Current PSYCHIATRY

Traumatic brain injury: Choosing drugs to assist recovery

Some agents can worsen neurobehavioral symptoms

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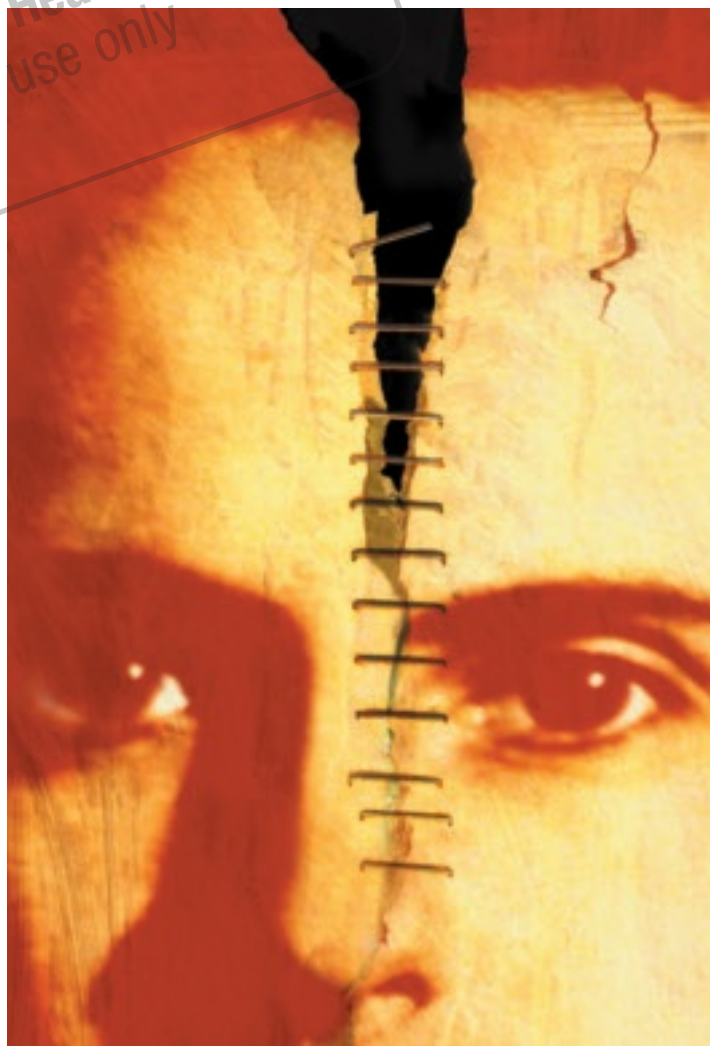

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Choosing medications for patients with traumatic brain injury (TBI) requires caution; some drugs slow their recovery, and no standard post-TBI treatment exists.

As consulting psychiatrist on a TBI rehabilitation team, I am asked to manage enduring cognitive and emotional problems—aggression, apathy, learning disabilities, dementia—in patients with moderate to severe head injuries. This article describes how we apply available evidence to treat neurobehavioral symptoms in these patients.

CASE: AN IRAQ WAR CASUALTY

The physical medicine and rehabilitation service asks for help in managing agitation, anxiety, and nightmares in Mr. N, age 20, a U.S. combat soldier. While on patrol 2 months ago in Iraq, he suffered a penetrating right frontoparietal brain injury from an improvised explosive device.

continued

Table 1

Using Glasgow Coma Scale (GCS) scores to evaluate brain injury severity

Component	Response	Score
Best eye response	No eye opening	1
	Eye opening to pain	2
	Eye opening to verbal command	3
	Eyes open spontaneously	4
Best verbal response	No verbal response	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Confused	4
	Oriented	5
Best motor response	No motor response	1
	Extension to pain	2
	Flexion to pain	3
	Withdrawal from pain	4
	Localizing pain	5
	Obeys commands	6

GCS total score ≥12 is mild injury, 9 to 11 is moderate, and ≤8 is severe (90% of patients with scores ≤8 are in a coma). Coma is defined as not opening eyes, not obeying commands, and not saying understandable words. Composite scores with eye, verbal, and motor responses (such as E3V3M5) are clinically more useful than totals.

Source: Reference 2.

Mr. N has undergone a right temporoparietal craniectomy with debridement, ventriculostomy placement, and scalp flap closure. He has had seizures and then pancreatitis—thought to be caused by divalproex prescribed to treat the seizures. Divalproex was replaced with phenytoin at our hospital, and the pancreatitis resolved.

HOW SERIOUS AN INJURY?

TBI ranges from self-limited concussion to devastating, permanent CNS impairment and life-long disability. Brain injuries from sudden impact—from assaults, falls, motor vehicle accidents, combat, or sports—can cause diffuse axonal injury and confusion or unconsciousness, even without radiographic evidence of cerebral bleeding, edema, or mass effect.

No hierarchy or nomenclature is universally accepted for TBI. The term "concussion" is generally used for milder injury and TBI for more-severe injuries.

Concussion. The American Academy of Neurology defines concussion as a trauma-induced alteration in mental status that may or may not involve loss of consciousness. Confusion and amnesia—the hallmarks of concussion—may occur immediately after the head trauma or several minutes later.[1] This definition recognizes three concussion grades:

- Grade 1: confusion lasts <15 minutes, with no loss of consciousness (LOC)
- Grade 2: confusion persists >15 minutes but without LOC
- Grade 3: concussion with LOC. The confusional state is marked by disorientation, delayed verbal and motor responses, inattention, incoordination, emotional lability, and slurred or incoherent speech.

TBI. The severity of an injury with LOC is usually determined by four factors: the patient's initial Glasgow Coma Scale (GCS) score in the emergency department (*Table 1*),[2] neuroimaging, duration of coma, and duration of posttraumatic amnesia (PTA).

- Mild TBI: GCS 13 to 15, LOC <20 to 30 minutes, PTA <24 hours, and normal neuroimaging studies.[1,3]
- Moderate TBI: GCS 9 to 12, LOC 30 minutes to 7 days, and PTA 24 hours to 7 days.
- Severe TBI: GCS ≤8, LOC, and PTA >7 days,[4] or any focal neuroimaging abnormalities.[3]

CASE CONTINUED: 'THEY'RE HURTING ME'

Mr. N meets criteria for severe TBI. He is periodically agitated and aggressive and refuses to return to physical therapy, complaining that rehabilitation nurses are intentionally hurting him. He occasionally hits the staff and throws things. His medications include:

- phenytoin, 100 mg every 6 hours for seizure prophylaxis
- lamotrigine, 50 mg bid for seizure prophylaxis
- zolpidem, 5 mg as needed at bedtime for pain
- methadone, 10 mg/d for pain
- oxycodone, 5 mg every 4 hours as needed for breakthrough pain.

Mr. N's recovery 2 months after injury is rated as Rancho level IV, indicating that he remains confused and agitated. He requires maximal assistance with bed mobility and transfers, upper and lower extremity dressing, and rolling his wheelchair with both feet. He is incontinent of bowel and bladder.

Table 2

10-level Rancho Los Amigos Scale for assessing TBI recovery

Level	Cognitive and adaptive function	Assistance required
I	No response	Total assistance
II	Generalized response	Total assistance
III	Localized response	Total assistance
IV	Confused/agitated	Maximal assistance
V	Confused, inappropriate non-agitated	Maximal assistance
VI	Confused, appropriate	Moderate assistance
VII	Automatic, appropriate	Minimal assistance
VIII	Purposeful, appropriate	Stand-by assistance
IX	Purposeful, appropriate	Stand-by assistance on request
X	Purposeful, appropriate	Modified independent

Source: Traumatic Brain Injury Resource Guide. www.neuroskills.com/tbi/rancho.html.

ASSESSING PROGRESS

For patients such as Mr. N, TBI recovery progress is measured with the Rancho Los Amigos Scale.

The original Rancho scale—developed in 1972 by staff at the Rancho Los Amigos rehabilitation hospital in Downey, CA—described eight levels of cognitive and adaptive functioning, from coma and total care through normal cognition and independence. A 1997 revised version separates the highest cognitive functioning level (VIII, purposeful, appropriate function) into three parts, expanding the scale to 10 levels (*Table 2*).[5]

Of course, not all TBI patients begin recovery at Rancho level I, and unfortunately not all achieve level X. Some experience dementia caused by head trauma, with persistent memory impairment and cognitive deficits in language, apraxia, agnosia, or executive function.[6]

Most patients recover as predicted by the initial injury's severity. Others experience diffuse cerebral swelling with sudden, rapid deterioration after what appeared to be a grade 1 or grade 2 concussion. Diffuse cerebral swelling is sometimes considered a "second-impact syndrome," but it can also occur after a single impact.[7] A second TBI is not universally believed to cause the precipitous decline, but animal studies suggest an additive effect of rapid sequential TBI.[8]

Post-TBI syndromes. Concussion and TBI share diffuse axonal injury as a putative pathophysiologic mechanism. Post-concussion and post-TBI

Table 3

Medications with potential to impede TBI recovery*

Class	Medications
Alpha-2 agonist	Clonidine
Antidepressant	Trazodone
Antiepileptic	Phenytoin, phenobarbital
Benzodiazepine	Diazepam
Neuroleptic	Haloperidol, thioridazine

* Suggested by animal or clinical studies
Source: References 11-20

syndromes are similar but vary in severity and duration. Signs and symptoms include headache, light-headedness or dizziness, poor attention and concentration, irritability with low frustration tolerance, anxiety or depression, sensitivity to bright light or loud noise, and sleep disturbance.[1]

Recovery for a patient such as Mr. N with Rancho level IV to V TBI may be complicated by marked mood lability, spontaneous aggression, psychomotor agitation, extremely short attention with marked distractibility, little to no short-term memory, and noncooperation with treatment and care. Patients may also show disorders of diminished motivation, characterized by normal consciousness but decreased goal-directed behavior and affective flattening.[9]

CASE CONTINUED: CALLING IN REINFORCEMENTS

Besides combat nightmares, Mr. N is experiencing other signs of posttraumatic stress disorder (PTSD): intrusive memories of dead comrades, anhedonia, insomnia, irritability, and hypervigilance. We recommend a trial of citalopram, 10 mg/d, but within 1 week he becomes more irritable, agitated, and aggressive, with worsening sleep. We arrange a meeting to obtain collateral information from Mr. N's aunt, mother, and clinical psychologist. We learn that a first-degree relative had bipolar disorder, and Mr. N lived with various relatives during childhood.

As a child, Mr. N was easily angered, hyperactive, unpredictably aggressive with peers, and impulsive. He was diagnosed with "explosive disorder and attention disorder" at age 8. A psychiatrist prescribed methylphenidate (which helped) and paroxetine (which worsened his behavior and aggression). Based on this history, we make a presumptive diagnosis of comorbid bipolar disorder.

TREATING PSYCHOPATHOLOGY

Comorbidities. Adolescents and adults with pre-existing attention-deficit/hyperactivity disorder or bipolar disorder may be predisposed to carelessness or risk taking that lead to accidents and TBI. Likewise, alcoholism and substance use disorders are risk factors for head injuries. These pre-existing conditions will complicate the post-TBI course and must be treated concurrently.

Depression and PTSD may follow a head injury and complicate recovery. In fact, post-TBI symptoms—poor sleep, poor memory and concentration, and irritability—are common to both depression and PTSD.

A team approach. Regardless of its severity or recovery stage, TBI requires multidisciplinary treatment. Physical, occupational, and speech therapies are essential initially. As recovery progresses, vocational rehabilitation may need to be added. Throughout rehabilitation, supportive individual and family therapy can help patients reintegrate into the community. Psychologists, neuropsychologists, and clinical social workers are indispensable to the treatment team.

MEDICATION PRECAUTIONS

Using medications to manage post-TBI syndromes is difficult and controversial. No standard regimen exists, and few clinical trials guide treatment. Small, uncontrolled studies (human and animal)

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suggest commonly prescribed drugs may worsen outcomes (*Table 3, page 60*).[10,11] For example:

- Cognitive function improved in three TBI patients after thioridazine was discontinued in two and haloperidol in one.[12]
- Haloperidol given to 11 patients with TBI made no difference in rehabilitation outcomes when compared with 15 patients who did not receive the antipsychotic. Those receiving haloperidol also had longer post-trauma amnesia (5 to 30 weeks), compared with the untreated group (1 to 18 weeks).[13]
- In animal studies of TBI, motor recovery was slowed with haloperidol but not olanzapine,[14,15] and with clonidine,[16] phenytoin,[17] and trazodone.[18] Phenobarbitol[19] and diazepam[20] have been associated with delayed behavioral recovery and chronic behavior problems, respectively, in rats with TBI. How these agents might affect human patients is speculative.

Apathy and inattention. A review of 63 papers found no strong evidence that drugs are effective for TBI's neurobehavioral disorders, although weak evidence shows that some drug classes can reduce target symptoms—such as psychostimulants for apathy, inattention, and slowness (*Table 4, page 66*).[21] Other reports suggest reasonable approaches:

- Psychostimulants have improved recovery of motor function in animal trials if given before physical therapy.[14]
- Stimulants and dopaminergic agonists such as bromocriptine and amantadine might help disorders of diminished motivation.[22]
- Dextroamphetamine and methylphenidate have improved impulsivity, memory, and concentration in a patient with TBI.[23]

Agitation and aggression in TBI are more difficult to treat than apathy or inattention. Some authors[15,24] suggest that atypical antipsychotics are more effective than neuroleptics for these symptoms and less likely to cause adverse effects (*Table 5, page 67*).

continued

Table 4

Drugs considered safe and effective for TBI neurobehavioral symptoms

Target symptom(s)	Drug	Usual daily dosage*
Apathy	Amantadine	100 to 400 mg
	Bromocriptine	1.25 to 100 mg
Cognition	Donepezil	
Inattention	Dextroamphetamine	5 to 60 mg
	Methylphenidate	10 to 60 mg
Depression, PTSD symptoms	Fluoxetine	20 to 80 mg
Agitation, mood stabilization	**Anticonvulsants**	
	Lamotrigine	25 to 200 mg
	Divalproex sodium	10 to 15 mg/kg/day†
	Carbamazepine	400 to 1,600 mg‡
	Atypical antipsychotics	
	Olanzapine	2.5 to 20 mg
	Quetiapine	50 to 800 mg
	Risperidone	0.5 to 6 mg
	Ziprasidone	20 to 160 mg
	Beta blocker	
	Propranolol	20 to 480 mg

PTSD: posttraumatic stress disorder
* Dosage may be divided; see full prescribing information.
† Adjust dosage to achieve serum level of 50 to 100 mcg/mL.
‡ Adjust dosage to achieve serum level of 4 to 12 mcg/mL.

Small studies of anticonvulsants for post-TBI agitation report:

- valproic acid might improve behavioral control and decrease aggression, and it did not worsen performance on neuropsychological testing
- carbamazepine reduced agitation in seven TBI patients and reduced anger outbursts in 8 of 10 others
- gabapentin caused paradoxical effects in two TBI patients[25]
- lamotrigine improved agitation in one TBI patient.[26]

Five studies show preliminary evidence that beta blockers (usually propranolol) can reduce assaultive behavior and temper outbursts in TBI patients. Relatively high dosages are usually needed, such as:

- propranolol, 420 to 520 mg/d
- pindolol, 60 mg/d
- metoprolol, 200 mg/d.[21]

Psychiatric comorbidity. In TBI patients with comorbid bipolar disorder, mood stabilization with an atypical antipsychotic, anticonvulsant (divalproex sodium, carbamazepine), or a combination of the two is first-line therapy. No evidence suggests that using lithium in the absence of mania improves aggression, agitation, or other neurobehavioral symptoms in TBI patients.[21]

Depression and PTSD in TBI patients are considered indications for selective serotonin reuptake inhibitors (SSRIs). Animal data suggest that fluoxetine is safe for patients with TBI,[27] though no human data have been published.

For PTSD with bipolar depression, we usually prescribe lamotrigine or combine an atypical antipsychotic with an SSRI. Lithium would be second-line therapy. PTSD with bipolar mania is more difficult to treat because little evidence guides medication choices. As with depression and PTSD, we usually combine an atypical antipsychotic with an SSRI. We try to control manic and psychotic symptoms first, then add the

SSRI for anxiety after the mood becomes more stable.

Cognitive impairment. A dozen published studies and case reports indicate that donepezil improves cognition in subacute and chronic TBI. For example:

- An open-label trial showed subjective improvement in cognitive functions in 8 of 10 patients given donepezil.[28]
- In a double-blind, placebo-controlled, crossover trial, short-term memory and attention improved with donepezil in 18 patients with post-acute TBI, as shown by neuropsychological test scores.[29]
- A retrospective case-control study showed no significant difference in cognitive outcome between controls and 18 patients prescribed donepezil but did suggest that cognition improved more rapidly when patients started donepezil earlier in recovery.[30]

Table 5

Dosing atypical antipsychotics for agitation and aggression in TBI

Drug	Initial daily dosage*	Maximum daily dosage*
Aripiprazole	2.5 to 5 mg	30 mg
Olanzapine	2.5 mg	20 mg
Quetiapine	12.5 to 50 mg	800 mg
Risperidone	0.25 mg	8 mg
Ziprasidone	20 mg	160 mg

*Daily dosages may be divided

CASE CONTINUED: BACK TO REHAB

We replace Mr. N's phenytoin with carbamazepine, 700 mg/d (serum level about 12 mcg/mL), discontinue citalopram, and start him on quetiapine as a mood stabilizer, titrating the dosage to 600 mg/d over 3 weeks. We select quetiapine based on experience using it as a mood stabilizer and carbamazepine for additional mood stabilization and seizure prophylaxis.

We continue methadone and oxycodone at the same dosages for pain management, with good results. We eventually switch him from zolpidem to trazodone, 50 mg as needed at bedtime. We discontinue lamotrigine because he is no longer having seizures.

Mr. N tolerates quetiapine and carbamazepine well. The nursing staff reports he is much less irritable and aggressive and his sleep has improved, but he is not oversedated. He returns to and participates in physical, occupational, and speech therapies.

TIPS FOR USING MEDICATIONS

Many TBI patients are unusually sensitive to or intolerant of medication side effects. Because no randomized, controlled clinical trials support using any medication in these patients, be cautious. The following recommendations can help:

- **Use psychotropics** with a low risk of complications.
- **Start with low dosages and increase gradually** to assess side effects and efficacy of medication trials.
- **Give full trials** and adequate dosing before you decide a medication has not improved symptoms sufficiently.

Bottom Line

No psychotropics are approved to treat enduring cognitive and emotional symptoms of traumatic brain injury (TBI). Some common medications may impair patients' recovery. When trying medications reported as potentially useful for target TBI symptoms, start low and go slow to assess side effects and effectiveness.

continued

- **Monitor** closely for side effects.
- **Seek information** from family members to evaluate a medication's effectiveness, as patients' cognitive deficits may limit their ability to reliably report symptoms.

Related resources

- Silver JM, McAllister TW, Yudofsky SC (eds). *Textbook of traumatic brain injury*. Arlington, VA: American Psychiatric Press, 2005.
- Traumatic Brain Injury Resource Guide. www.neuroskills.com

DRUG BRAND NAMES

Amantadine • Symmetrel
Bromocriptine • Parlodel
Carbamazepine • Tegretol
Citalopram • Celexa
Clonidine • Catapres
Dextroamphetamine • Dexedrine
Diazepam • Valium
Divalproex sodium • Depakote
Donepezil • Aricept
Fluoxetine • Prozac
Gabapentin • Neurontin
Haloperidol • Haldol
Lamotrigine • Lamictal
Methadone • Dolophine
Methylphenidate • Ritalin
Metoprolol • Lopressor
Olanzapine • Zyprexa
Oxycodone • Oxycontin
Paroxetine • Paxil
Phenobarbital • Luminal
Phenytoin • Dilantin
Pindolol • Visken
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal
Thioridazine • Mellaril
Trazodone • Desyrel
Ziprasidone • Geodon
Zolpidem • Ambien

DISCLOSURE

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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