

# Traumatic brain injury: Choosing drugs to assist recovery

Some agents can worsen neurobehavioral symptoms

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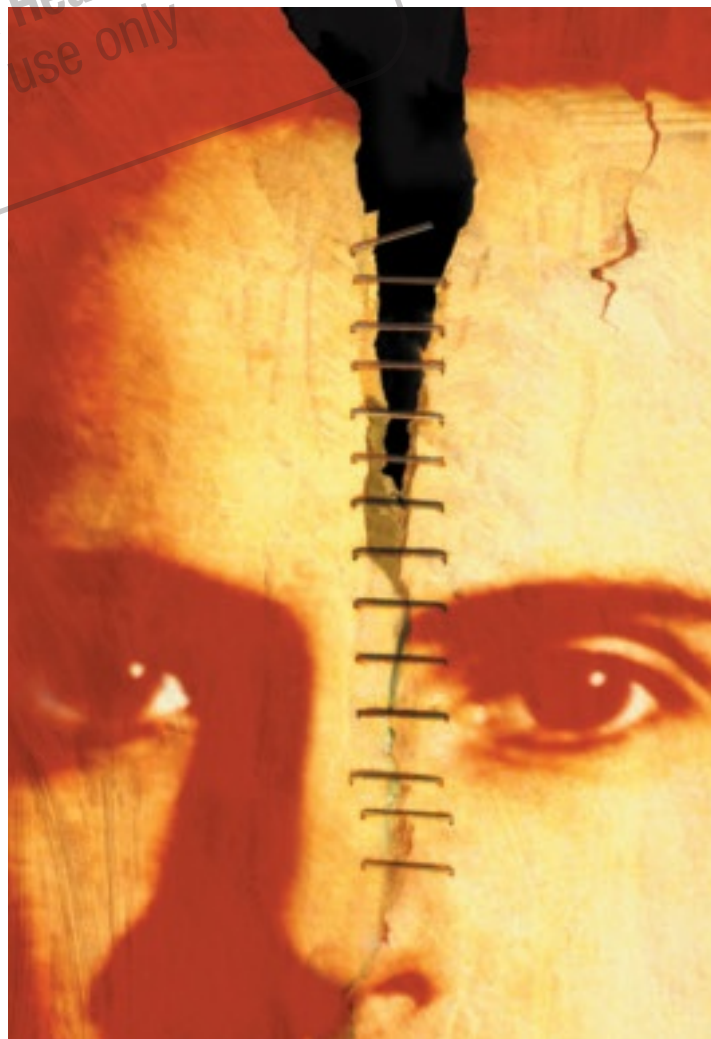
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**C**hoosing medications for patients with traumatic brain injury (TBI) requires caution; some drugs slow their recovery, and no standard post-TBI treatment exists.

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.



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continued



Table 1

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

Component	Response	Score
<b>Best eye response</b>	No eye opening	1
	Eye opening to pain	2
	Eye opening to verbal command	3
	Eyes open spontaneously	4
<b>Best verbal response</b>	No verbal response	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Confused	4
	Oriented	5
<b>Best motor response</b>	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  $\geq 12$  is mild injury, 9 to 11 is moderate, and  $\leq 8$  is severe (90% of patients with scores  $\leq 8$  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.<sup>1</sup> 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*),<sup>2</sup> 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.<sup>1,3</sup>
- Moderate TBI: GCS 9 to 12, LOC 30 minutes to 7 days, and PTA 24 hours to 7 days.
- Severe TBI: GCS  $\leq 8$ , LOC, and PTA >7 days,<sup>4</sup> or any focal neuroimaging abnormalities.<sup>3</sup>

**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.

**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*).<sup>5</sup>

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](http://www.neuroskills.com/tbi/rancho.html).

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.<sup>6</sup>

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.<sup>7</sup> A second TBI is not universally believed to cause the precipitous decline, but animal studies suggest an additive effect of rapid sequential TBI.<sup>8</sup>

**Post-TBI syndromes.** Concussion and TBI share diffuse axonal injury as a putative pathophysiological 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.<sup>1</sup>

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.<sup>9</sup>

**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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## Traumatic brain injury

vasodilatation, thinking abnormal, decreased libido, and sweating. **Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD—Body as a Whole:** asthenia, headache, flu syndrome, accidental injury, abdominal pain. **Cardiovascular:** vasodilatation, hypertension, palpitation. **Digestive:** nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. **Metabolic/Nutritional:** weight loss. **Nervous System:** dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonía, paresthesia, libido decreased, agitation, anxiety, twitching. **Respiratory System:** pharyngitis, yawn, sinusitis. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. **Vital Sign Changes:** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS—Sustained Hypertension**). **Laboratory Changes:** Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR—N=6,670.** "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, proctitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports:** agranulocytosis, anaphylaxis, aplastic anemia, catatonía, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE:** Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE:** Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

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suggest commonly prescribed drugs may worsen outcomes (Table 3, page 60).<sup>10,11</sup> For example:

- Cognitive function improved in three TBI patients after thioridazine was discontinued in two and haloperidol in one.<sup>12</sup>
- 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).<sup>13</sup>
- In animal studies of TBI, motor recovery was slowed with haloperidol but not olanzapine,<sup>14,15</sup> and with clonidine,<sup>16</sup> phenytoin,<sup>17</sup> and trazodone.<sup>18</sup> Phenobarbital<sup>19</sup> and diazepam<sup>20</sup> 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).<sup>21</sup> Other reports suggest reasonable approaches:

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

**Agitation and aggression** in TBI are more difficult to treat than apathy or inattention. Some authors<sup>15,24</sup> 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*
<b>Apathy</b>	Amantadine	100 to 400 mg
	Bromocriptine	1.25 to 100 mg
<b>Cognition</b>	Donepezil	
<b>Inattention</b>	Dextroamphetamine	5 to 60 mg
	Methylphenidate	10 to 60 mg
<b>Depression, PTSD symptoms</b>	Fluoxetine	20 to 80 mg
<b>Agitation, mood stabilization</b>	<b>Anticonvulsants</b>	
	Lamotrigine	25 to 200 mg
	Divalproex sodium	10 to 15 mg/kg/day <sup>†</sup>
	Carbamazepine	400 to 1,600 mg <sup>‡</sup>
	<b>Atypical antipsychotics</b>	
	Olanzapine	2.5 to 20 mg
	Quetiapine	50 to 800 mg
	Risperidone	0.5 to 6 mg
	Ziprasidone	20 to 160 mg
	<b>Beta blocker</b>	
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<sup>25</sup>
- lamotrigine improved agitation in one TBI patient.<sup>26</sup>

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.<sup>21</sup>

**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.<sup>21</sup>

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,<sup>27</sup> 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.<sup>28</sup>

- 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.<sup>29</sup>

- 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.<sup>30</sup>

### 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.

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

### 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.

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.

**BottomLine**

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.

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### 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](http://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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