From the Field of Play to the Field of Combat: A Review of the Pharmacological Management of Concussion

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Received, August 29, 2011.
Accepted, January 11, 2012.
Published Online, January 27, 2012.

Traditionally, the medical management of concussion has involved close observation and physical and cognitive rest. Most postconcussive symptoms resolve spontaneously and require only conservative treatment. However, some patients have prolonged recoveries and may benefit from treatment with medications. Some naturally occurring compounds demonstrate multimechanistic neuroprotective properties and may be potential treatment considerations. For the most part, however, current treatments are symptom based for those with persistent postconcussive symptoms. The evidence supporting the various pharmacologic treatments in concussion is equivocal. The choice of which medication to use for a patient depends on the symptom characteristics, and each decision should be made on an individual-case basis. There is a need for well-designed trials investigating the efficacy of various medical therapies.

KEY WORDS: Concussion, Mild traumatic brain injury, Pharmacotherapy, Postconcussive syndrome, Sports, Symptoms

Neurosurgery 70:1520–1533, 2012 DOI: 10.1227/NEU.0b013e31824cebe8 www.neurosurgery-online.com

During recent years, there has been increasing attention focused on the neurological sequelae of sports-related traumatic brain injury (TBI), particularly concussion. Each year, an estimated 1.6 to 3.8 million sports-related concussions occur in the United States alone.[1] Additionally, an estimated 2.3 million military personnel have been deployed to the conflicts in Afghanistan and Iraq since late 2001.[2,3] Between 10% and 25% of US military troops returning from Iraq or Afghanistan have had a concussion while deployed, with blast injury secondary to improvised explosive devices being the most common cause.[4-8] It has been reported that the prevalence of postconcussive headache nears 37% in returning US Army soldiers who have sustained a concussion in combat zones in the Middle East.[4,9]

Traditionally, the medical management of concussion has involved close observation and physical and cognitive rest. As we have learned more about concussion over the years, it has become clear that the use of a multifaceted assessment and serial testing can provide a better framework for determining effective individualized patient management strategies. Treatment for patients with concussion is centered on symptom management and education of the patient, family, and other significant contacts (athletic trainers, teachers, coaches, employers, etc). Although the role of education in the management of these patients has been investigated at length,[10-20] there have been no randomized, controlled trials of the pharmacological treatment of concussion symptoms. As has been demonstrated in prior reviews, the evidence is equivocal for many of the medications used to manage the postconcussive patient.[10,21,22] In most cases, the studies involve patients with moderate and severe TBI and fail to look at the efficacy of these medications in a concussion cohort alone.

The symptomatic treatment of concussion can be challenging, in part because of patient heterogeneity. Although no standardized approach exists, a number of effective adjunctive medical therapies for symptoms can, when used appropriately in an individualized manner, improve

ABBREVIATIONS: PCS, postconcussion syndrome; **PPCS,** prolonged postconcussion syndrome; **PTSD,** posttraumatic stress disorder; **SSRI,** selective serotonin reuptake inhibitor; **TBI,** traumatic brain injury

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outcomes. The purpose of this narrative review is to provide an organized, comprehensive overview of the available pharmacological treatment options and strategies for concussion management based on the most current available medical literature. Additionally, the review highlights the need for improved trials investigating the efficacy of the various medical therapies described.

PATIENTS AND METHODS

The primary means of identifying studies to be included in the literature review was an electronic search of the English literature from 1900 to 2011 with MEDLINE, PubMed, and the Cochrane Database using the following search terms: brain injury, head injury, concussion, postconcussion syndrome, TBI, pharmacotherapy, pharmacology, treatment, and intervention, as well as the symptoms according to which this review is arranged. The associated medical subheadings (MeSH) for each database were used preferentially when provided. In addition, any relevant references from the evaluated literature were searched and included in the review to ensure a thorough capture of the literature.

Pathophysiology of Concussion

To appreciate the basis for these potential treatments, one must have a general understanding of the pathophysiology underlying concussion. As defined by the consensus statement generated from the 3rd International Conference on Concussion in Sport (Zurich 2008), a concussion is a complex pathophysiological process affecting the brain that is induced by traumatic biomechanical forces.[23] Simply put, it is a temporary disruption of brain function that typically resolves spontaneously. It can be caused either by a direct blow to the head, face, or neck or by a blow elsewhere on the body with an "impulsive" force transmitted to the head.

Although the acute clinical symptoms are largely thought to reflect a functional disturbance, we know that the mechanical trauma of a concussion may result in neuropathological changes at the ultrastructural level (particularly in those patients with subacute or chronic symptoms), which ultimately initiates a complex cascade of neurochemical and neurometabolic events.[24-32] At the cellular level, we have come to learn that there is neuronal membrane disruption, or mechanoporation, that leads to ionic shifts and an increase in intracellular glutamate and calcium.[24,26,29,33] Additionally, mitochondrial dysfunction leads to a failure in ATP and an increase in reactive oxygen species.[34,35] Concussion may also compromise or alter the control of cerebral blood flow, cerebrovascular reactivity, and cerebral oxygenation.[36]

There is also accumulating evidence that neuroinflammatory cascades play a significant role in the pathogenesis of disease after concussion and possibly repetitive subconcussive injury.[37] The spectrum of postconcussive disease includes acute symptoms, postconcussion syndrome (PCS), persistent or prolonged PCS (PPCS), mild cognitive impairment, chronic traumatic encephalopathy, and dementia pugilistica.[38-42] The role of neuroinflammation and immunoexcitotoxicity in the genesis of these postconcussive processes has recently been reviewed.[37] The acute and chronic timing of some of these cascades may have important implications in the treatment of concussed individuals.

To Treat or Not to Treat?

Most patients who sustain a concussion have a spontaneous, sequential resolution of their symptoms within a period of 7 to 10 days.[23,43-46] Some patients have a prolonged recovery and will display signs and symptoms of concussion past the usual period. Different time points have been suggested in the literature as to when a patient can be considered to exhibit a PCS. For some, a diagnosis of PCS may be made when symptoms resulting from concussion last for > 3 months after the injury.[47] In addition, PCS has been described in the literature as symptoms lasting > 10 days.[48] A small minority of patients will have symptoms lasting > 6 months; this is referred to as PPCS.[49] Still, discrepancy exists in the literature regarding the timing of this phenomenon because PPCS has been described by other standards as symptoms lasting > 3 months.[50] We consider the persistence of symptoms between 6 weeks and 3 months to be consistent with PCS and any symptoms lasting > 3 months as a PPCS.[51]

When deciding whom should be treated pharmacologically, one should consider first whether the patient symptoms have exceeded the typical recovery period and second whether the symptoms are negatively affecting the patient's life to such a degree that the possible benefit of treatment outweighs the potential adverse effects of the medication being considered.[22]

We tend to explore naturally occurring supplements and compounds as an initial therapeutic approach to concussion patients. Recently, there has been an immense interest in natural compounds and nutraceuticals (ie, food derivatives or dietary supplements and herbal remedies that provide health benefits). Some of these preparations and compounds have been used for centuries to treat illness, and they have become more popular in society lately, particularly because of their relatively few side effects.[52] The use of natural antiinflammatory agents for pain relief has been described,[53] and we have recently reviewed some potential natural neuroprotective compounds that may be useful for patients with concussion, including eicosapentaenoic acid/docosahexaenoic acid or fish oil, docosahexaenoic acid alone, curcumin, resveratrol, creatine, green tea, ginseng, *Scutellaria baicalensis, Salvia miltiorrhiza*, and vitamins E, C, and D.[52,54-57] If neuroinflammation is a possible common substrate, it would seem reasonable that therapeutic options should at least include some antiinflammatory mechanisms of action.[37,52] We feel that such compounds address the underlying pathophysiological processes (particularly neuroinflammation) and thus aid in patient and disease management. When patients have persistent symptoms despite conservative efforts and a natural therapeutic approach, then we consider pharmacological symptom treatment options. Although no clinically validated pharmacological treatment has been shown to speed recovery or to ameliorate the deficits attributed to TBI,[58] patients with PCS or PPCS may benefit from symptomatic medical treatment while they are healing.[13,58-60]

There are several general points to keep in mind when considering using medication to treat postconcussion symptoms. In our experience, it is best to avoid medications that lower the seizure threshold. Additionally, we have found that medications should not be prescribed that may cause confusion or contribute to cognitive slowing, fatigue, or daytime drowsiness, which could potentially confound the clinical examination. We also feel that, in general, therapies should be initiated at the lowest effective dose and then titrated slowly on the basis of tolerability, side effects, and clinical response. All patient medications and over-the-counter supplements should be reviewed. These basic principles have been similarly reflected in other reviews on concussion management.[10,22,23] Treatment of concussion should be symptom specific, and these symptoms are generally grouped into 4 categories[22,23,60]: somatic complaints, sleep disturbance, emotional difficulties, and cognitive difficulties (Tables 1-5). It is important to remember that a complex relationship exists between the various concussion symptoms and that alleviating 1 symptom may improve others.

TABLE 1. Pharmacotherapy for Somatic Symptoms: Headache[a]

Symptom	Class	Medication	Brand Names	Dosing	Side Effects
Headache	Analgesics	Acetaminophen	Tylenol	500 to 1000 mg 3-4 times daily (maximum daily dose, 4000 mg)	Usually rare; at high doses/overdoses, vomiting, liver and kidney failure
		Aspirin	Bayer, Bufferin, Ecotrin	81 or 325 mg daily	GI upset, ulcers, bleeding, nausea, headache
	NSAIDs	Ibuprofen	Advil, Motrin	600-800 mg 3 times daily	GI upset, GI ulcers, GI bleeding, dizziness, nausea, vomiting, loss of appetite, arrhythmia, confusion; prolonged use in concussion patients can lead to rebound headaches
		Naproxen	Aleve, Naprosyn	550-850 mg twice daily	
		Diclofenac	Voltaren, Cataflam	50-100 mg daily (divided doses)	
	Antidepressants	Amitriptyline	Elavil, Endep, Vanatrip	10-25 mg QHS; titrate up for effect (usually doses of $\leq$ 150 mg)	Nausea, GI upset, weakness, blurred vision, changes in appetite, drowsiness, dizziness, arrhythmia, motor tics, seizures, hallucination, unusual bleeding
		Nortriptyline	Aventyl, Pamelor	10-25 mg QHS; titrate as above	
	Anticonvulsants	Valproic acid	Depakene, Depakote	250 mg twice daily; can titrate up in increments of 250 mg for effect; (maximum daily dose, 1500 mg)	Drowsiness, dizziness, headache, diarrhea, constipation, heartburn, appetite changes, weight changes, back pain, agitation, mood swings
		Topiramate	Topamax, Topiragen	15-25 mg QHS and slowly raised to as high as 100 mg twice daily	Lack of coordination, impaired memory/ concentration, irritability, headache, weakness, motor tic, GI upset, hair loss, appetite changes
		Gabapentin	Neurontin, Gabarone, Vanatrex, Horizant	300 mg 3 times daily and may be slowly raised as high as 1200 mg 3 times daily	Dizziness, headache, blurred vision, anxiety, memory problems, motor tics, increased appetite
	β-Adrenergic antagonists	Propranolol	Inderal, Innopran	40-320 mg daily (divided doses)	Abdominal cramps, fatigue, insomnia, nausea, depression, impotence, lightheadedness, slow heart rate, low blood pressure, cold extremities, shortness of breath or wheezing; not to be used in patients with asthma
		Metoprolol	Lopressor, Toprol	25 mg twice daily; can increase dose up to 100 mg twice daily if needed	
	Ergot preparations (abortive)	Dihydroergotamine	DHE45, Migranal	Intranasal vs IM/SQ vs IV (0.5-1 mg, maximum, 2 mg/d)	Abnormal skin sensations, anxiety, diarrhea, dizziness, flushing, sweating, nausea, vomiting
	Triptans (abortive)	Sumatriptan	Imitrex, Alsuma	Oral: 25-100 mg prn; intranasal: 10-20 mg BID prn; SQ: 6 mg	Unusual taste (nasal formulation), paresthesias, hyperesthesia, dizziness, chest tightness, dizziness, vertigo, tingling, hypertension, injection site reactions, flushing, chest pressure, heaviness, jaw or neck pain
		Zolmitriptan	Zomig	Oral: 5-10 mg; intranasal: 5 mg	
		Rizatriptan	Maxalt	5-10 mg; can repeat dose 2 h from first dose (maximum, 30 mg/d)	

[a]GI, gastrointestinal; NSAIDs, nonsteroidal antiinflammatory drugs; prn, as needed; QHS, at bedtime; SQ, subcutaneous.

TABLE 2. Pharmacotherapy for Somatic Symptoms: Dizziness, Fatigue, Nausea[a]

Symptom	Class	Medication	Brand Names	Dosing	Side Effects
Dizziness	Vestibular suppressants	Meclizine	Antivert, Bonine, Medivert	12.5-50 mg every 4 to 6 h prn	Hallucinations, blurred vision, dry mouth, constipation, dizziness, drowsiness
		Scopolamine	Scopace, Transderm-Scop Maldemar	0.5-mg patch every 3 d prn	Dry mouth, topical allergy, tachyarrhythmia, drowsiness, dizziness, restlessness, blurred vision, dry or itchy eyes, flushing, nausea, vomiting, headache
		Dimehydrinate	Dramamine, Driminate	50 mg every 4 to 6 h prn	Dizziness, drowsiness, dry mouth/throat
	Benzodiazepines	Lorazepam	Ativan	0.5 mg twice daily	Sedation, dizziness, weakness, unsteadiness, depression, loss of orientation, headache, respiratory depression; caution should be used because these medications can cause physical dependence
		Clonazepam	Ceberclon, Klonopin, Valpax	0.25-0.5 mg twice daily	
		Diazepam	Valium, Valrelease	2-10 mg daily	
Fatigue	Neurostimulants	Methylphenidate	Ritalin, Concerta, Metadate	5 mg twice daily; can titrate up total daily dose by 5 mg every 2 wk to a maximum of 20 mg twice daily	Insomnia, decreased appetite, GI upset, headaches, dizziness, motor tics, irritability, anxiousness, tearfulness
		Dextroamphetamine	Adderall, Dexadrine ProCentra	5 mg daily; can titrate up for effect (maximum daily dose, 40 mg)	Anxiety, GI upset, insomnia, irritability, euphoria, starting episodes
		Modafanil	Provigil	100 mg every morning; can increase by 100 mg, using divided doses (maximum daily dose, 400 mg)	Headache, dizziness, feeling nervous or agitated, nausea, diarrhea, insomnia, dry mouth, hallucinations, depression
		Amantadine	Symadine, Symmetrel	100-400 mg daily	Dizziness, blurred vision, anxiety, insomnia
		Atomoxetine	Strattera	40 mg daily (single or divided doses); can titrate up for effect (maximum daily dose, 100 mg)	Dry mouth, irritability, nausea, decreased appetite, constipation, dizziness, sweating, dysuria, sexual problems, weight changes, palpitations, tachycardia, hypertension
Nausea	Antiemetics	Ondansetron	Zofran	4 mg every 4 times daily prn	Dizziness, drowsiness, anxiety, diarrhea, blurred vision, dry mouth, stuffy nose, tinnitus, weight gain, swelling, impotence, constipation, lightheadedness
		Phenergan	Phenergan, Pentazine, Promethagan	12.5 to 25 mg 4 times daily prn	

[a]GI, gastrointestinal; prn, as needed.

Somatic Symptoms

The initial treatment of somatic complaints in a concussion patient starts with a thorough clinical evaluation and is based on individual symptom presentation (Tables 1 and 2). Posttraumatic headaches are the most common symptom reported after a concussion and occur acutely in $> 90\%$ of patients.[61-64] There may be an increased risk of hemorrhage within the first 24 to 48 hours after concussion.[65] In general, aspirin and other nonsteroidal antiinflammatory drugs are avoided in the acute

TABLE 3. Pharmacotherapy for Sleep Disturbances[a]

Class	Medication	Brand Names	Dosing	Side Effects
Sedative-hypnotics	Zolpidem	Ambien, Edluar, Zolpimist	5 mg QHS; can increase to 10 mg QHS if poor results	Drowsiness, headache, dizziness, lightheadedness, unsteady walking, difficulty with coordination, constipation, diarrhea, heartburn, stomach pain, changes in appetite, paresthesias, unusual dreams
Serotonin modulators	Trazodone	Desyrel, Oleptro	25-50 mg QHS	Headache or heaviness in head, nausea, vomiting, bad taste in mouth, stomach pain, diarrhea, constipation, changes in appetite or weight, weakness, nervousness, decreased, concentration, confusion, nightmares, tinnitus
α-Adrenergic antagonists	Prazosin	Minipress	1 mg QHS; may slowly increase/titrate dose for effect (maximum daily dose, 10 mg QHS)	Dizziness, drowsiness, dry mouth, frequent urination, headache, lack of energy, nausea lightheadedness, nasal congestion, weakness
Supplement	Melatonin	Health Aid Melatonin, VesPro Melatonin, SGard	0.3-5 mg QHS	Daytime sleepiness, sleepwalking, confusion, headache, dizziness, abdominal discomfort

[a]QHS, at bedtime.

period so as to not induce or exacerbate intracranial hemorrhage, although no controlled trials have demonstrated this theoretical risk, albeit an extremely small one.[46] Additionally, in concussion patients, rebound headaches are common with prolonged nonsteroidal antiinflammatory drugs and narcotic use and can potentially complicate the recovery process.[66-68] For this reason, acetaminophen is a logical choice for the treatment of the postconcussion headache in the acute period. Most patients will have a spontaneous resolution of their headache; however, those patients who go on to develop persistent headaches as a part of a PCS may require further treatment.

Management of headache in TBI may be difficult and complex because of the many possible underlying factors. Most patients who develop persistent headaches after concussion have tension-type or migrainelike headaches[67-70]; however, some patients with cervicogenic pain, myofascial injury, temporomandibular joint injury, or muscles spasms in the superior trapezius and semispinalis capitis muscles in the suboccipital region can also present with headaches.[46,71] The medications selected for treatment usually reflect the character of the headaches. Should a headache seem to be secondary to cervicogenic pain, myofascial injury, or muscle spasms, patients may benefit from treatment with a muscle relaxant. Antidepressants are commonly used to treat postconcussion headaches despite the equivocal evidence in the literature.[10,13] Positive or negative, most of the evidence is weak (Level III) in part because of poor study design, heterogeneous patient populations, and a lack of adequate control subjects.[10,22] In addition, the variation in medication regimens (ie, dose, duration, start of treatment) across studies makes it difficult to synthesize the data. The antidepressant amitriptyline has shown efficacy in the treatment of postconcussion headaches in some studies.[10,72,73] In 1 retrospective review that looked at 23 mild TBI patients treated with amitriptyline for posttraumatic headaches, 56% and 34% of patients had an excellent and a good recovery, respectively.[72] In this study, there also seemed to be more favorable outcomes for patients who were younger, were female, and started on medication shortly after injury.[72] It is important to recognize that such a study is limited by its design and very small sample size, making it difficult to draw any definitive conclusions from the study. Another study looked at amitriptyline treatment in 12 depressed nonmild TBI patients with headaches and compared them with 10 depressed concussion patients with headaches.[74] They concluded that postconcussive headaches were not successfully managed with amitriptyline. Interestingly, although all patients in the depressed, nonmild TBI group exhibited headache improvement after 4 weeks of amitriptyline, none of the patients in the depressed, mild TBI group exhibited improvement with their headaches.[74] Amitriptyline is used in the treatment of tension-type and migrainelike headache not associated with trauma and thus remains a good option for postconcussive headaches.[22,67,69,70] One additional benefit of amitriptyline may be its sedative effects, which can sometimes provide relief for those also suffering from sleep disturbances after a concussion.[22,66,67,70]

One study reviewed 34 patients treated with repetitive administration of intravenous dihydroergotamine and metoclopramide for postconcussion headache.[75] Patients varied in the period of time they had headaches after trauma, ranging from 1 day to > 3 years. All patients displayed at least 3 other PCS symptoms, including memory problems, impaired concentration, sleep problems, dizziness, and anxiety. A good to excellent overall headache response to dihydroergotamine therapy was achieved by 28 patients (85%).[75] Patients also obtained good to excellent relief of memory problems (91% of patients), sleep problems (94%), and dizziness (88%). Dihydroergotamine seemed to be well tolerated, and no serious or unexpected adverse reactions were reported.[75]

Valproic acid is a medication believed to affect the function of the neurotransmitter γ-aminobutyric acid in the human brain. Its mechanism of action includes enhanced neurotransmission of γ-aminobutyric acid via inhibition of γ-aminobutyric acid transaminase; however, several other

TABLE 4. Pharmacotherapy for Emotional Symptoms[a]

Symptom	Class	Medication	Brand Names	Dosing	Side Effects
Depression	Tricyclic antidepressants	Amitriptyline	Elavil, Endep, Vanatrip	10-25 mg QHS; titrate up for effect (usually doses of ≤ 150 mg)	Nausea, GI upset, weakness, blurred vision, changes in appetite, drowsiness, dizziness, arrhythmia, motor tics, seizures, hallucination, unusual bleeding
		Nortriptyline	Aventyl, Pamelor	10-25 mg QHS; titrate as above	
	Selective serotonin reuptake inhibitors	Sertraline	Zoloft	25 mg daily; can increase weekly in 25-mg increments (maximum daily dose, 200 mg)	Aggressiveness, strange changes in behavior, suicidal thoughts/ behavior, extreme changes in mood, insomnia, nausea, dry mouth, decreased libido, dizziness, diarrhea
		Citalopram	Celexa	10 mg daily; can titrate dose up for effect (maximum daily dose, 80 mg)	Constipation, decreased sexual desire or ability, diarrhea, dizziness, drowsiness, dry mouth, increased sweating, lightheadedness
		Escitalopram	Lexapro	10-20 mg daily	Nausea, dizziness, GI upset, increased appetite, hallucination, arrhythmia
		Paroxetine	Paxil	20 mg daily; can titrate dose up for effect (maximum daily dose, 50 mg)	Anxiety, blurred vision, constipation, decreased sexual desire or ability, diarrhea, dizziness, drowsiness, dry mouth, loss of appetite, nausea, nervousness, stomach upset
		Fluoxetine	Prozac	20 mg daily; can increase maintenance dose up to 80 mg daily	Anxiety, nausea, motor tics, decreased appetite, weakness
	Other anti-depressants				
		Bupropion	Wellbutrin, Zyban	Dose depends on if immediate release vs sustained release vs extended release; (maximum daily dose, 450 mg)	Seizures, delirium, hallucinations
Anxiety	Benzodiazepines	Lorazepam	Ativan	0.5 mg twice daily	Sedation, dizziness, weakness, unsteadiness, depression, loss of orientation, headache, respiratory depression; caution should be used because these medications can cause physical dependence
		Clonazepam	Ceberclon, Klonopin, Valpax	0.25-0.5 mg twice daily	
		Diazepam	Valium, Valrelease	2-10 mg daily	

[a]GI, gastrointestinal; QHS, at bedtime.

mechanisms of action have been proposed in recent years.[76] Valproic acid also blocks voltage-gated sodium channels and T-type calcium channels. These particular mechanisms make valproic acid a broad-spectrum anticonvulsant drug.[76] Valproic acid has been found useful for the treatment of migraine and chronic daily headaches. Thus, another study sought to determine the effectiveness of divalproex sodium in the treatment of chronic daily posttraumatic headaches.[77] Those authors performed a retrospective review of 100 patients treated with divalproex

TABLE 5. Pharmacotherapy for Cognitive Symptoms[a]

Class	Medication	Brand Names	Dosing	Side Effects
Neurostimulants	Methylphenidate	Ritalin, Concerta, Metadate	5 mg twice daily; can titrate up total daily dose by 5 mg every 2 wk to a maximum of 20 mg twice daily	Insomnia, decreased appetite, GI upset, headaches, dizziness, motor tics, irritability, anxiousness, tearfulness
	Dextroamphetamine	Adderall, Dexadrine ProCentra	5 mg daily; can titrate up for effect (maximum daily dose, 40 mg)	Anxiety, GI upset, insomnia, irritability, euphoria, starting episodes
	Modafanil	Provigil	100 mg every morning; can increase by 100 mg using divided doses (maximum daily dose, 400 mg)	Headache, dizziness, feeling nervous or agitated, nausea, diarrhea, insomnia, dry mouth, hallucinations, depression
	Amantadine	Symadine, Symmetrel	100-400 mg daily	Dizziness, blurred vision, anxiety, insomnia
	Atomoxetine	Strattera	40 mg daily (single or divided doses); can titrate up for effect (maximum daily dose, 100 mg)	Dry mouth, irritability, nausea, decreased appetite, constipation, dizziness, sweating, dysuria, sexual problems, weight changes, palpitations, tachycardia
Selective serotonin reuptake inhibitors	Sertraline	Zoloft	25 mg daily; can increase weekly in 25-mg increments (maximum daily dose, 200 mg)	Aggressiveness, strange changes in behavior, extreme changes in mood, insomnia, nausea, dry mouth, decreased libido, dizziness, diarrhea
	Fluoxetine	Prozac	20 mg daily; can increase maintenance dose up to 80 mg daily	Anxiety, nausea, motor tics, decreased appetite, weakness
Acetylcholinesterase inhibitors	Donepezil	Aricept	5-10 mg daily	Severe diarrhea, severe nausea or vomiting, weight loss, stomach pain, fainting spells, bradycardia, difficulty passing urine, worsening of asthma, stomach ulcers
	Rivastigmine	Exelon	1.5 mg twice daily; can be titrated for effect (maximum daily dose, 200 mg)	Diarrhea, dizziness, drowsiness, headache, loss of appetite, nausea, stomach upset, vomiting
	Galantamine	Razadyne	4 mg twice daily initially, then increased to goal 8 to 12 mg twice daily (also available in extended-release form)	Diarrhea, dizziness, headache, loss of appetite, nausea, stomach upset, drowsiness, weight loss
Others	Cytidine diphosphate choline	Citicoline	250-500 mg daily	Increased body temperature, sweating, nausea loss of appetite

[a]GI, gastrointestinal.

sodium for posttraumatic headaches of ≥ 2 months, all resulting from mild head injuries, defined in the study as having a period of unconsciousness < 20 minutes, a Glasgow Coma Scale ≥ 13, and posttraumatic amnesia lasting < 48 hours. For patients to be included in the study, their charts had to show at least 1 month (or more) of treatment with divalproex. Dosing had been individualized for optimum therapeutic effect. Starting dose was generally 250 mg daily (sometimes as 125 mg taken twice a day). This was increased by 250 mg/wk, depending on patient response. Maximum doses were 500 mg 3 times a day. No other prophylactic medications were used. After at least 1 month of treatment, 60% of patients in the study had mild to moderate improvement in their headaches; 48% either showed no response (26%) or discontinued treatment because of side effects (14%) that included nausea, weight gain, hair loss, and tremor; and 58% of patients who showed improvement had a change in their headache pattern from daily to episodic. So, the authors concluded that divalproex sodium appears to be safe and effective for the treatment of persistent postconcussive headaches.[77]

To determine the outcomes of acute and prophylactic medical therapies prescribed for chronic posttraumatic headaches after mild head trauma in US Army soldiers, a retrospective cohort study was conducted with 100 soldiers undergoing treatment for chronic posttraumatic headaches at a single center.[4] Response rates to various headache abortive medications were determined. Treatment outcomes were also compared between subjects with blast-induced injury and nonblast posttraumatic headache. Headache frequency decreased by 41% among nonblast patients compared with the 9% decrease seen among blast-injury patients. A significant decline in headache frequency occurred in the 29 patients treated with topiramate (100 mg divided daily) but not in the 48 patients

treated with a low-dose tricyclic antidepressant. Additionally, a significantly greater proportion of patients (70%) who used a triptan-class medication experienced reliable headache relief within 2 hours compared with the 42% of subjects using other headache abortive medications. The authors concluded that triptan-class medications appeared to be effective for aborting posttraumatic headaches in military troops attributed to a concussion from a blast injury or nonblast injury and that topiramate appeared to be an effective headache prophylactic therapy in those same patients.[4] Interestingly, this study also compared baseline characteristics between patients who did and did not have a $\geq$ 50% reduction in headache frequency at follow-up compared with baseline. Only 2 baseline factors were significantly associated with a favorable outcome: nonblast injury mechanism and poor sleep quality. Time since onset of headache, headache frequency, analgesic overuse, number and severity of concussions, posttraumatic stress disorder (PTSD), depression, overall burden of postconcussive symptoms, and self-reported memory impairment were not significantly associated with the change in headache frequency 3 months after the start of treatment.

Other options exist for persistent headaches after a concussion; however, as with the previously mentioned treatments, there is scant literature to use to direct treatment selection. Consequently, the treatments for postconcussive headaches are based on those that are prescribed for characteristically similar but etiologically distinct headache disorders (migrainelike, tension-type, clusterlike, etc). For posttraumatic headaches, the distinctions are relative and numerous features may be common to all. Nonetheless, several reviews discuss the use of β-blockers, calcium channel blockers, triptans, and gabapentin as potential medical therapies for persistent postconcussive headaches, mostly on the basis of their use in other headache disorders.[22,66,67,70]

Some small reports and studies have looked at the use of some of these other treatments in patients with posttraumatic headaches.[4,73,78-81] For example, triptans are a family of tryptamine-based drugs traditionally used as abortive medication in the treatment of migraines and cluster headaches. Their action is attributed to their binding to serotonin 5-HT_{1B} and 5-HT_{1D} receptors in cranial blood vessels, causing their constriction and subsequent inhibition of proinflammatory neuropeptide release. These drugs may be effective because they act on serotonin receptors in nerve endings and the blood vessels.[82-84] One case series reported 4 patients with posttraumatic headaches after mild TBI treated with subcutaneous sumatriptan.[81] Of 32 treated attacks, there was adequate headache relief in 95%, with the average time to relief of 51 minutes. Another small case series discussed the treatment of 7 patients with posttraumatic headaches after mild TBI with subcutaneous sumatriptan and reported headache relief by 20 minutes.[80] Another example is the use of β-blockers for the treatment of migrainelike headaches. The mechanism is unclear, but β -blockers may work by decreasing prostaglandin production, although they may also prevent headaches through their effect on serotonin or a direct effect on arteries. One study reported the use of propranolol alone or in combination with amitriptyline in 30 patients with headache after minor head trauma.[73] Twenty-one patients (70%) reported "a dramatic reduction in the frequency and severity of their headaches." Thus, in certain circumstances in which trials with other medications have proven ineffective, such medications may make reasonable choices, albeit anecdotally.

Dizziness and disequilibrium are also common somatic symptoms experienced by the postconcussive patient. These symptoms have been reported in $>$ 30% of people sustaining a concussion.[85] The differential diagnosis for these symptoms is broad; thus, the patient interview, medication review, and clinical examination often guide the clinician in determining the plan of care and determining whether they are even related to the concussion. Although vestibular suppressants have been shown to be effective acutely for vestibular disorders, the same cannot be said for chronic dizziness after a concussion.[86] No studies have demonstrated the effectiveness of such medications after a concussion; however, studies using objective balance assessments have shown that nonpharmacological interventions such as vestibular rehabilitation may be a useful alternative.[87-90] If chronic postconcussive dizziness is severe enough to significantly limit functional activities of daily living, a brief trial of a vestibular suppressant may be warranted. Careful consideration should be given to the use of these medications in PCS patients, given the effects on arousal and memory and their addictive qualities.[61] Potential medical therapies for persistent postconcussive dizziness include meclizine, scopolamine, and dimenhydrinate. In general, treatment with benzodiazepines (although possibly effective) should be avoided if possible given their sedating and addictive qualities.

Fatigue is another common symptom reported in postconcussion patients. Medications, substance use, and lifestyle can also contribute to fatigue; thus, all medical and psychological issues and modifiable factors should be addressed first. The importance of distinguishing such confounding factors is best highlighted by the overlap between depression and fatigue, which could limit the effectiveness of certain pharmacologic agents. All conservative measures should be taken before pharmacotherapy is initiated for fatigue. Although neurostimulants are widely used in TBI (particularly severe TBI),[22,91-94] there is no research evidence to support the use of these medications for fatigue in concussion. The pharmacological agents that have been assessed in mild to severe TBI, with variable success, include methylphenidate, modafinil, and amantadine.[22,92,93]

In general, posttraumatic nausea occurs frequently in the acute period after concussion and less commonly as a part of a PCS. Persistent nausea in postconcussion patients most commonly occurs in association with persistent dizziness or secondary to medication effects.[95] Before treating patients with antiemetics such as ondansetron, the clinician should be sure to review the patient's history thoroughly and to attempt to define any triggers or patterns. Other somatic symptoms that typically follow a concussion acutely such as vision difficulties (ie, diplopia, blurred vision, photophobia), hearing difficulties (ie, altered acuity, phonophobia), and changes in appetite tend to resolve spontaneously with conservative measures and rarely require further treatment.[95]

Sleep Disturbance Symptoms

Difficulties with sleep often occur acutely after a concussion and are a common source of significant morbidity, especially for student athletes because they tend to markedly affect school performance.[22,63] Patients may have difficulty falling asleep or staying asleep or may suffer from insomnia. Sleep hygiene is one of the first issues that should be addressed and discussed with patients.[22,61,96] Patients should be advised to eliminate distractions from the bedroom (television, stereo, video games, telephones, computers). Bedtime should be spent sleeping. Reducing the sources of stimulation can help the patient fall asleep and stay asleep. Having patients return to and engage in daytime physical and mental activities, within each individual's functional limits, will help to establish a regular, normalized sleep-wake pattern. Additionally, those with sleep disturbances should avoid caffeine, nicotine, and alcohol use and minimize daytime naps.[22]

If conservative measures do not suffice, sleep agents may assist patients with PCS (Table 3). Trazodone is an antidepressant with 5-HT_{2A} receptor antagonist and some serotonin reuptake inhibitor properties.[22,97] It has

anxiolytic and hypnotic effects, with fewer anticholinergic and sexual side effects than other antidepressants; thus, it is commonly used to treat sleep disturbances after concussion.[22,97] Some clinicians prefer to use other common agents such as zolpidem or tricyclic antidepressants.[96]

Prazosin is a selective α-1 receptor antagonist best known for its use in the treatment of hypertension, anxiety, and PTSD. A recent observational study examined whether treatment with sleep hygiene counseling and oral prazosin would improve sleep, headaches, and cognitive performance.[98] The cohort of patients included 126 veteran soldiers with blast-induced mild TBI during deployment in Operation Iraqi Freedom or Operation Enduring Freedom. Of the 126 veterans, 74 had comorbidities, including frequent, severe headaches and residual deficits on neurological examination, neuropsychological testing, or both. Of these veterans, 71 had PTSD and only 5 had restful sleep. After 9 weeks of treatment, 65 veterans reported restful sleep, and a significant number of patients had improved headaches and cognitive assessment scores.

Other clinicians prefer to use melatonin as a sleep agent. Melatonin is an endogenous hormone produced primarily by the pineal gland and converted from serotonin. The production of melatonin is greatest during times of darkness, and its levels are lowest during the day.[22] The high efficacy, high safety profile, and virtual lack of toxicity of melatonin make it of interest in clinical medicine.[99] Prior studies have shown it to be effective and safe for use in TBI patients, with most studies using 5-mg dosing.[97,100-104] Melatonin is an over-the-counter supplement; its recommended dosage is 0.3 to 5 mg.[105,106] This is considered to be a safe and effective dosage.[105,106] Generally, it is a good idea to start first at lower melatonin doses and then gradually increase the dosage until the most effective dosage is found. The basic mechanism by which melatonin produces sleepiness in humans is unclear, although 3 main hypotheses have been proposed. The mechanism of action of melatonin may involve a phase shift of the endogenous circadian pacemaker, a reduction in core body temperature, and/or a direct action on somnogenic structures of the brain.[107]

Emotional Symptoms

Emotional symptoms are common in postconcussive patients.[23,63] Patients may report irritability, depression, apathy, anxiety, PTSD, personality changes, disinhibited behavior, or emotional lability. Restrictions on activity, in addition to the removal of an athlete from their teammates or a soldier from his/her fellow troops, can also lead to depression. Many of the acute emotional symptoms are short-lived and can be managed conservatively with coping strategies, professional counseling, and support of family and friends.[22] However, those patients with persistent postconcussive emotional/behavioral symptoms may benefit from pharmacological treatment in addition to nonpharmacological therapeutic measures[22] (Table 4). Anxiolytics such as benzodiazepines can be used in low doses for patients with symptoms of anxiety; however, they should be avoided if at all possible because of their sedating effects.[22,95] In general, antidepressants have been used globally for most emotional symptoms.[22]

Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) have been investigated as therapeutic options in the treatment of TBI-related depression.[108,109] Some studies suggest that although amitriptyline has been useful in treating primary depression, it may not be as effective for treating post-TBI depression.[10,108,110,111] As with the medical treatments for other concussion symptoms, most of the evidence for SSRI use in concussion comes from small, uncontrolled/open studies and case reports rather than large randomized trials. That being said, SSRIs have become the primary treatment for TBI-associated depression because of their perceived clinical efficacy and relatively few side effects.

In 1 study, an 8-week, nonrandomized, single-blind, placebo run-in trial of sertraline was conducted on 15 patients diagnosed with major depression between 3 and 24 months after a mild TBI.[112] On the Hamilton Depression Rating Scale, at least 13 patients (87%) had a decrease in their score of ≥ 50% ("response"), and 10 patients (67%) achieved "remission" of their depression by week 8 of sertraline treatment.[112] There was also a statistically significant improvement in other postconcussive symptom, including psychological distress, anger, aggression, and cognitive variables of psychomotor speed and recent verbal/visual memory. Thus, treating depression after a concussion may also improve other cognitive symptoms or deficits in patients.[113]

Another study examined the rates of response and remission associated with citalopram treatment for major depression after TBI.[114] Patients with major depression after mild to moderate TBI were treated with citalopram for either 6 weeks (n = 54) or 10 weeks (n = 26). The Hamilton Depression Rating Scale was used to assess depression severity and treatment effect. At 6 weeks, 54 subjects were assessed and 27.7% responded with 24.1% in remission. At 10 weeks, 26 subjects were assessed and 46.2% responded with 26.9% in remission. The authors concluded that although the response rate in their patient cohort was substantially lower than previously reported for patients with TBI, it was comparable to the results of the largest effectiveness trial of citalopram for general outpatients with major depression in the absence of TBI.[114] Once a response or remission is achieved, it is uncertain how long therapy should be continued in this patient population.[115] Other SSRIs have also been investigated.[21,116,117] Paroxetine was found to be just as effective as citalopram in improving emotional symptoms in 1 study,[116] and another study found significant improvement in mood with fluoxetine treatment in post-TBI patients,[117] although the TBI populations were heterogeneous in these studies.

Cognitive Symptoms

Cognitive complaints and symptoms are extremely common in the first hours and days after a concussion.[22,23,63,118,119] Patients frequently report difficulty with memory and concentration. Advances in computerized neuropsychological testing have revealed qualitative deficits in memory, complex attention, or working memory and speed of mental and motor performance.[23,45,118-120] The majority of patients who sustain a concussion have a resolution of their acute cognitive symptoms within days to a few weeks. A subgroup of individuals continue to have both subjective symptoms and persistent deficits on formal neuropsychological testing, and these patients may benefit from a trial of medications (Table 5).

Although no studies have investigated the role of methylphenidate strictly in the setting of concussion, it has been studied more than other cognitive agents in TBI.[121-125] There is evidence to support the use of methylphenidate in treating deficits in attention, processing speed, and general cognitive functioning.[22,108] One study investigated 34 adults with moderate to severe TBI and attention complaints in the postacute phase of recovery in a 6-week, randomized, double-blind, placebo-controlled, repeated crossover study of methylphenidate administration.[124] They found that methylphenidate had a clinically significant effect on processing speed, attention, and some aspects of on-task behavior in naturalistic tasks. The effect of subacute administration of methylphenidate on recovery from moderate to moderately severe closed-head injury was explored in a double-blind, placebo-controlled trial.[121] The study included 23 patients ranging in from 16 to 64 years of age. Head injury severity ranged from moderately severe to "complicated mild" (defined as Glasgow Coma Scale from 13 to 15 with evidence of cerebral

contusion on computed tomography scan). Thirty-day follow-up was based on 12 patients, whereas 90-day evaluation was based on 9 patients, with complicated mild head injuries excluded from the analyses. Although this study was clearly limited by a small and very heterogeneous patient size, subacute administration of methylphenidate after moderately severe head injury appeared to enhance the rate but not the ultimate degree of recovery.[121] Not all studies have shown such a benefit from methylphenidate, however, and caution should be exercised when prescribing methylphenidate because of its potential to lower seizure thresholds.[21,22,125]

Amantadine is another potential medication used to manage postconcussive neurocognitive recovery.[126,127] Amantadine appears to act through several pharmacological mechanisms, but no dominant mechanism of action has been identified. A dopaminergic and noradrenergic agent, it may also be a weak *N*-methyl-D-aspartate receptor antagonist. The role of amantadine in TBI has been investigated, with equivocal evidence in the literature regarding its efficacy. Several studies have suggested that amantadine is safe and may improve cognitive functioning.[128,129] In 1 study of 22 patients with mild, moderate, and severe TBI, amantadine was found to significantly improve executive function testing.[128] Additionally, positron emission tomography scans demonstrated a significant increase in left prefrontal cortex glucose metabolism that correlated with improved cognitive testing. Amantadine may be particularly effective in pediatric patients.[130,131] On the other hand, a small prospective, randomized, double-blind, placebo-controlled study did not find positive results with amantadine treatment in 10 heterogeneous patients with TBI.[132] Although the study had numerous limitations, the authors concluded that there was no difference in rate of cognitive improvement between those subjects given amantadine and those given placebo.

Cholinergic dysfunction is thought to underlie the memory impairment in patients with Alzheimer disease, and postconcussive patients with cognitive symptoms share some similarities in the memory and attention deficits seen in Alzheimer disease.[46] Donepezil is a long-acting acetylcholinesterase inhibitor shown to improve cognition in Alzheimer disease patients. There is accumulating evidence that donepezil administration improved overall function, as well as short- and long-term memory.[133-136] Donepezil also reduced anxiety, depression, and apathy in some patients.[134] Newer-generation acetylcholinesterase inhibitors such as rivastigmine and galantamine have also been investigated with similar promising results.[137-142] Cytidine diphosphate choline, an intermediate precursor in the synthesis of phosphatidylcholine, is thought to lead to increased brain acetylcholine levels. One study explored treatment of postconcussion symptoms for 1 month after mild to moderate TBI with cytidine diphosphate choline.[143] This small double-blinded, placebo-controlled study of 14 patients found that cytidine diphosphate choline produced a significantly greater reduction in postconcussion symptoms than placebo. The patients also had a significant improvement in recognition memory for designs.[143] There is still a need for further studies to determine the efficacy of cholinergic agents in treating the neurocognitive symptoms in postconcussion patients. Several other pharmacological agents such as fluoxetine, sertraline, atomoxetine, bromocriptine, and pramiracetam have been investigated as treatment for postconcussive cognitive symptoms; however, the evidence is limited.[21,22,108,117]

DISCUSSION

It is paramount to have a consistent and cohesive multidisciplinary approach when treating concussion patients with somatic, sleep, cognitive, and/or behavioral impairments. Although the treatment team can be composed of healthcare practitioners from multiple disciplines of medicine, all should seek to achieve common objectives collaboratively. Fortunately, most postconcussive symptoms resolve spontaneously and require only conservative treatment. Subgroups of patients have prolonged recoveries, however, and may benefit from treatment with medications. The choice of which medication to use for a patient depends on the symptom qualities, and each decision should be made on an individual-case basis. As has been demonstrated in this review, the evidence supporting the pharmacologic treatment of persistent concussion symptoms is equivocal.

Concussion in the Military: Points of Consideration

Concussion has become a silent epidemic in athletics and among military personnel. Although the pharmacological treatment of symptoms has been described in broad general categories, several nuances between these 2 groups must be considered. As noted in the consensus statement generated from the 3rd International Conference on Concussion in Sport, there are a range of "modifying" factors that may influence the investigation and management of concussion, including the mechanism of injury.[23] The differential response observed in the previously mentioned study of headache management in military personnel exposed to blast- vs non–blast-induced concussive injuries demonstrates the importance of such modifying factors.[4] To identify more effective treatment strategies, it will be important to determine and to understand the reasons why non–blast-induced posttraumatic headaches respond better to prophylactic therapies than blast-induced headaches.[4]

Premorbid/comorbid conditions can also be considered modifying factors and include a history of migraine, depression, or other mental health disorders; PTSD; attention deficit hyperactivity disorder; and sleep disorders. Psychological issues can particularly complicate concussion management because they may trigger somatic symptoms or contribute to a vicious cycle of pain and emotional problems.[70] Alternatively, persistent headaches after concussion may perpetuate emotional symptoms.[70] Large populations of Operation Iraqi Freedom and Operation Enduring Freedom veterans who have sustained TBI suffer from PTSD or have both a history of TBI and current PTSD.[144,145] Symptoms that may be attributable to concussion or mild TBI overlap considerably with the symptoms of PTSD. It is also unknown whether findings from civilian populations with a history of both concussion and PTSD are applicable to individuals with combat-related concussion and PTSD. Additionally, soldiers are exposed to multiple stressors with or without suffering blast-induced TBI, making diagnosis and treatment even more difficult. One study of experimental blast-induced TBI in rats demonstrated that experimental conditions alone,

particularly the exposure to blast acoustics, increased anxiety and triggered specific behavioral and molecular changes without evidence of injury.[146] These findings, albeit in an animal model, highlight the possible role of combat-related stressors in the development of posttraumatic symptoms.

Such observations stress how the mechanism of trauma (blast vs nonblast), the context of the injury (battlefield vs not on a battlefield), or possible underlying comorbidities may have significant implications for treatment outcomes. Thus, many of the pharmacological treatments that have been described for use in civilian or sports-related concussion may not be transferrable to military personnel with combat-related TBI and vice versa. A recent excellent review noted that current evidence-based practices to screen, diagnose, prospectively evaluate, and, more important, treat postconcussion symptoms or PTSD may be less accurate or effective if and when these conditions occur together.[144] No well-designed studies have evaluated treatment effectiveness in this population.[147] Thus, there is a particular need to develop an evidence base to identify best practices to diagnose and manage patients with concussion/PTSD in our military veterans, which may differ from civilian care.

Limitations

Our review has several limitations that should be taken into account. First, we limited our literature search to articles in the English language from 1900 to 2011, so studies published in other languages may have been missed. With regard to certain search terms, there has been no universally accepted terminology, increasing the difficulty of the literature review. For example, no universal definition has been accepted for concussion over the years, and there is much overlap in the literature with mild TBI. As another example, some articles used the term posttraumatic headache, whereas others used the term post-traumatic headache. In addition, although our review found several satisfactory responses to pharmacological treatments, it is possible that many more negative results were not published. Another limitation is that this article lacks the "quality" of a true systematic review. That being said, the last systematic review of treatments for mild TBI/concussion was in 2005.[10] That review identified 8 studies that met the inclusion criteria, and the authors concluded that there was insufficient evidence that any specific drug treatment was effective for 1 or more symptoms of mild TBI.[10] Since then, there has continued to be a lack of quality evidence for the use of pharmacotherapy in concussion management.

CONCLUSION

This comprehensive review has described the available pharmacological treatment options and strategies for concussion based on the most current available medical literature, regardless of the quality of evidence. Having the full scope of evidence in the practitioner's management armamentarium should aid in dealing with complex postconcussion symptoms. That being said, it cannot be emphasized enough that treating patients with postconcussive symptoms is not an easy task. Although we may have a variety of medications at our disposal, at this time, a clear inability exists to precisely treat concussion symptoms pharmacologically in this difficult population. Additionally, many of these medications can be considered off-label in their use and carry several drug interactions or side effects, as demonstrated in the tables of this review. Strong consideration must be given to discovering and using translational treatments that target the underlying pathophysiology. As noted, an increasing number of well-designed studies are investigating the neuroprotective potential of nutraceutical preparations, and although the clinical evidence is still fairly thin, such a treatment approach may prove to be more successful than symptom management. Ultimately, understanding the limitations of the medical evidence should enable the practitioner to better educate postconcussive patients regarding the potential therapeutic approaches. Finally, in addition to providing a management framework, this review underscores the clear need for well-designed trials investigating the efficacy of both naturally occurring neuroprotective compounds and the various symptomatic medical therapies noted.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

This is a good review article on the medical therapies to treat prolonged postconcussive symptoms. Many factors come into play in the decision to treat these symptoms pharmacologically. One factor is the severity of symptoms affecting the patient's daily living, including school performance for athletes. Another is the duration of symptoms, particularly when it exceeds the typical recovery period. Other factors that could affect the decision to use medical treatment for the symptoms of concussion are parents' and teachers' feedback regarding the younger patients' physical, emotional, and cognitive changes noted after the traumatic brain injury. Without a doubt, the benefits of medical treatment for concussion symptoms should justify the potential side effects of these medications. There is scant literature regarding the medical management of concussion. This article highlights the great need to develop large multicenter, controlled studies to evaluate the various medical therapies in treating prolonged postconcussive symptoms.

A question for the future is whether functional magnetic resonance imaging (MRI) would be an adjunctive tool for clinical assessment to decide which patients should be considered for treatment of depression. Functional MRI suggests that a depressed mood after concussion may reflect an underlying pathophysiology abnormality consistent with a limbic-frontal model of depression.[1,2] Numerous postconcussion symptoms such as lack of concentration, fatigue, and sleeping difficulty overlap with depression manifestation. Currently, functional MRI is available only for research purposes.

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1. Chen J, Johnston K, Collie A, et al. A validation of the Post Concussion Symptom Scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry*. 2007;78(11):1231-1238.
2. Chen J, Johnston K, Frey S, et al. Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage*. 2004;22(1):68-82.

The authors are complimented for providing a scholarly review of the pharmacotherapy literature in mild traumatic brain injury. They accurately indicate that the evidence for various pharmacologic agents is equivocal and that treatment should be based individually on symptom characteristics. The authors also provide tables on medications, which should be a very useful resource for practitioners.

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