CHAPTER 11

Pharmacologic Management of the Patient With Traumatic Brain Injury

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Medication management for individuals who have sustained a traumatic brain injury (TBI) remains one of the most confusing, challenging, and rewarding areas of medicine. The challenges associated with the management of these individuals is understandable; the human brain is perhaps the most complex and poorly understood structure in the universe. We are only beginning to appreciate the nuances of its function.

To add further complexity to the situation, no two injuries are exactly alike. Our current crude method of classification of brain injury into "mild, moderate, and severe" categories remains woefully inadequate. The challenges brought on by the complexity of this situation has manifest itself in the generally scant objective evidence to support the use of medications following brain injury. Because the situation is far more complex than "mild, moderate, and severe," and researchers continue to group together many individuals in the same category, the resulting output has been numerous failed trials and inadequate objective information to guide clinicians in "evidence-based practice."

Despite this, through careful observation and collection of a plethora of anecdotal information, as well as borrowing from experience in treatment and research into medical management of other neurologic conditions, some generalities can be gleaned. This chapter will focus on what is generally considered the standard of practice for medication administration in the rehabilitation of individuals following TBI.

PHILOSOPHY OF MEDICATION MANAGEMENT AFTER BRAIN INJURY: GENERAL GUIDELINES

There are some general concepts regarding medication management after TBI that are important to follow when possible. In today's medical care climate, with pressures placed on the pace of rehabilitation by our current reimbursement system, these concepts are getting harder to follow. However, these guidelines should be followed whenever possible.

*It is more important what **not** to give than what **to** give*

Given the complexity of the brain, as well as the nuances associated with its injury, there is a strong argument to do nothing. Knowing that the brain will recover neurologically to a large degree without any medication, rehabilitation efforts should be focused on standard therapy and biological support. In fact, there may be more evidence regarding the potential harm that certain classes of medications may do to the recovering brain. Understanding the harmful impact that these medications may have, and avoiding these medications, may in the long run have more benefit to these patients than even administrating other ones.

Err on the side of cognition

Often, clinicians are faced with a choice between treating a condition associated with TBI and the potentially adverse consequences of the treatment. A perfect example of this is spasticity management. Therapy staff will often strongly encourage physicians to administer antispasticity medications in an attempt to improve some aspect of a patient's function. However, almost all of these medications have untoward cognitive side effects. Often, a choice must be made between *cognitive function* and *physical function*. When given this choice, directing your actions on improving cognitive function is usually preferred when caring for patients with brain injury.

Pick a direction and go with it

There are often patients who present with two or more competing problems, wherein treating one may worsen another. A clinician needs to avoid the temptation to place a patient on two different medications with competing pharmacologic mechanisms of action; for example, do not place a patient on both a pro- and

an antidopaminergic medication at the same time. In these cases, *de duobus malis minus eligendum*—pick the lesser of two evils and go that direction. Additionally, the previous rule applies—err on the side of cognition. In many cases, *doing nothing* may be the most appropriate course of action.

One change at a time

It is best to start making one change and observing the effects before making another change, either adding or removing a medication or making dose adjustments.

Start low, go slow

This rule may be the most difficult to follow in today's fast-paced rehabilitation environment. However, following injury, nerve cells are lost, affecting the neurotransmitter levels and the presence of receptors and the nerves that they work on, making any medication administration effect potentially different from that in an uninjured brain. It is imperative to be judicious in the initial dosing of medication.

Observe the effects of your changes carefully

It is important to closely monitor the changes that each change has in the patient's cognitive and functional performance. Patients may exhibit effects from medication administration that will be unexpected.

Be willing to change direction if results necessitate it

Keep in mind that the injured brain may not respond to medications normally. Disrupted pathways, insufficient receptors, and breakdown of the blood-brain barrier are some of the many factors that may change the way the individual responds to medication administration. Carefully observe if the medication is having the intended effect, or in some cases, a different effect altogether. The astute clinician must be willing to change direction when the clinical circumstances require it.

COGNITION

Disorders of Consciousness and Hypoarousal

Recent research into disorders of consciousness (DOC) has resulted in an exponential increase in the understanding of this problem. There is now potential for cautious optimism where previously there was little to no hope for individuals with DOC following TBI. The findings in research on patients with DOC has led to treatments that are useful in individuals with hypoarousal and slowed cognitive processing speed following brain injury as well. Arousal is the foundation upon which every other cognitive function in the brain rests. Therefore improving arousal is the most basic facet of improving cognitive function following TBI.

Amantadine is an antiviral agent with antiparkinsonian actions. Its mechanism of action is not fully understood, but it appears to increase dopamine availability in the central nervous system (CNS) and also acts as a weak *N*-methyl-D-aspartate (NMDA) antagonist. It has been shown to improve arousal in patients with moderate to severe TBI.[1] In a placebo-controlled trial of 184 patients in a vegetative or minimally conscious state 1–4 months from TBI, patients received for 4 weeks either amantadine or placebo while in the inpatient rehabilitation setting. Those in the treatment group had an increased rate of recovery as measured by the Disability Rating Scale (DRS) during the 4-week treatment period. Overall improvement in DRS was similar between the groups at 6 weeks.[2] In a placebo-controlled, crossover study of 35 subjects in the acute phase after TBI, a trend toward more rapid functional improvement was demonstrated during the 6-week amantadine treatment.[3]

Bromocriptine is a dopamine agonist at the dopamine type 2 receptor. It was noted to improve arousal in a small, retrospective chart review of five patients in vegetative state.[4] Bromocriptine may also have dual use as an agent to improve autonomic instability in individuals exhibiting dysautonomia in association with impaired level of arousal.

Levodopa/carbidopa has also been used in DOC. Levodopa is a precursor of dopamine. Carbidopa is a decarboxylase inhibitor that inhibits the peripheral conversion of levodopa to dopamine and increases the availability of levodopa in the CNS. Haig and Ruess reported the case of a 24-year-old man in a vegetative state 6 months after TBI who, within days of starting levodopa/carbidopa, became responsive and conversant.[5] Additionally, Matsuda et al. reported four cases of patients in persistent vegetative states and one case of a patient in a minimally conscious state who had improved responsiveness when levodopa was initiated for parkinsonian symptoms.[6,7] A prospective study of eight patients in the vegetative state for an average duration of 104 days after TBI showed improvement in consciousness, with seven patients recovering consciousness with incremental doses of levodopa.[8]

Modafinil is a CNS stimulant that promotes wakefulness through an unclear mechanism of action. In a recent small retrospective pilot study, modafinil was associated with improved arousal in patients with prolonged DOC.[9] The efficacy of modafinil for treating fatigue and excessive daytime sleepiness (EDS) in

patients with chronic TBI has also been investigated. In a small placebo-controlled, double-blind pilot study, administration of modafinil for 6 weeks improved EDS, but not fatigue.[10] In contrast, a double-blind, placebo-controlled crossover trial of 53 patients with TBI at least 1 year postinjury found that modafinil (400 mg daily) had no significant effect on EDS or fatigue.[11]

Zolpidem is a nonbenzodiazepine sedative-hypnotic that acts as a γ-aminobutyric acid (GABA) agonist with preferential binding to the ω-1 receptor. Several case reports have reported a paradoxical increase in arousal with the use of zolpidem in patients with DOC.[12–21] A placebo-controlled, double-blind, single-dose, crossover study of 84 patients with DOC for at least 4 months found a temporary response in 4.8% of patients after a 10 mg dose of zolpidem. Responders could not be distinguished from nonresponders based on demographic or clinical features.[20] The temporary response may necessitate more frequent dosing to maintain arousal.

Methylphenidate is a CNS stimulant that increases dopamine and norepinephrine levels by blocking reuptake. Few studies have investigated its effect on improving arousal. Martin and Whyte performed a meta-analysis of a series of single-subject repeated crossover trials in 22 patients with DOC secondary to brain injury and found no significant effect of methylphenidate on responsiveness or command following.[22] However, another study demonstrated that individuals with severe TBI had shorter intensive care unit and total hospital lengths of stay.[23] The hypothesis behind this effect is that methylphenidate improved the level of arousal in individuals who received it, allowing them to progress more quickly. Methylphenidate is associated with numerous anecdotal reports of improved arousal and is frequently used in this setting by clinicians. However, clinicians must exercise caution with this medication early after injury because it may exacerbate autonomic dysfunction, particularly tachycardia and hypertension.

Additional dopaminergic agents that have been investigated in DOC include pramipexole and apomorphine. Patrick et al. performed a small randomized, double-blind trial with 10 children and adolescents who were treated with either pramipexole or amantadine. Both groups showed improvement, and there was no difference in arousal between the two medications.[24] In an open-label pilot study, subcutaneous apomorphine was continuously infused in eight patients in vegetative or minimally conscious state after TBI. Improvements were seen within 1 day to 1 month, and seven patients recovered consciousness.[25]

There have also been limited reports suggesting improvement in arousal in patients with DOC with intrathecal baclofen therapy.[26–28]

Attention and Processing Speed

Disorders of attention and processing speed are extremely common following brain injury. Impairments in attention and processing speed have effects on many downstream cognitive functions, such as memory and executive function. Attempts to treat attention problems are often a focus of clinicians trying to improve the overall cognitive function in individuals following brain injury. Most clinicians utilize medications that are typically used for attention disorders in other non-TBI populations. Unfortunately, despite much anecdotal evidence of efficacy, there is little objective evidence supporting the use of particular medications for attention problems following TBI.

Methylphenidate is probably the single medication most widely studied for use for various problems after TBI. Several studies have supported the use of methylphenidate to improve attention and/or processing speed after brain injury. In a randomized controlled trial of 34 patients with moderate to severe TBI in the postacute phase of recovery, 6 weeks of methylphenidate resulted in an increase in processing speed and attentiveness with some on-task behaviors.[29] In a randomized, crossover, double-blind study of 40 patients with moderate to severe TBI in the postacute phase, methylphenidate (0.3 mg/kg twice a day) demonstrated improvement in processing speed.[30] A smaller prospective multiple baseline design study demonstrated improved attention with methylphenidate in patients in the subacute phase of acquired brain injury.[31] Additionally, a randomized, placebo-controlled, double-blind trial in 23 patients in the subacute phase after complicated mild to moderately severe TBI showed an improvement in attention with 30 days of methylphenidate.[32]

Dextroamphetamine is another CNS stimulant that has been studied in patients with TBI with attentional impairments. In a single-subject double-blind, placebo-controlled crossover study, dextroamphetamine resulted in improved cognitive processing efficiency in a patient with TBI 5 years earlier.[33] A retrospective chart review of patients with severe TBI reported a positive effect on attention with dextroamphetamine.[34] Lisdexamfetamine dimesylate, a prodrug of dextroamphetamine, has recently been studied in the moderate to severe TBI population. A randomized, double-blind, placebo controlled crossover trial of 13 patients in the postacute phase of injury demonstrated improvement in sustained attention and working memory with lisdexamfetamine dimesylate.[35]

Donepezil is an acetylcholinesterase inhibitor that is commonly used in the treatment of Alzheimer disease. One randomized, placebo-controlled crossover trial of patients in the postacute period after TBI demonstrated improvement in attention with donepezil.[36] A smaller case series of patients with chronic TBI reported significant improvement in processing speed, learning, and divided attention with donepezil.[37]

Atomoxetine is a selective norepinephrine reuptake inhibitor used for the treatment of attention-deficit/hyperactivity disorder. There have been limited investigations for its use in TBI, but there is much anecdotal evidence supporting its efficacy for attention disorders following TBI.[38] One randomized, placebo-controlled, crossover trial of patients with chronic moderate to severe TBI with subjective attentional difficulties demonstrated no improvement in attention with 2 weeks of atomoxetine therapy.[39]

Bromocriptine is also a medication that has been used to treat attentional deficits following TBI. Like other medications, however, objective evidence is lacking. One double-blind, placebo-controlled, crossover pilot study investigating the effect of bromocriptine on attention in patients with moderate to severe TBI was conducted in the postacute period of recovery. No improvement in attention was found with bromocriptine treatment.[40]

Like other dopaminergic medications, amantadine has also been used for attention impairment. In a series of patients with frontal lobe dysfunction, improved attention with amantadine treatment was demonstrated.[41] Conversely, in a small double-blind, placebo-controlled, crossover trial of 10 patients with moderate to severe TBI in the subacute phase of recovery, amantadine demonstrated no effect on attention.[42]

Citicoline is available in the United States as a nutraceutical and has been used clinically outside the United States for many years for stroke and head trauma. A large, randomized, double-blind trial of 1213 patients with mild to severe TBI demonstrated no difference in attention, processing speed, memory, or functional status with 90 days of citicoline compared with placebo.[43]

Memory

Memory impairment is also very common following TBI with up to 80% found to have ongoing problems with memory following TBI.[44] This is frequently cited as one of the most "problematic" long-term issues following TBI.

The mainstay of treatment of memory disorder following TBI are the acetylcholinesterase inhibitors. These medications act by preventing the breakdown of acetylcholine in the synapse, making it more bioavailable. This effect is hypothesized to occur primarily in the hippocampus. Originally this effect was noted with physostigmine.[45,46] However, the effect is too short-acting to be practical for most patients. Donepezil is currently the most commonly used medication in this class, with most research evidence supporting its use. A randomized, placebo-controlled crossover trial demonstrated memory improvement in the postacute period after TBI with donepezil.[36] Notably, in the initial treatment group, improvements were sustained after the washout period and placebo phase, suggesting a carryover effect of donepezil. This effect has also been observed clinically. A smaller study using a single-subject research design also demonstrated improvement in memory with donepezil.[47] Similarly, a single-subject multiple baseline design study of three adolescents with severe TBI demonstrated improved memory with donepezil.[48]

Rivastigmine is another acetylcholinesterase inhibitor that has been studied in patients with TBI with persistent cognitive impairment. Objective evidence of efficacy, however, is lacking. In a large, randomized, double-blind, placebo-controlled trial of 157 patients with mild to severe TBI, no significant difference was found in cognition with rivastigmine treatment.[49] A posthoc analysis of more severely impaired patients found some significant improvements in the rivastigmine group. In a randomized, double-blind, placebo-controlled crossover trial of patients with mild to severe TBI, no significant improvement was found with rivastigmine treatment in the majority of computerized neuropsychologic tests. Significant improvement was also reported in subtraction test and 10- to 15-min vigilance test.[50]

Galantamine is another acetylcholinesterase inhibitor that has been utilized for memory dysfunction following TBI. No human subject trials have been performed, although anecdotal evidence suggests that it is effective. A rodent study demonstrated cognitive improvement following TBI.[51]

Memantine is an NMDA antagonist that is indicated for moderate to severe Alzheimer dementia. Anecdotal evidence suggests that it has efficacy for improving memory impairment in individuals with TBI. Although no human studies have been done for patients with TBI, rodent studies demonstrate evidence of neuroprotective effects following brain trauma.[52,53] Anecdotal reports indicate that some patients may have irritability and worsening behavior problems with memantine.

Ginkgo is a dietary supplement that is derived from the *Ginkgo biloba* tree and has been reported to have

neuroprotective and cognition-enhancing properties.[54,55] At this time no studies investigating its use in humans with TBI have been published.

Methylphenidate is often used to enhance general cognitive performance, including memory. Its mechanism is likely "upstream" improvements in attention and processing speed rather than direct effect on memory function. However, in a double-blind, placebo-controlled trial, a single dose of methylphenidate (20 mg) resulted in significant improvement in working memory and visuospatial attention compared with placebo.[56] In contrast, two randomized controlled trials have reported no effect of methylphenidate on memory after TBI.[32,57]

Executive Functioning

There have been a limited number of studies investigating potential pharmacotherapies for executive dysfunction after brain injury. One case study reported improvements in executive function in a patient 5 years post-TBI with amantadine. Further improvements were noted with the addition of levodopa/carbidopa.[41] An open-label study of patients with chronic TBI reported significant improvements in executive function with amantadine treatment (400 mg daily). Positron emission tomography was performed on six of these patients and demonstrated increased left prefrontal cortex glucose metabolism with treatment.[58] Additionally, a randomized, double-blind, placebo-controlled crossover trial of patients with severe TBI demonstrated improvement in executive function with low-dose bromocriptine.[59]

Aphasia

The role of pharmacotherapies in the treatment of aphasia and communication impairments post-TBI has not been established. In patients with poststroke aphasia, several investigations have studied the effect of medications that augment catecholaminergic and cholinergic functions. Medications that may aid in the improvement of poststroke aphasia include donepezil,[60,61] galantamine,[62] dextroamphetamine,[63,64] memantine,[65] and piracetam.[66–68] Studies of the effectiveness of bromocriptine and levodopa have been mixed (Table 11.1).[69–72]

Agitation

Agitation is a common occurrence following a TBI. Due to a lack of consensus on a singular definition, the incidence has been reported to range from 11% to 70% following a moderate to severe injury.[73,74] In 1997, a survey of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation was conducted to determine national patterns of defining agitation.[75] Following this survey, a unifying definition for posttraumatic agitation was devised.

TABLE 11.1
Medications for Cognition

Problem	Medication	Dosing (Start/Max)	Common Side Effects	Comments
Hypoarousal	Amantadine	Start: 100 mg bid Max: 200 mg bid dose in the morning and at noon	Dizziness, insomnia, nausea	Contraindicated in pregnancy, breastfeeding; likely epileptogenic
	Bromocriptine	Start: 2.5 mg bid Max: 10 mg bid Dose in the morning and noon	Nausea, constipation	Uncontrolled hypertension, breast feeding, preeclampsia
	Levodopa/Carbidopa	Start: 50 mg/25 mg bid	Constipation, dizziness, orthostatic hypotension	Contraindicated in closed-angle glaucoma, MAOi therapy, melanoma
	Zolpidem	Start: 5 mg daily Max dose for paradoxical arousal is unknown	Sedation	Only effective in select subpopulation with disorder of consciousness
	Modafinil	Start: 100 mg bid Max: 200 mg bid Dose in the morning and at noon	Headache, nausea	

Continued

TABLE 11.1
Medications for Cognition—cont'd

Problem	Medication	Dosing (Start/Max)	Common Side Effects	Comments
Attention and processing speed	Methylphenidate	Start: 10 mg bid Max: 72 mg/day Various formulations	Anorexia, nausea, vomiting, insomnia	May worsen anxiety, glaucoma, contraindicated with MAOi therapy; concern for abuse
	Atomoxetine	Start: 18 mg daily Max:100 mg daily	Xerostomia, nausea, insomnia	Closed-angle glaucoma, MAOi therapy, pheochromocytoma
	Dextroamphetamine	Start: 5 mg daily Max: 60 mg daily	Headache, irritability, insomnia, anorexia	Substance abuse, glaucoma, hyperthyroidism, MAOi therapy, arteriosclerosis
	Lisdexamfetamine	Start: 30 mg daily Max: 70 mg daily	Anorexia, insomnia, irritability, xerostomia	Contraindicated in MAOi therapy
Memory	Donepezil	Start: 5 mg daily Max: 10 mg daily	Diarrhea, insomnia, nausea, headache	
	Rivastigmine	Start: 1.5 mg bid Max: 6 mg bid	Diarrhea, nausea, vomiting, anorexia, dizziness	
	Galantamine	Start: 4 mg bid Max: 12 mg bid	Diarrhea, nausea, vomiting,	
	Memantine	Start: 5 mg daily Max: 10 mg bid	Headache, diarrhea, dizziness	Has been associated with increased irritability in TBI

bid, twice daily; *MAOi*, monoamine oxidase inhibitor; *Max*, maximum; *TBI*, traumatic brain injury.

Posttraumatic agitation was defined as "a subtype of delirium unique to survivors of a TBI in which the survivor is in the state of post-traumatic amnesia and there are excesses of behavior that include some combination of aggression, akathisia or inner restlessness that may manifest in motor activity, disinhibition, and/or emotional lability."[76]

Addressing posttraumatic agitation is a critical component of brain injury rehabilitation. The first step to accurate diagnosis and treatment is the identification of factors that may be contributing to or confounding the diagnosis such as pain, infections and metabolic derangements, atypical seizure activity, endocrine dysfunction such as hyperthyroidism, and drug or alcohol withdrawal.[77] Once such factors are corrected, environmental and behavioral modifications should be utilized as first-line treatment. Promoting good sleep patterns and sleep hygiene is of critical importance. In addition, minimizing sensory stimulation can help mitigate agitation. Examples include reducing ambient noise, dimming lights, and limiting the number of individuals interacting with a patient to avoid overstimulation. For patients with akathisia, allowing freedom of movement through supervised ambulation or wheelchair mobility may help behavior. Physical restraints can worsen agitation and should be avoided whenever possible. If restraints are necessary due to patient safety concerns, less restrictive restraints such as bed enclosures, wheelchair wraparound belts, and soft mitts should be utilized. Finally, a structured behavioral plan may help in identifying precipitating behaviors and providing clinical staff with safe techniques for intervention.

Pharmacologic interventions may need to be utilized if a patient continues to be at risk for self-harm or causing harm to others despite environmental and behavioral modification. Certain classes of medications including typical antipsychotics and benzodiazepines should generally be avoided because of their potential to impair neurorecovery.[78,79] A 2006 Cochrane review found nonselective β-blockers such as propranolol to have the most evidence for treatment of posttraumatic agitation.[80] This medication also treats posttraumatic

TABLE 11.2
Medications for Agitation

Medication	Starting Dose	Common Side Effects	Comments
Propranolol	10 mg prn	Sedation, hypotension, bradycardia, orthostasis	Also helpful for dysautonomia
Trazodone	25 mg prn	Sedation, priapism	Avoid high doses
Valproic acid	125 mg bid	Hepatic impairment, sedation, weight gain, rash	
Carbamazepine	100 mg bid	Blood dyscrasias, Syndrome of Inappropriate AntiDiuretic Hormone Release (SIADH), hepatic impairment, rash	
Risperidone	0.5 mg prn	Sedation, akathisia, metabolic impairment	
Quetiapine	25 mg prn	Sedation, anticholinergic side effects	May result in confusion in elderly patients
Olanzapine	2.5 mg prn	Sedation, rash, metabolic impairment, weight gain, hypotension, dizziness	Available as injection; may have a paradoxical arousal effect at low doses
Ziprasidone	Oral 20 mg prn IM 10 mg prn	QT prolongation, hypotension, dizziness, electrolyte disturbance, metabolic changes, akathisia	
Buspirone	5 mg bid	Dizziness, nausea, headache, nervousness, light-headedness.	Contraindicated with MAOi
Amantadine	100 mg daily	Dizziness, insomnia, nausea	Contraindicated in pregnancy, breastfeeding; Is likely epileptogenic

bid, twice daily; *IM*, intramuscular; *MAOi*, monoamine oxidase inhibitor.

autonomic dysregulation and therefore serves as an ideal medication choice for patients with concurrent issues. Side effects to monitor for include hypotension and bradycardia. Trazodone, a commonly used sleep agent, may be effective in decreasing agitation and can be utilized in the inpatient rehabilitation setting as a first-line "as-needed" agent during episodes of increased agitation and is often the drug of choice of "experts" in the field of brain injury medicine.[81] Mood stabilizers such as valproic acid and carbamazepine can also be utilized. A retrospective study demonstrated decreased agitation within 1 week of valproic acid administration in over 90% of sampled patients.[82] Potential adverse effects may include medication toxicity, hepatotoxicity, and thrombocytopenia. In addition to valproic acid, studies have demonstrated the effectiveness of carbamazepine in treating posttraumatic agitation.[83,84] Potential adverse effects may include medication toxicity, renal failure, hyponatremia, and hematologic dysfunction. In addition, the possible teratogenic side effects of mood stabilizers must be considered with use in the female population. Atypical antipsychotics such as risperidone and quetiapine have also been utilized in the treatment of agitation. These agents are generally favored over typical antipsychotics given less dopamine blockade, which results in a safer side effect profile and less potential for extrapyramidal symptoms, and multiple studies suggesting impairment in neurologic and functional recovery with typical antipsychotics. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported to reduce post-TBI aggression and irritability.[85] In addition, buspirone, a serotonin 1A receptor partial agonist, may be useful in addressing agitation related to anxiety.[86] Interestingly, neurostimulants such as amantadine are increasingly being trialed for the treatment of posttraumatic agitation given that irritability and aggression may partially stem from slowed cognitive processing speed and the inability to effectively process sensory information (Table 11.2).[87,88]

SLEEP DISTURBANCE

Sleep disturbances have been reported in up to 70% of patients with TBI.[89] Regulating sleep is vital to cognitive recovery and is often the first point of intervention in the acute inpatient rehabilitation setting.

TBIs can result in a variety of sleep-wake disorders including insomnia, EDS, narcolepsy, sleep-related breathing disorders, and circadian rhythm sleep disorders

(CRSD). Insomnia is a common post-TBI sleep disorder, reported in 30%–60% of patients.[90] It is characterized by difficulty falling asleep or maintaining sleep. EDS has been reported in 14%–57% of patients[90] and is defined by the American Academy of Sleep Medicine as the inability to maintain wakefulness and alertness during the major waking episodes of the day. Of note, EDS must be differentiated from fatigue, which is a subjective lack of mental or physical energy. Narcolepsy is a less prevalent post-TBI sleep disorder, which involves poor control of sleep-wake cycles with rapid eye movement sleep intrusion into the wake state. Classically, it involves a tetrad of symptoms including EDS, cataplexy (a sudden and transient episode of muscle weakness), hypnagogic or hypnopompic hallucinations (visual or auditory perceptions upon falling or awakening from sleep), and sleep paralysis.[91] Sleep-related breathing disorders can occur following TBI and include obstructive sleep apnea caused by upper airway obstruction or central sleep apnea, which involves an intermittent neurologically mediated loss of respiratory effort. CRSD have also been reported following TBI and are defined as a mismatch between endogenous sleep-wake rhythms and the 24-h external light-darkness cycle. Often, melatonin secretion and body temperature are altered in CRSD.[90]

The diagnosis and treatment of post-TBI sleep disorders is a critical component of brain injury rehabilitation. The evaluation of sleep disturbances should first involve a comprehensive clinical interview. The interview should obtain key information related to pre- and postinjury patterns of sleep, sleep quality and quantity, the presence of EDS and daytime napping, and a review of systems to assess for other factors that may be contributing to the sleep disturbance. Such factors may include pain, mood disturbances, bowel and bladder dysfunction, movement disorders, medications, and the intake of other substances including caffeine, alcohol, and nicotine. In addition to the clinical interview, other subjective and objective measures may aid in diagnosis. Common subjective measures used include sleep diaries, sleep logs, and self-report questionnaires such as the Pittsburgh Sleep Quality Index and the Insomnia Severity Index for assessment of sleep quality and insomnia, the Epworth Sleepiness Scale for EDS, and the Morningness-Eveningness or Sleep Timing Questionnaires for CRSD. Objective measures include polysomnography and actigraphy.

The treatment of post-TBI sleep disorders usually requires a multifactorial approach including both nonpharmacologic and pharmacologic interventions. First, environmental and behavioral changes should be instituted to promote sleep hygiene. This includes developing a regular sleep schedule, following a daily bedtime routine, creating a restful bedroom environment with minimal light and optimal temperature, avoiding late night screen time, minimizing daytime napping, engaging in daily exercise, and limiting evening caffeine, alcohol, and nicotine intake. Other nonpharmacologic treatments supported by the literature include cognitive behavioral therapy, acupuncture, and bright light therapy. Finally, Continuous Positive Airway Pressure (CPAP) should be utilized for the treatment of sleep-related breathing disorders such as obstructive sleep apnea.

Certain classes of sleep medications are generally avoided in the TBI population because of potential adverse effects. Benzodiazepines may impair neurologic recovery as noted in prior animal studies[92,93] and can cause daytime sedation and anterograde amnesia. Anticholinergic medications such as tricyclic antidepressants (TCAs) and diphenhydramine can have detrimental cognitive side effects and potentially lower the seizure threshold.[94]

Trazodone is often used to promote sleep maintenance following a TBI. At lower doses, it acts as an effective hypnotic agent by blocking 5-hydroxytryptamine (HT)2A receptors and H1 histamine and α1 adrenergic receptors.[95] Melatonin has also been utilized in the treatment of TBI-related sleep disturbances. A 2016 study found that patients with TBI showed 42% less melatonin production overnight compared with healthy controls,[96] and a preliminary trial found that the use of melatonin was associated with improved daytime alertness.[97] Ramelteon is a melatonin receptor agonist approved by the Food and Drug Administration for the treatment of insomnia with sleep onset abnormalities. Preliminary evidence from a double-blind placebo-controlled trial demonstrated improvements in total sleep time and some aspects of cognitive functioning following a 3-week trial of ramelteon.[98] Other nonbenzodiazepine agents such as zolpidem and eszopiclone have been utilized to promote sleep initiation and maintenance following a TBI, although there are little data describing its effectiveness in this patient population. Amitriptyline is often useful for sleep and concomitant headache, but cognitive impairment and anticholinergic side effects limit its usefulness. It is frequently used with success for individuals with mild TBI. Finally, mirtazapine may be considered for use in patients with concomitant mood and appetite disturbances (Table 11.3).

MOOD AND PSYCHIATRIC ISSUES

Patients who have sustained a TBI may exhibit a number of comorbid psychiatric issues during their recovery. In many cases, treatment is the same as it would be

TABLE 11.3
Medications for Sleep

Medication	Dosing (Start/Max)	Common Side Effects	Comments
Trazodone	Start: 25 mg Max: 200 mg Dose once at bedtime	Sedation, priapism	Higher doses may result in antihistaminic effects
Melatonin	Start: 2 mg Max: unknown	Drowsiness	Timing of dosing is important
Ramelteon	Start: 8 mg Max: 8 mg	Depression, hallucinations, somnambulation, amnesia, hypogonadism	
Zolpidem	Start: 5 mg Max: 10 mg	Somnambulation, dizziness, headache	
Eszopiclone	Start: 1 mg Max: 3 mg	Behavior change, headache, unpleasant taste	Caution with liver impairment
Amitriptyline	Start: 25 mg Max: 150 mg	Anticholinergic side effects, worsening confusion	Avoid with moderate to severe TBI
Mirtazapine	Start: 15 mg Max: 45 mg	Suicidality, orthostatic hypotension, dizziness, weight gain, hepatic impairment	Case reports of agranulocytosis, contraindicated with MAOis

MAOis, monoamine oxidase inhibitors; *TBI*, traumatic brain injury.

for idiopathic psychiatric issues, with some reservations based on the need to keep in mind the concepts of neuroplasticity and recovery. Many psychotropic medications have adverse effects on neurologic and functional recovery, which must be kept in mind.

A review was conducted of psychotropic medications used for patients following moderate to severe TBI in an inpatient rehabilitation setting.[99] In a sample of 2130 patients, the most frequently administered medications were narcotic analgesics (72% of sample), followed by antidepressants (67%), anticonvulsants (47%), anxiolytics (33%), hypnotics (30%), stimulants (28%), antipsychotics (25%), and antiparkinson agents (25%). This study indicated that the use of psychotropic medications increased, rather than decreased, during the course of rehabilitation. Males and more severely impaired individuals tended to receive more psychotropic medications than other groups.

Depression

As many as 90% of individuals who have sustained brain injury will experience a transient episode of depression,[100] making it the most common mood disorder following TBI. In one study, 42% of patients referred for rehabilitation following TBI met the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for major depression.[101] In a 15-year follow-up, approximately 1% of individuals with TBI will commit suicide.[102] Antidepressant medications, therefore, are some of the most commonly prescribed medications in post-TBI care.[99]

There is general consensus among clinicians who care for individuals with TBI that antidepressant medications, particularly the SSRIs, facilitate neurologic recovery following TBI. However, objective evidence to support this is lacking, and in fact, one study demonstrated longer lengths of stay in inpatient rehabilitation for individuals who were prescribed antidepressants during their rehab stay.[103]

In general, because of their favorable side effect profile, and general lack of cognitive side effects, SSRIs are considered the drug class of choice for depression following TBI. There are several medications in this class. Sertraline, citalopram, and escitalopram are preferred because of better side effect profiles, quicker onset of action, and less sedation than other medications in this class, such as fluoxetine and paroxetine. This class has the added benefit of a secondary indication for anxiety as well.

The newer, serotonin-norepinephrine reuptake inhibitors (SNRIs) are also considered effective choices for depression. Medications in this class include duloxetine and venlafaxine. These medications have the added benefit of being effective treatments for neuropathic pain.

TABLE 11.4
Medications for Depression

Medication	Dosing (Start/Max)	Common Side Effects	Comments
Sertraline	Start: 50 mg daily Max: 200 mg daily	Nausea, diarrhea, tremor, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Citalopram	Start: 20 mg daily Max: 40 mg daily	QT prolongation, nausea, dizziness, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Escitalopram	Start: 10 mg daily Max: 20 mg daily	Suicide risk, nausea, diarrhea, insomnia, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Paroxetine	Start: 20 mg daily Max: 50 mg daily	Asthenia, sweating, nausea, diarrhea, decreased appetite, somnolence, dizziness, tremor, dry mouth, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Fluoxetine	Start: 20 mg daily Max: 60 mg daily	Unusual dreams, decreased libido, anorexia, tremor	Contraindicated with MAOis, monitor for serotonin syndrome
Amitriptyline	Start: 25 mg daily Max: 200 mg daily	Anticholinergic, sedation, confusion, seizures, confusion, ataxia, tremors, peripheral neuropathy, dizziness, weakness, fatigue, headache, paralytic ileus, hyperpyrexia, urinary retention, constipation, blurred vision, mydriasis, dry mouth	Acceptable for use in mild TBI, avoid in moderate to severe TBI; after prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise
Duloxetine	Start: 40 mg daily Max: 120 mg divided daily	Nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, sweating	Contraindicated with MAOis and narrow angle glaucoma
Venlafaxine	Start: 75 mg daily Max: 225 mg divided daily	Hypertension, insomnia, nervousness, dizziness	Contraindicated with MAOis and narrow-angle glaucoma; avoid use in myasthenia gravis

MAOis, monoamine oxidase inhibitors; *TBI*, traumatic brain injury.

TCAs are considered acceptable choices for depression following TBI, and have the added benefit of being useful for sleep. However, as this class of antidepressant is often associated with anticholinergic side effects, they are sometimes poorly tolerated. In addition, worsening confusion is often seen with the use of this class of medication, making it a group that is often avoided following TBI of greater severity. The most commonly used medication in this class is amitriptyline.

Monoamine oxidase inhibitors (MAOis) are considered to have excellent efficacy for refractory depression. However, the extensive list of drug and food interactions in this class makes this a category that most clinicians avoid following TBI.

Bupropion is an antidepressant medication in the aminoketone class. Its mechanism of action differs from that of tricyclics, SSRIs, MAOis, and SNRIs. It is theorized that its mechanism of action is both dopaminergic and noradrenergic.[104] This drug differs from other antidepressants in that it has an activating effect, rendering the patient more alert. It is also not associated with the sexual side effects, sedation, and weight gain seen with many other antidepressants, especially the SSRIs. In theory, its mechanism of action and side effect profile would seem to make it an ideal medication for use following brain injury. One case report has suggested improvement in refractory motor restlessness following TBI with this medication.[105] However, caution must be used with this medication, especially in more severely injured patients, because of the associated risk of lowering the seizure threshold. Most clinicians prefer to avoid bupropion for patients with TBI for this reason.

Other medications are often useful as adjunct medications for the treatment of depression. In particular, the traditional neurostimulants such as methylphenidate, are often used as "bridge" medications while starting another antidepressant because of the delayed onset of action of other antidepressants.[106,107] Other dopaminergic medications may also be used in this way, although they are not usually as efficacious (Table 11.4).

TABLE 11.5
Medications for Anxiety

Medication	Dosing (Start/Max)	Common Side Effects	Comments
Buspirone	Start: 5 mg bid Max: 20 mg tid	Dizziness, nervousness, insomnia, lightheadedness, nausea, headache	Avoid in combination with MAOis
Citalopram	Start: 20 mg daily Max:40 mg daily	QT prolongation, nausea, dizziness, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Escitalopram	Start: 10 mg daily Max: 20 mg daily	Suicide risk, nausea, diarrhea, insomnia, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Paroxetine	Start: 20 mg daily Max: 50 mg daily	Asthenia, sweating, nausea, diarrhea, decreased appetite, somnolence, dizziness, tremor, dry mouth, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Fluoxetine	Start: 20 mg daily Max: 60 mg daily	Unusual dreams, decreased libido, anorexia, tremor	Contraindicated with MAOis, monitor for serotonin syndrome
Sertraline	Start: 25 mg daily Max: 200 mg daily	Nausea, diarrhea, tremor, decreased libido	Not a first-line agent for anxiety, must titrate very slowly; contraindicated with MAOis

MAOis, monoamine oxidase inhibitors.

Anxiety

The second most common mood disorder seen following TBI is anxiety. One meta-analysis found that 37% of subjects with brain injury experienced "clinically relevant anxiety."[108] Anxiety has been associated with poorer outcomes, including poorer return to work rates and community reintegration following TBI.[109] Additionally, recent research has suggested a strong relationship between anxiety and subjective neurocognitive fatigue following TBI.[110] Therefore anxiety remains one of the most significant barriers to successful outcomes following TBI.

Complicating the treatment of anxiety is the fact that most anxiolytic medications are associated with significant cognitive side effects and may have an adverse impact on neuroplasticity and recovery. Benzodiazepines are the primary culprit in this area. Although demonstrably efficacious for many symptoms present following TBI, benzodiazepines are associated with impairment of neurologic recovery mechanisms and are therefore medications traditionally believed to be avoided following TBI.[111] Add to this the fact that benzodiazepines are strongly associated with sedation and disruption of normal sleep architecture, strong consideration should be given to using other medication classes before using a benzodiazepine for the routine treatment of anxiety following TBI.

The class of SSRIs are noted to be good for the treatment of anxiety. Like with treatment of depression, the side effect profile is relatively favorable, and these medications are both efficacious and well tolerated. Paroxetine, citalopram, and escitalopram are probably the most effective medications in this class, although paroxetine is often associated with clinically significant sedation. Citalopram and escitalopram have both been associated with reduction of anxiety symptoms in both rodent and human studies following TBI.[112–114]

Buspirone is a 5-HT1A receptor agonist that is associated with anxiolytic effects. It does not have affinity for GABA receptors. It has mild affinity for D2 dopamine receptors. Although clinical use of busprione has been historically thought to be associated with serotonergic syndrome, more recent research has largely dispelled this notion.[115] It has been found to be an effective anxiolytic with a benign side effect profile[116] for individuals with TBI (Table 11.5).[117]

Emotional Lability/Mania

Emotional lability is often associated with other psychiatric issues following TBI and may exacerbate the expression of these issues. Often, treatment of lability is necessary in association with treatment of other underlying mood conditions. Comorbid treatment of

mood issues with a mood-stabilizing medication has often been found to be more effective than treatment with a solitary agent alone. This is particularly true in the case of patients with agitated or explosive behavior.

Historically, emotional lability has been treated in psychiatric populations with lithium salts. Although lithium can be an effective treatment, its narrow therapeutic window and the need for reliable administration make it a difficult medication to use in the TBI population. It additionally may be associated with adverse outcomes.[118–124] However, more recent evidence suggesting potential neuroprotective effects may warrant its reevaluation as a useful treatment following TBI, if conditions for appropriate therapeutic management are present.[125–130]

More commonly, mood-stabilizing antiepileptic drugs (AEDs) are the drugs of choice for emotional lability following TBI.[131,132] Carbamazepine and valproic acid are frequently used. Both work relatively quickly, but both are associated with issues requiring frequent laboratory monitoring. Carbamazepine is associated with bone marrow suppression, which may result in anemia and pancytopenia. It is also associated with development of the syndrome of inappropriate antidiuretic hormone release. Valproic acid is associated with hepatic enzyme impairment, blood dyscrasias, and considerable sedation and weight gain. Another AED often used for emotional lability, which may have a superior side effect profile, is lamotrigine.[133–135] Lamotrigine is associated with a life-threatening rash in a small percentage of patients and must be titrated slowly to avoid this effect. This makes it difficult to effectively use this drug in the inpatient setting. Of these three medications, valproic acid tends to have the strongest mood-stabilizing effect.

SSRIs have also been frequently used for mood stabilization, but traditionally with those with more of a depressed affect.[114,136,137] Caution should be exercised for individuals with bipolar-type presentation, as monotherapy with SSRIs may result in mania (Table 11.6).

Involuntary Emotional Expressive Disorder

A mood disorder that has received considerable attention recently is the involuntary emotional expressive disorder (IEED). This syndrome is also known by many different names, such as pseudobulbar affect disorder, emotional incontinence, and involuntary laughing and crying. The hallmark of this disorder is outbursts

TABLE 11.6
Medications for Emotional Lability/Mania

Medication	Dosing (Start)	Common Side Effects	Comments
Valproic acid	125 mg bid	Hepatic impairment, sedation, weight gain, rash	Monitor for hepatic impairment
Carbamazepine	100 mg bid	Blood dyscrasias, SIADH, hepatic impairment, rash	May cause SIADH, blood dyscrasias including pancytopenia
Lamotrigine	25 mg daily/400 mg daily in divided doses	Suicidal thoughts, dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash	May cause life-threatening rash, use extreme caution in patients already taking valproic acid
Citalopram	20 mg/40 mg daily	QT prolongation, nausea, dizziness, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Escitalopram	10 mg/20 mg	Suicide risk, nausea, diarrhea, insomnia, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Paroxetine	20 mg/50 mg	Asthenia, sweating, nausea, diarrhea, decreased appetite, somnolence, dizziness, tremor, dry mouth, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Fluoxetine	20 mg/60 mg	Unusual dreams, decreased libido, anorexia, tremor	Contraindicated with MAOis, monitor for serotonin syndrome
Sertraline	25 mg/200 mg	Nausea, diarrhea, tremor, decreased libido	Not a first-line agent for anxiety, must titrate very slowly; contraindicated with MAOis

TABLE 11.6
Medications for Emotional Lability/Mania—cont'd

Medication	Dosing (Start)	Common Side Effects	Comments
Lithium	300 mg tid/titrate to therapeutic level	Tremor, polyuria, thirst, nausea,	Difficult to use in TBI due to narrow therapeutic window significant toxicity with supratherapeutic levels, may cause renal or hepatic impairment; may cause encephalopathy with concomitant administration of neuroleptics; use caution with diuretics, calcium channel blockers, SSRI's, acetazolamide
Valproic Acid	125 mg bid	Hepatic impairment, sedation, weight gain, rash	Monitor for hepatic impairment
Carbamazepine	100 mg bid	Blood dyscrasias, SIADH, hepatic impairment, rash	May cause SIADH, blood dyscrasias including pan-cytopenia

bid, twice daily; *MAOis*, monoamine oxidase inhibitors; *SSRIs*, selective serotonin reuptake inhibitors; *TBI*, traumatic brain injury; *tid*, thrice daily.

of expressed emotion, particularly laughing or crying, that occur out of proportion to the feeling of the individual. This disorder often results in socially awkward situations wherein the expression of emotion is inappropriate for the setting. For instance, the individual may involuntarily begin laughing uncontrollably at a funeral or in a church. Individuals with IEED will state that the emotion expressed is either inconsistent or out of proportion to how they actually feel internally. In addition, it is characteristic for the emotional expression to start and stop suddenly. The physiologic explanation of this syndrome is theorized to be disruption of pathways that connect the centers of emotional experience to the centers of emotional expression in the brain.

A combination treatment of dextromethorphan and quinidine (DXM-Q, brand name Nuedexta) has been formulated specifically to treat this condition.[138–142] Dextromethorphan has been known to have psychoactive properties for many years, yet its duration of action is quite short because of its rapid metabolism. Quinidine blocks the metabolism of dextromethorphan, increasing the duration of action. Because quinidine may affect the QT interval, it is necessary to perform electrocardiography before and after the initiation of this medication. Additionally, clinicians should be aware of the theoretical risk of seizures with the administration of dextromethorphan, although this has not seemed to be a problem in clinical practice.

Recent literature has suggested that SSRIs and TCAs may be equally effective in the treatment of IEED as DXM-Q.[143–145] Several case reports have suggested a significant improvement in IEED symptoms with sertraline in particular. One open-label trial suggested that the combination of paroxetine and DXM-Q was successful.[146] Another medication with anecdotal reports of benefit in IEED is lamotrigine (Table 11.7).[147]

Neuroses/Perseveration/Paranoia

Frequently, patients with brain injury will experience paranoid ideation, perseveration, or other neurotic behaviors or thought processes during their rehabilitation course. Often, these symptoms interfere with the rehabilitation process as the object of paranoid ideation often is associated with the treating clinicians. This is most likely to occur during the period of posttraumatic amnesia (PTA), although it can persist for longer periods. Typical perseverative thought processes often involve ideas that individuals feel that they need to leave the rehabilitation setting immediately to take care of some sort of business and that the treating therapists and physicians are somehow intending to harm them. Other subjects of perseveration include pain. When pain is the subject of the perseveration, it becomes difficult to engage the patient in any type of therapeutic activity because the patient believes that the pain will be exacerbated.

The treatments for neuroses, paranoia, and perseverative behavior are similar. In most cases, low doses of an atypical neuroleptic works quite well. Risperidone, ziprasidone, olanzapine, and quetiapine are all often useful. With all of these medications, the clinician

TABLE 11.7
Medications for Involuntary Emotional Expressive Disorder

Medication	Dosing (Start/Max)	Common Side Effects	Comments
DXM/q	Tabs contain 20 mg DXM and 10 mg Q Start: 1 tab daily Max: 1 tab bid	Diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased γ-glutamyltransferase, and flatulence	May cause QT prolongation; get EKG before and after starting. Contraindicated with MAOis
Citalopram	Start: 20 mg daily Max: 40 mg daily	QT prolongation, nausea, dizziness, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Escitalopram	Start: 10 mg daily Max: 20 mg daily	Suicide risk, nausea, diarrhea, insomnia, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Paroxetine	Start: 20 mg daily Max: 50 mg daily	Asthenia, sweating, nausea, diarrhea, decreased appetite, somnolence, dizziness, tremor, dry mouth, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Fluoxetine	Start: 20 mg daily Max: 60 mg daily	Unusual dreams, decreased libido, anorexia, tremor	Contraindicated with MAOis, monitor for serotonin syndrome
Sertraline	Start: 25 mg daily Max: 200 mg daily	Nausea, diarrhea, tremor, decreased libido	Not a first-line agent for anxiety, must titrate very slowly; contraindicated with MAOis

DXM, dextromethorphan; *MAOis*, monoamine oxidase inhibitors; *Q*, quinidine.

must monitor sedation, akathisia, metabolic function including glucose metabolism, and extrapyramidal side effects. The newer neuroleptic aripiprazole has outstanding potential for use in this area because it seems to be less associated with the typical extrapyramidal side effects and sedation than the other medications. However, this medication takes longer to reach steady state and therefore may not be as useful in the inpatient setting, where rapid efficacy is necessary. If monotherapy with a neuroleptic is ineffective, often the addition of a mood-stabilizing agent will result in success. Carbamazepine and valproic acid are both effective in this situation.

Use of neurostimulant medications in patients exhibiting these symptoms should be avoided. Often, neurostimulants will aggravate these symptoms. If a patient is on a neurostimulant medication and is exhibiting these symptoms, the first step is to stop those medications to see if the symptoms resolve (Table 11.8).

Psychosis/Hallucinations

Some patients with brain injury may exhibit florid hallucinations and psychotic behavior. In many cases, the psychotic behavior is associated with overtreatment with neurostimulant medications. Amantadine, which is becoming more commonly used following brain injury, is the most common culprit. However, all dopaminergic medications can be associated with psychosis. When this occurs, the first step is to discontinue the potentially offending medications.

If discontinuation of other medications does not result in resolution of the psychotic behavior, the treatment of choice is atypical neuroleptic medications. For patients with brain injury, risperidone, ziprasidone, olanzapine, and quetiapine have all been used with success. In a meta-analysis on evidence to support treatment of neurobehavioral consequences in 2006, olanzapine was reported to have the best objective evidence for the treatment of psychotic symptoms following TBI.[148] Treatment with typical neuroleptics, particularly haloperidol, is considered to be contraindicated following brain injury. Several studies have demonstrated worse functional outcomes in both animal and human studies for individuals given haloperidol following brain injury.[149–156] Additionally there are several case reports of individuals with brain injury developing neuroleptic malignant syndrome (NMS) following administration of haloperidol.[157–160] Patients with TBI appear to be more at risk for developing NMS than the general population. The explanation for this phenomenon is that individuals with TBI are dopamine-depleted or dopamine-insufficient as a result of their injury. Placing these patients on a high-potency neuroleptic may tip the balance and result in NMS (Table 11.9).

TABLE 11.8
Medications for Neuroses/Perseveration/Paranoia

Medication	Starting Dose	Common Side Effects	Comments
Risperidone	0.5 mg prn	Sedation, akathisia, metabolic impairment	
Quetiapine	25 mg prn	Sedation, anticholinergic side effects	May result in confusion in elderly patients
Olanzapine	2.5 mg prn	Sedation, rash, metabolic impairment, weight gain, hypotension, dizziness	Available as injection; may have a paradoxical arousal effect at low doses
Ziprasidone	Oral 20 mg prn IM 10 mg prn	QT prolongation, hypotension, dizziness, electrolyte disturbance, metabolic changes, akathisia	Available as injection
Valproic acid	125 mg bid	Hepatic impairment, sedation, weight gain, rash	Not for monotherapy
Carbamazepine	100 mg bid	Blood dyscrasias, SIADH, hepatic impairment, rash	Not for monotherapy

IM, intramuscular; *SIADH*, syndrome of inappropriate antidiuretic hormone release.

TABLE 11.9
Medications for Psychosis/Hallucinations

Medication	Starting Dose	Common Side Effects	Comments
Risperidone	0.5 mg prn	Sedation, akathisia, metabolic impairment	
Quetiapine	25 mg prn	Sedation, anticholinergic side effects	May result in confusion in elderly patients
Olanzapine	2.5 mg prn	Sedation, rash, metabolic impairment, weight gain, hypotension, dizziness	Available as injection; may have a paradoxical arousal effect at low doses
Ziprasidone	Oral 20 mg prn IM 10 mg prn	QT prolongation, hypotension, dizziness, electrolyte disturbance, metabolic changes, akathisia	Available as injection

IM, intramuscular.

Aggression/Explosive Behavior

Aggressive behavior often needs to be differentiated from "agitation" following TBI. Classically, individuals exhibiting agitated behavior are still in a state of PTA, and are beginning to emerge into the ability to perform purposeful behavior, whereas individuals with TBI may exhibit aggressive behavior at any point in their recovery. The aggressive behavior is usually in response to an external stimuli, and is not internally driven as in the classically agitated, confused patient. These individuals often have injury to the limbic system, particularly the amygdalae, resulting in dysregulation of emotional responses.

Treatment for aggressive outbursts and explosive behavior is often refractory to treatment typically utilized in agitated patients. The most efficacious treatment is often β-blockade, particularly with propranolol.[161] Careful monitoring of cardiac function is necessary, as bradycardia and hypotension may limit the use of this class of medications. Also, the clinician must monitor the patient for development of depression, which is strongly associated with β-blockade.

Other treatments utilized for aggressive/explosive behavior have included mood-stabilizing agents, atypical neuroleptics, and SSRIs.[114,137,148,161] Recently, studies have suggested that amantadine may have a role in this situation.[162] Theoretically, amantadine improves cognitive processing speed, which may improve irritability that is associated with aggression and explosive behavior. However, clinicians must closely monitor the frequency of the outbursts and abandon this course of treatment if the patient's condition worsens (Table 11.10).

NEUROLOGIC ISSUES

Posttraumatic Seizures

Posttraumatic seizures (PTSs) are classified as immediate, early, or late PTSs. Immediate seizures occur within 24 h of the inciting event. Early seizures occur after 24 h

TABLE 11.10
Medications for Aggression/Explosive Behavior

Medication	Starting Dose	Common Side Effects	Comments
Propranolol	10 mg bid	Diarrhea, vomiting, dizziness, fatigue	Hypotension, bradycardia, bronchial asthma, decompensated heart failure, pheochromocytoma, second- or third-degree heart block
Valproic acid	125 mg bid	Hepatic impairment, sedation, weight gain, rash	Not for monotherapy
Carbamazepine	100 mg bid	Blood dyscrasias, SIADH, hepatic impairment, rash	Not for monotherapy
Risperidone	0.5 mg prn	Sedation, akathisia, metabolic impairment	Do not use with paliperidone
Quetiapine	25 mg prn	Sedation, anticholinergic side effects	May result in confusion in elderly patients
Olanzapine	2.5 mg prn	Sedation, rash, metabolic impairment, weight gain, hypotension, dizziness	Available as injection; may have a paradoxical arousal effect at low doses
Ziprasidone	Oral 20 mg prn IM 10 mg prn	QT prolongation, hypotension, dizziness, electrolyte disturbance, metabolic changes, akathisia	Available as injection
Citalopram	Start: 20 mg daily Max: 40 mg daily	QT prolongation, nausea, dizziness, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Escitalopram	Start: 10 mg daily Max: 20 mg daily	Suicide risk, nausea, diarrhea, insomnia, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Paroxetine	Start: 20 mg daily Max: 50 mg daily	Asthenia, sweating, nausea, diarrhea, decreased appetite, somnolence, dizziness, tremor, dry mouth, decreased libido	Contraindicated with MAOis, monitor for serotonin syndrome
Fluoxetine	Start: 20 mg daily Max: 60 mg daily	Unusual dreams, decreased libido, anorexia, tremor	Contraindicated with MAOis, monitor for serotonin syndrome
Amantadine	Start: 100 mg bid Max: 200 mg bid Dose in morning and at noon	Dizziness, insomnia, nausea	Contraindicated in pregnancy, breastfeeding; likely is epileptogenic

bid, twice daily; *IM*, intramuscular; *MAOis*, monoamine oxidase inhibitors; *SIADH*, syndrome of inappropriate antidiuretic hormone release.

but within 7 days of the inciting event. Late seizures occur more than 7 days after the trauma. Posttraumatic epilepsy (PTE) is defined as recurrent and unprovoked seizures.[163] Immediate and early PTSs are considered provoked, whereas late PTSs are considered unprovoked. Therefore two late seizures must occur before diagnosing one with PTE.

Several clinical trials have shown that AEDs are effective in reducing early PTS but do not appear to alter the natural history of late PTSs.[164] According to the latest guidelines issued by the Brain Trauma Foundation in 2007, PTS prophylaxis is recommended for the first 7 days following TBI.[165] A number of AEDs have been studied for prophylaxis of PTSs following TBI. Phenytoin has been the most well-studied AED for PTS prophylaxis. The first double-blind placebo-controlled trial involving the use of phenytoin for PTS prophylaxis was published in 1990.[166] Subjects received either phenytoin or placebo for 12 months. The percentage of early seizures in the phenytoin group was 3.6% versus 14.2% for the placebo group. At 1 year, the percentage of subjects in the phenytoin group who had experienced at least one seizure was 26.5% versus only 15.7% in the placebo group. These findings demonstrated the

TABLE 11.11
Common Medications for Seizures Following Traumatic Brain Injury

Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Phenytoin	Prophylaxis: 100 mg tid Max: 625 mg/day	Rash, gingival enlargement, ataxia, nystagmus, constipation, nausea/vomiting, confusion	Concomitant use with delavirdine, concomitant use with rilpivirine
Valproate	Prophylaxis: 250 mg tid Max: 60 mg/kg/day	Peripheral edema, alopecia, weight gain **Serious:** Thrombocytopenia, hepatotoxicity, hyperammonemia encephalopathy	Hepatic disease, urea cycle disorders, mitochondrial disorders
Levetiracetam	Prophylaxis: 500 mg bid Max: 3000 mg/day	Loss of appetite, decreased bone mineral density, dizziness, irritability	
Carbamazepine	Prophylaxis: 200 mg bid Max: 1200 mg/day	Hypotension, constipation, nausea, vomiting, diplopia, nystagmus **Serious:** Agranulocytosis, aplastic anemia	Bone marrow depression, concomitant use of monoamine oxidase inhibitors or nonnucleoside reverse transcriptase inhibitors
Lamotrigine	25 mg daily/400 mg daily in divided doses	Vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea	May cause life-threatening rash, use extreme caution in patients already taking valproic acid

bid, twice daily; *tid*, thrice daily.

benefit of seizure prophylaxis only for the first 7 days following TBI.

Other AEDs have also been studied, although less extensively than phenytoin. One other study evaluated valproic acid for the prophylaxis of late PTS in moderate or severe TBI.[167] Subjects were randomized to phenytoin treatment group for 1 week, valproic acid treatment group for 1 month, or valproic acid treatment group for 6 months. There was no significant difference in early PTS between groups. Although there was no statistical difference in late PTS between the groups, there were more seizures at 6 months in both valproic acid groups when compared with the phenytoin group (15% in phenytoin group treated for 1 week, 16% in valproic acid group treated for 1 month, and 24% in valproic acid group treated for 6 months). This study further highlighted that longer duration of seizure prophylaxis did not decrease the incidence of late PTS.

Levetiracetam is a newer AED that is commonly used for PTS prophylaxis. This has not been as extensively studied as phenytoin or valproic acid. One study compared levetiracetam with phenytoin in 52 subjects with severe TBI.[168] Each group was treated for 7 days with either levetiracetam or phenytoin. There was no significant difference in early PTS between the groups.

The Brain Trauma Foundation recommends the use of phenytoin for early PTS prophylaxis. However, in clinical practice, newer AEDs such as levetiracetam are commonly used because of more favorable pharmacokinetic and side effect profiles. Additionally, there have been some data to suggest that phenytoin may negatively affect cognitive outcomes at 6 months when used for seizure prophylaxis.[169] There was no difference in cognitive outcomes noted at 12 or 24 months when comparing the phenytoin and control groups (Table 11.11).

Disorder of Initiation

Disorders of initiation are likely underappreciated during the early phases of rehabilitation following TBI, even though their incidence has been reported as high as 67% following TBI.[170] Those who have disorders of initiation will typically do well in a structured rehabilitation program. They may struggle, however, in real-world situations with less structure. Disorders of initiation are sometimes referred to as apathy, which is defined as diminished motivation in the presence of normal consciousness, attention, cognitive capacity, and mood.[170] It should be noted, however, that patients with initiation disorders are not "unmotivated" to participate in rehabilitation—in fact, they typically do well participating in rehabilitation when cued to do so. Instead, the neurologic insult has impaired their ability to initiate this behavior on their own.

TABLE 11.12
Medications for Disorder of Initiation

Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Methylphenidate	Start: 5–10 mg bid Max: 60 mg/day	Nervousness, insomnia, anorexia, tachycardia, palpitations, dizziness	Angina, concomitant use of monoamine oxidase inhibitors, glaucoma, heart failure, hyperthyroidism, severe hypertension
Dextroamphetamine/amphetamine	Start: 5–10 mg bid Max: 60 mg/day	Nervousness, insomnia, anorexia, tachycardia, palpitations, dizziness	Angina, concomitant use of monoamine oxidase inhibitors, glaucoma, heart failure, hyperthyroidism, severe hypertension
Amantadine	Start: 50–100 mg bid Max: 200 mg bid	Nausea, insomnia, hallucinations, agitation, anxiety	Contraindicated in pregnancy, breastfeeding
Bromocriptine	Start: 2.5 mg bid Max: 10 mg bid	Nausea, constipation, diarrhea, dizziness	Breastfeeding, syncopal migraine, uncontrolled hypertension
Pramipexole	Start: 0.125 mg tid Max: 1.5 mg tid	Orthostatic hypotension, constipation, nausea, dizziness, extrapyramidal movements, insomnia	None

bid, twice daily; *tid*, thrice daily.

Before initiating pharmacologic therapy for the treatment of disorders of initiation, other medical conditions that could contribute to the clinical presentation, such as hydrocephalus, neuroendocrine dysfunction, or mood disorder, should be ruled out. If a mood disorder is present, consideration should be given to starting more activating antidepressants, such as fluoxetine, sertraline, desipramine, or venlafaxine.

There has been little systematic research performed studying disorders of initiation following TBI. Pharmacologic treatment of disorders of initiation typically target the dopaminergic and norepinephrine pathways. Typical agents include neurostimulants, such as methylphenidate or dextroamphetamine/amphetamine, which increase both dopamine and norepinephrine. Dopamine receptor agonists, such as bromocriptine or pramipexole, may also be considered. Powell reported on 11 patients with TBI or subarachnoid hemorrhage who all showed improvement in their baseline assessments of participation in therapy after initiating bromocriptine and increasing by 2.5 mg every week up to a dose of 5–10 mg twice a day.[171] Amantadine, which increases the endogenous release of dopamine and also targets the glutamatergic pathway, may also improve initiation.[41]

No single agent has been shown to be superior to another for the treatment of disorders of initiation. Selection of pharmacologic therapy should take into account the presence of other neurobehavioral comorbidities such as depression or attention deficits (Table 11.12).

Movement Disorders

Mechanical head trauma may disrupt deep brain motor nuclei (basal ganglia, thalamus, subthalamus) and cerebellum, as well as the white matter tracts associated with these structures.[172] Retrospective studies have estimated the prevalence of movement disorders following severe TBI at approximately 22%.[173] Tremors, dystonia, parkinsonism, myoclonus, and choreiform movements are the most common movement disorders that manifest following head trauma.

Tremor is the most common movement disorder following TBI.[172] There are four types of tremor: rest, postural, action, and intention tremor. Resting tremor is often associated with parkinsonism. Postural tremor occurs with steady tonic contraction, such as holding a utensil, whereas action tremor occurs with smooth movement. Intentional tremor can be thought of as the terminal exacerbation of an action tremor. Approximately 20% of severe TBI survivors will develop a tremor.[173] Fortunately, this is more often transient than permanent. Systemic illness or medications often may be related to the presence of the tremor. Antipsychotics, including metoclopramide, are often used in the brain injury population and may cause tremors. There have been no controlled trials that have investigated the efficacy of medications for the management of posttraumatic tremors. Before treating posttraumatic tremors, consideration should be given as to whether or not the tremor is interfering with the patient's function.

First-line treatment for action and intentional tremors includes propranolol, a nonselective β-antagonist. Primidone is an antiepileptic that is commonly used to treat action or intentional tremor. Other antiepileptics, such as levetiracetam or topiramate, may also be considered.

Dystonia is excessive contraction of agonist and antagonist muscles. Dystonia may often be overlooked in the TBI population given that hypertonia is often attributed to spasticity. Cogwheeling with passive movement of the extremities may be appreciated on examination when dystonia is present. If the passive resistance to movement is not velocity dependent, it suggests that hypertonia may be attributed to dystonic rigidity. Anticholinergic medications, such as trihexyphenidyl, are often used to treat dystonia. However, in the TBI population this is not the ideal drug of choice for the treatment of dystonia because of sedation and negative impact on cognition. Trial of dopaminergic agents in the TBI population for the treatment of dystonia is a reasonable option, especially in patients who are in need of neurostimulation. Dopaminergic agents have provided contradictory results for the treatment of dystonia. Some studies have reported on improvement of dystonia with carbidopa/levodopa,[174] whereas others have reported worsening dystonia. The varied response is likely due to the heterogeneity in mixed population studies.[175] Botulinum toxin has been shown to be safe and effective in the treatment of dystonia in several open and controlled studies.[176]

Parkinsonism is the occurrence of two or more of the following: rigidity, resting tremor, and bradykinesia.[172] Parkinsonism can occur when the nigrostriatal dopaminergic projections or basal ganglia are damaged as a result of the traumatic injury. Dopaminergic agents typically used in idiopathic Parkinson disease are the most effective treatment for posttraumatic parkinsonism (see Table 11.13).

Myoclonus is described as lighteninglike jerks that can be either focal or multifocal. Any disease process that causes cortical irritability can cause myoclonus. Historically, valproic acid and clonazepam have been used as first-line agents for the treatment of myoclonus. As mentioned earlier, given the known inhibitory effects of benzodiazepines on neural plasticity and the negative influence on cognition, it is preferable to avoid the use of clonazepam in the TBI population. More recently, there has been increasing evidence that levetiracetam is also effective in the treatment of myoclonus.[177] This is especially encouraging given levetiracetam's relatively favorable pharmacokinetic and side effect profile.

Chorea is a hyperkinetic movement disorder that can be seen following TBI. Chorea is typically described as having the appearance of dancing or restless fidgeting. Athetosis may be considered a subtype of chorea and is at the slower end of the spectrum. Ballism is on the other end of the spectrum and may result in violent flinging of the extremity. These hyperkinetic movement disorders are thought to be due to impaired inhibitory basal ganglia output.[172] Neuroleptics are typically the first-line agent for the treatment of chorea (Table 11.13).[178]

Fatigue

Defining fatigue is difficult because it is a multidimensional construct.[179] Physiologic fatigue is functional organ failure generally caused by excessive energy consumption and depletion of essential substrates of physiologic functioning, such as hormones or neurotransmitters. Psychologic fatigue is defined as a state of weariness related to reduced motivation, prolonged mental activity, or boredom that occurs in situations such as chronic stress, anxiety, or depression.[180]

Mental fatigue is among one of the most common symptoms reported following TBI.[181] The prevalence of fatigue varies by study ranging from 30% to 70%.[182] The cause of fatigue following TBI continues to be debated, although it is likely multifactorial in nature. For instance, comorbidities such as depression, insomnia, and neuroendocrine abnormalities are likely to influence one's subjective sense of fatigue. One study found no significant difference in fatigue ratings across the severity spectrum of TBI.[183] Greater time since injury was associated with higher fatigue levels. Similar rates of fatigue between the severe and mild TBI populations highlights the subjective nature of fatigue in that the experience of fatigue is reliant on awareness. The mild TBI population likely has a greater awareness of fatigue compared with the severe TBI population.

The coping hypothesis suggests that individuals with TBI expend greater psychophysiologic costs to maintain stable performance over time. One study evaluated the relationship between subjective fatigue and performance on a vigilance task.[184] Individuals with TBI performed at a stable level throughout the 45-min vigilance task but had higher subjective ratings of fatigue compared with the control population.

When considering pharmacologic options for the treatment of posttraumatic fatigue, consideration should first be given to the treatment of comorbidities that may be influencing one's subjective experience of fatigue. When treating depression, consideration may be given to using more activating antidepressant medications, such as fluoxetine, sertraline, or

TABLE 11.13
Medications for Movement Disorders

Problem	Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Action/intention tremor	Propranolol	Start: 10 mg tid Max: 160 mg bid	Diarrhea, vomiting, dizziness, fatigue	Hypotension, bradycardia, bronchial asthma, decompensated heart failure, pheochromocytoma, second- or third-degree heart block
Action/intention tremor	Primidone	Start: 12.5 mg qhs Max: 250 mg qhs	Ataxia, vertigo	Porphyria
Dystonia	Trihexyphenidyl	Start: 1 mg daily Max: 15 mg/day divided qid	Nausea, xerostomia, dizziness, blurred vision, nervousness, sedation	Narrow-angle glaucoma
Dystonia/ Parkinsonism	Carbidopa/ levodopa	Start: 10/100 mg tid–qid Max: 200/2000 mg/day	Nausea, confusion, dizziness, headache	Narrow-angle glaucoma, history of melanoma, concomitant administration of MAOis
Parkinsonism	Amantadine	Start: 50–100 mg bid Max: 200 mg bid	Nausea, insomnia, hallucinations, agitation, anxiety	Pregnancy or breastfeeding
Parkinsonism	Pramipexole	Start: 0.125 mg tid Max: 1.5 mg tid	Orthostatic hypotension, constipation, nausea, dizziness, extrapyramidal movements, insomnia, hallucinations	Malignant melanoma, orthostatic hypotension, psychotic disorders, renal insufficiency
Parkinsonism	Ropinirole	Start: 0.25 mg tid Max: 4 mg tid	Orthostatic hypotension, constipation, nausea, dizziness, fatigue	Orthostatic hypotension, bradycardia, psychotic disorders, dyskinesia, renal failure
Myoclonus	Valproic acid	Start: 125–250 mg bid Max: 60 mg/kg/day	Peripheral edema, alopecia, weight gain **Serious:** Thrombocytopenia, hepatotoxicity, hyperammonemia encephalopathy	Hepatic disease, urea cycle disorders, mitochondrial disorders
Myoclonus	Clonazepam	Start: 0.5 mg bid–tid Max: 4 mg/day	Ataxia, dizziness, fatigue	Acute narrow-angle glaucoma, liver disease
Myoclonus	Levetiracetam	Start: 250 mg bid Max: 1500 mg bid	Vomiting, decreased bone mineral density, dizziness, irritability, fatigue	pancytopenia, blood dyscrasias, renal insufficiency, psychosis
Chorea	Risperidone	Start: 0.5 mg bid Max: 16 mg/day	Sedation, akathisia, metabolic impairment	Do not use with paliperidone
Chorea	Olanzapine	Start: 2.5–5 mg daily Max: 20 mg/day	Sedation, rash, metabolic impairment, weight gain, hypotension, dizziness	Breast cancer, diabetes, hypercholesterolemia, neutropenia, parkinsonism, QT prolongation, orthostatic hypotension

bid, twice daily; *tid*, thrice daily.

TABLE 11.14
Medications for Fatigue

Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Fluoxetine	Start: 20 mg daily Max: 80 mg/day	Diarrhea, nausea, insomnia, anxiety	Concomitant use of monoamine oxidase inhibitors, concomitant use of pimozide or thioridazine
Sertraline	Start: 25–50 mg daily Max: 200 mg/day	Diarrhea, nausea, dizziness, abnormal ejaculation, reduced libido	Concomitant use of monoamine oxidase inhibitors, concomitant use of disulfiram, pimozide
Modafinil	Start: 100 mg bid Max: 400 mg/day	Nausea, headache, insomnia, anxiety	psychosis, hypertension, angina, severe liver or kidney disease.
Methylphenidate	Start: 5–10 mg bid Max: 60 mg/day	Nervousness, insomnia, anorexia, tachycardia, palpitations, dizziness	Angina, concomitant use of monoamine oxidase inhibitors, glaucoma, heart failure, hyperthyroidism, severe hypertension
Dextroamphetamine/amphetamine	Start: 5 mg bid Max: 60 mg/day	Nervousness, insomnia, anorexia, tachycardia, palpitations, dizziness	Angina, concomitant use of monoamine oxidase inhibitors, glaucoma, heart failure, hyperthyroidism, severe hypertension
Amantadine	Start: 50–100 mg bid Max: 200 mg bid	Nausea, insomnia, hallucinations, agitation, anxiety	Contraindicated in pregnancy, breastfeeding

bid, twice daily.

SNRIs. Neuroendocrine abnormalities should also be corrected because hypothyroidism or hypogonadism could potentially be contributing to fatigue. It is important to treat insomnia because this can certainly contribute to fatigue.

Neurostimulants are the most common form of pharmacologic treatment of posttraumatic fatigue. Modafinil was studied in a randomized placebo-controlled trial in 53 patients with severe TBI.[11] There was no significant difference in Fatigue Severity Scale with a total daily dose of modafinil 400 mg at weeks 4 and 10. There was a significant improvement in the Epworth Sleepiness Scale at weeks 4 and 10. Methylphenidate was found to significantly improve mental fatigue in a dose-dependent manner, as assessed by the Mental Fatigue Scale in a group of 51 subjects with mild TBI.[185] Other neurostimulants such as amantadine and dextroamphetamine/amphetamine could also be considered, but there have not been systematic studies that have investigated their use in posttraumatic fatigue (Table 11.14).

Paroxysmal Sympathetic Hyperactivity

A syndrome of agitation, restlessness, diaphoresis, hyperthermia, hypertension, tachycardia, tachypnea, hypertonia, and extensor posturing is often seen following severe TBI. There have been a number of terms given to this syndrome over the years including dysautonomia, autonomic (sympathetic) storming, diencephalic seizures, or midbrain dysregulatory syndrome. Paroxysmal sympathetic hyperactivity (PSH) has been proposed as an all-encompassing term for the syndrome.[186]

Activation of the sympathetic nervous system is one of the most common features of PSH syndrome. Propranolol is frequently used in PSH to blunt sympathetic outflow. Propranolol is a nonselective β-antagonist that acts on the β-1 and β-2 receptors. It is highly lipophilic and therefore crosses the blood-brain barrier. Labetalol and clonidine may also be considered for blockade of sympathetic hyperactivity. Labetalol is a nonselective β-receptor antagonist and selective α-blocker (α-1 receptors). Labetalol is considered moderately lipophilic. Clonidine is an α-2 agonist that lowers blood pressure and also can have a behavior-stabilizing effect.

It can be useful to consider other clinical entities that mimic PSH syndrome when selecting other agents to treat clinical features of PSH. NMS has several overlapping clinical features of PSH, including hyperthermia, rigidity, and autonomic instability. NMS is typically seen with long-term use of antipsychotic agents with potent dopamine blockade. There have also been case reports of NMS with the withdrawal

TABLE 11.15
Medications for Paroxysmal Sympathetic Hyperactivity (PSH)

Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Propranolol	Start: 10 mg tid Max: 320 mg/day	Diarrhea, vomiting, dizziness, fatigue	Hypotension, bradycardia, bronchial asthma, decompensated heart failure, pheochromocytoma, second- or third-degree heart block
Labetalol	Start: 50 mg bid Max: 2400 mg/day	Orthostatic hypotension, nausea, dizziness, nasal congestion, fatigue	Bronchial asthma, cardiogenic shock, second- and third-degree heart block, severe bradycardia
Clonidine	Start: 0.1 mg bid Max: 2.4 mg/day	Xerostomia, headache, somnolence	Hypotension
Bromocriptine	Start: 2.5 mg bid Max: 10 mg bid	Nausea, constipation, diarrhea, dizziness	Breastfeeding, syncopal migraine, uncontrolled hypertension
Dantrolene	Start: 25 mg daily Max: 400 mg qid	Flushing, diarrhea, somnolence hepatotoxicity	Hepatic disease
Morphine	Start: 15 mg q 4 hours Max: Dependent on opioid tolerance	Pruritus, constipation, nausea, light headedness, urinary retention	Concomitant use of MAOis, GI obstruction, hypercarbia, respiratory depression

bid, twice daily.

of dopaminergic agents, such as carbidopa/levodopa or amantadine.[187] This is particularly important to consider given that patients with TBI are often placed on neuroleptic agents, such as haloperidol for "agitation." Use of metoclopramide has also been known to induce NMS.[188] Consideration should be given to initiating dopaminergic agents, such as bromocriptine, a D_2 receptor agonist, in a patient with PSH, particularly those who present with muscle rigidity, hyperthermia, and autonomic instability.

Clinical features that mimic malignant hyperthermia (tachycardia, hyperthermia, and tachypnea) should also be considered when treating PSH. Malignant hyperthermia has been reported to occur in cases of TBI without an inciting event, such as surgery or anesthesia.[189] Dantrolene is commonly used to treat malignant hyperthermia. Dantrolene blocks calcium release from the sarcoplasmic reticulum, resulting in the relaxation of sustained skeletal muscle contraction. This may help decrease hyperthermia and muscle rigidity. Dantrolene should be considered in a patient with PSH who presents with hyperthermia and sustained muscle contraction.

In refractory cases of PSH, consideration can be given to the use of morphine. Morphine is an opiate agonist. Morphine may be an effective agent in treating several features of PSH including hypertension, tachypnea, and tachycardia (Table 11.15).

Spasticity and Rigidity

Hypertonia is commonly seen following severe TBI. Hypertonia is increased resistance to passive movement and can have several causes. It is important to consider the different causes of hypertonia as each will have different treatment strategies.

Spasticity is a form of hypertonia that is defined as velocity-dependent resistance to passive muscle stretch. A positive relationship exists between the velocity with which the muscle is stretched (or joint moved) and resistance to movement. The control of muscle tone involves a feedback loop, which integrates information about muscle activity, position, and velocity.[190] When there is CNS damage following TBI, there may be loss of descending inhibitory influences in the muscle stretch reflex pathway, resulting in spasticity.

There are several pharmacologic agents used to treat spasticity following TBI. Most agents act on the CNS to facilitate the inhibitory influences on the muscle stretch reflex pathway that may be decreased due to CNS damage following TBI. Benzodiazepines were the first class of medications used to treat spasticity. Within the benzodiazepine family, diazepam is the one most

commonly used to treat spasticity. Diazepam agonizes the $GABA_A$ receptor, resulting in hyperpolarization and inhibitory outflow from the brainstem reticular formation and spinal cord descending tracts.[191] Benzodiazepines, however, should generally be avoided as first-line agents for the treatment of spasticity because of sedative effects and known inhibition of neuroplasticity.

Baclofen is also a GABA agonist that is commonly used to treat spasticity. Unlike diazepam, which is an agonist of the $GABA_A$ receptor, baclofen is a $GABA_B$ agonist. It causes hyperpolarization of the cell at both the presynaptic and postsynaptic levels, resulting in inhibition of both the monosynaptic and polysynaptic reflex pathways.[190] Much of the research in the use of baclofen for the treatment of spasticity has been performed in the spinal cord injury and multiple sclerosis populations. There has been little systematic research in the brain injury population. The sedative effects of baclofen are expected to be less than those of diazepam; however, sedation should be monitored for and patients cautioned of this potential side effect. Abrupt withdrawal should be avoided because there have been instances of new-onset seizures with abrupt withdrawal.[192] There has been conflicting evidence as to whether or not baclofen lowers the seizure threshold.

Tizanidine is an α-2 agonist that has been relatively well studied for the management of spasticity in TBI. Activation of the α-2 receptor results in inhibition of the release of excitatory neurotransmitters, such as glutamate and aspartate, because of negative feedback. Common side effects include hypotension and dizziness, but most prominently, and of particular concern in the brain injury population, it can also cause sedation. It also has the potential to cause liver damage, so liver function tests should be performed before the initiation of treatment, and again at 1, 3, and 6 months. A randomized placebo-controlled trial studied tizanidine in an acquired brain injury population. The primary outcome measure was change in the Modified Ashworth Scale of the wrist flexors assessed at 6 weeks. Tizanidine was started at twice daily dosing of 2 mg/day and increased to 36 mg/day, as tolerated. There was no statistical difference in the primary outcome at 6 and 18 weeks.[193]

Similar to tizanidine, clonidine is also an α-2 agonist. It acts both on the locus coeruleus and at the spinal cord level, enhancing presynaptic inhibition at the spinal cord level. It has demonstrated some efficacy in the treatment of spasticity, but primarily in the spinal cord injury population.[194] It should be noted that there is concern that clonidine may impair motor recovery following acquired brain injury.[195]

Dantrolene is an intriguing choice for the management of spasticity in the TBI population in that its mechanism of action is peripheral action, therefore it does not cause sedation. It acts by inhibiting the release of calcium from the sarcoplasmic reticulum, therefore inhibiting skeletal muscle contraction. Its most well-known side effect is for hepatotoxicity. Liver function tests should be checked weekly for the first month and then at least every other month for the first year.

Chemical neurolysis is commonly used to treat spasticity that is refractory to oral medications. Chemical neurolysis is particularly effective for the treatment of focal spasticity. There are two main agents for chemical neurolysis—phenol and botulinum toxin. Phenol was the first neurolytic agent used to treat spasticity. It decreases spasticity by denaturing proteins of both the motor and sensory nerves, resulting in decreased skeletal muscle tone. Its duration of effect is typically longer than that of botulinum toxin. Typical duration of action is three to 9 months, but it can also be longer.

Unlike phenol, botulinum toxin does not affect the sensory nerves. Botulinum toxin was approved for use in the United States in 1989. There are currently two botulinum toxin serotypes available for use in the United States—types A and B. Botulinum toxin inhibits the presynaptic release of acetylcholine from the synaptic vesicle. The Soluble NSF Attachment Protein Receptor (SNARE) complex attaches the synaptic vesicle to the cell membrane, thus allowing the release of acetylcholine into the neuromuscular junction. Botulinum toxin serotypes A and B act on different SNARE complex proteins. Type A cleaves Soluble NSF Attachment Protein-25 (SNAP-25), a protein attached to the acetylcholine vesicle, whereas Type B cleaves synaptobrevin, a protein attached to the cell membrane. The efficacy of botulinum toxin for the treatment of spasticity has been demonstrated in multiple sclerosis and TBI populations.[196,197]

Systemic side effects of botulinum toxin are possible. Relatively mild side effects include headache, flulike symptoms, fatigue, and nausea. More serious side effects include respiratory depression, dysphagia, and generalized weakness. Botulinum toxin serotype B seems to have more parasympathetic side effects, such as dry mouth and visual disturbance.[198]

Intrathecal baclofen may also be used for the treatment of generalized spasticity. Intrathecal baclofen was first approved by the Food and Drug Administration for use in the United States in 1996.[190] The advantage of an intrathecal delivery system is that a much lower dose of baclofen may be used to obtain adequate control of spasticity. With an intrathecal pump, baclofen is delivered into the subarachnoid space of the spinal

TABLE 11.16
Medications for Spasticity

Medication	Dosing (Start/Max)	Common Side Effects	Contraindications
Diazepam	Start: 2 mg tid Max: 10 mg qid	Hypotension, muscle weakness, somnolence	Acute narrow-angle glaucoma, myasthenia gravis, severe hepatic insufficiency, severe respiratory insufficiency, sleep apnea
Baclofen	Start: 5 mg tid Max: 80 mg/day	Hypotension, somnolence, urinary retention	None
Tizanidine	Start: 2 mg tid Max: 36 mg/day	Hypotension, xerostomia, asthenia, dizziness, somnolence	Concomitant use of potent CYP1A2 inhibitors
Clonidine	Start: 0.1 mg bid Max: 2.4 mg/day	Xerostomia, headache, somnolence	Hypotension
Dantrolene	Start: 25 mg daily–tid Max: 400 mg/day	Flushing, diarrhea, somnolence **Serious:** hepatotoxicity	Hepatic disease
Phenol	Dosing varies based on targeted muscles and severity of spasticity	Injection site reaction	None
Botulinum toxin	Dosing varies based on targeted muscles and severity of spasticity Max: 600 units	Injection site reaction **Serious:** Dysphagia	None but caution use in neuromuscular diseases

bid, twice daily.

cord. Although intrathecal baclofen may be used to treat spasticity in both the upper and lower extremities, it is typically more effective for the treatment of lower extremity spasticity because of limitations regarding catheter placement high in the cervical spine due to narrowing of the spinal canal. Before implantation of the intrathecal baclofen pump, a trial is first conducted to determine whether or not the patient had an adequate response to intrathecal baclofen. Risks associated with intrathecal baclofen pump implantation include infection, pump failure, catheter dislodgement or kinking, and cerebrospinal fluid leaks. Although rare, failure of the pump or catheter can lead to baclofen withdrawal and associated seizures.

As mentioned at the beginning of this section, care should be taken to differentiate the cause of hypertonia as different causes have varying treatment strategies. Refractory hypertonia despite escalating doses of spasticity medications should raise the suspicion that dystonia may be the cause of hypertonia. This is particularly true if cogwheeling of the extremity with passive range of motion is noted on examination. Resistance to passive range of motion that is not velocity dependent suggests the presence of dystonia or paratonia. It is possible that the presentation of hypertonia may be a mixed picture of spasticity, paratonia, or dystonic rigidity. This must be kept in mind when evaluating patients with hypertonia, as the treatment paradigms are different for these different conditions. (Table 11.16).

CONCLUSION

Medication management following TBI can be very challenging yet rewarding. Astute observation is critical in the practice. The information in this chapter should be considered as guidelines, and is not intended to replace the judgment of the clinician. As always, please refer to detailed prescribing information before the use of any medication.

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