants are contraindicated. In a patient with a traumatic brain injury, pharmacotherapy that provides neuroprotection is a priority.

standard benzodiazepine detoxification.[6] Additionally, patients who continued maintenance valproic acid following detoxification were completely abstinent at 6-week follow-up compared to patients who did not receive this maintenance therapy.[6]

Valproic acid was a particularly optimal medication choice for Mr. N due to its neuroprotective properties in the context of TBI, its ability to treat delirium,[7] its lack of abuse potential compared with benzodiazepines, and its potential efficacy for managing alcohol withdrawal and AUD.

Clinical Point

Valproic acid has neuroprotective properties and potential efficacy for treating delirium and alcohol withdrawal

OUTCOME Improvement and discharge

Mr. N is medically cleared for discharge. Although the psychiatry team initially was concerned about his willingness to attend follow-up appointments and adhere to proper cervical collar use, Mr. N becomes more cooperative with psychiatric care as his stay continues, and he is psychiatrically cleared for discharge 1 month after admission. Discharge plans include attending an intensive outpatient program, continuing the inpatient psychiatric medication regimen, participating in regular outpatient psychiatric follow-up, as well as following up with orthopedic surgery, neurosurgery, podiatry, and ear, nose, and throat for medical conditions.

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