# Management of Concussion and Post-Concussion Syndrome

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**Current Treatment Options in Neurology** 2006, **8:**415–426
Current Science Inc. ISSN 1092–8480


## Opinion statement

Concussion and mild traumatic brain injury (mTBI) are common clinical problems. However, the literature is not consistent in defining how concussion and mTBI are related. Although most patients with concussion recover within days to weeks, approximately 10% develop persistent signs and symptoms of post-concussion syndrome (PCS). There are no scientifically established treatments for concussion or PCS and thus rest and cognitive rehabilitation are traditionally applied, with limited effectiveness. This article presents a clinical model to suggest that concussion evolves to become mTBI after PCS has developed, representing a more severe form of brain injury. The basic pathophysiology of concussion is presented, followed by a recommended approach to the clinical evaluation of concussion in the emergency department and the physician's office. We evaluate the limited evidence-based pharmacologic treatment of acute concussion symptoms and PCS symptoms and also discuss return to activity recommendations, with an emphasis on athletes. Lastly, we suggest a promising new direction for helping patients recover from PCS.

## Introduction

Estimates of the number of individuals experiencing a brain injury in the United States vary from 1.5 to 2 million each year [1, Class II]. Most of these injuries (approximately 85%) are considered mild, but they may have long-term effects [2, Class II]. These estimates do not include concussions in which an individual did not sustain loss of consciousness (LOC) but which nonetheless may affect the individual's health for 1 week or more. Most individuals with concussion (approximately 75%) do not seek attention from a medical facility or medical practitioner unless the symptoms worsen or persist.

There is uncertainty about the definitions of mild traumatic brain injury (mTBI) and concussion. There is further uncertainty about the definition of post-concussion syndrome (PCS) and the cause and treatment of PCS. Although there has been much research on and increased understanding of the pathophysiology of concussion and mTBI, there is need for a model to clarify the diagnosis of each and ultimately a model for treatment. One purpose of this paper is to provide a framework for understanding concussion and how it fits into the continuum of injury to the brain. A second purpose is to provide a brief explanation of the pathophysiology of brain injury. The final goal is to provide a description of current treatment options and likely directions for future treatment given our increasing understanding of the pathophysiology of concussion.

The most commonly accepted definition of mTBI is that of the Centers for Disease Control and Prevention (CDC) and the American Congress of Rehabilitation Medicine: loss of consciousness for no more than 30 minutes or amnesia as a result of a mechanical force to the head, and a Glasgow Coma Scale (GCS) score of 13 to 15 [3••, Class III]. The most commonly accepted definition of concussion, developed by the American Academy of Neurology (AAN), is a trauma-induced alteration in mental status that may or may not involve loss of consciousness [4, Class III]. Although not explicitly stated in the AAN definition, there is the assumption

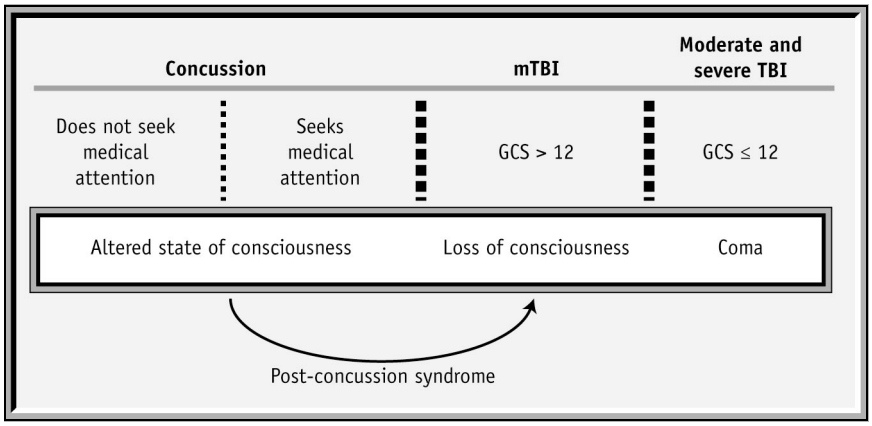


**Figure 1.** A model to describe the levels of head injury from concussion (temporary alteration of consciousness) to severe (permanent brain damage). Concussion effects are assumed to be transient with signs and symptoms that do not last more than 3 weeks. If signs and symptoms persist beyond 3 weeks, then the diagnosis is altered to reflect the more permanent nature of the injury: post-concussion syndrome. Individuals with post-concussion syndrome are more accurately diagnosed as mild traumatic brain injury (mTBI). GCS—Glasgow Coma Scale.

that concussion effects are transient, whereas mTBI is considered permanent or semi-permanent. The use of the different terms, mTBI and concussion, to describe the same injury is confusing for clinicians. Instead, clinicians tend to use the term concussion to describe instances in which an individual experiences transient alteration in mental status, especially from a sports-related head injury. mTBI is used to categorize patients with more serious head injury in which there was a (brief) loss of consciousness and a GCS score of 13 or 14 at some point after the injury.

Figure 1 describes the continuum of injury to the brain as experienced by individuals with a head injury. Most people who sustain a head injury experience an altered state of consciousness for a brief period but may not define the experience as a concussion [5, Class II]. In the world of sport this is often referred to as a "ding" or "bell ringer." The practice guidelines of the AAN describe a grade 1 concussion as symptom duration for no more than 15 minutes and no loss of consciousness. Athletes will often deny theses symptoms in order to continue playing their sport, even though their performance is often affected. If the injury occurs in a sports event it is likely to be observed by others, and there is a better chance that medical services will be sought. However, research on adolescents in particular indicates that approximately 75% of those with such injuries do not seek attention from a physician unless symptoms persist more that 24 hours [6, Class II]. The recommended response of the physician during the initial visit of someone with post-concussion is discussed later in this text.

Recent research on grade 1 concussions indicates that concussed individuals, even at this seemingly minor level, may experience impaired memory and renewed symptoms within 36 hours of the injury [5, Class II]. Renewed symptoms included headache, nausea, disturbed sleep, and balance problems. Current recommendations for on-field assessment are that athletes with grade 1 concussions should not be allowed to return to play, even if they report being symptom free. There is significant risk of a second, more debilitating injury. The extreme vulnerability of the slightly damaged brain is borne out by recent animal research [7, Class II].

Individuals who experience symptoms for more than 15 minutes or experience a brief loss of consciousness, convulsions, or vomiting as a result of a concussion are much more likely to seek immediate attention. These levels of concussion correspond to grades 2 and 3 of the AAN guidelines. Recent research indicates there is little point in distinguishing between grade 2 and 3 concussions because there is no apparent prognostic value [8, Class II]. For our purposes, such a concussion becomes an mTBI if the loss of consciousness exceeds 5 minutes as per the criteria of the American Psychiatric Association (DSM IV) but less than 30 minutes as per the CDC and the American Congress of Rehabilitation Medicine [3••, Class III]. Management of the concussed individual in the emergency department is discussed briefly in the treatment section.

On rare occasions, an individual can appear to have experienced a grade 1 concussion when symptoms abate after only a few minutes but then have a return of symptoms some time later. As researchers learn more about the metabolic changes that characterize concussion, we realize this delayed presentation of symptoms is quite possible and explainable. In these instances, the categorization of concussion should be upgraded to grade 2 or 3. One should also be cognizant of any other signs or symptoms of the patient's condition worsening in order to be alert to a possible intracranial hemorrhage. There are increasing recommendations in the sports concussion literature to define concussion severity in terms of the number, severity, and duration of symptoms after concussion rather than the immediate signs and symptoms such as loss of consciousness [9•, Class III].

Recent research on the metabolic changes that accompany concussion indicates that the brain should return to normal in 7 to 10 days [10, Class II]. Concurrent research on the cognitive changes that occur as a result of concussion also shows a return to normal for most individuals in 7 to 10 days [11]. Adolescents appear to take slightly longer to recover from concussion than do adults [11]. All patients generally report

that their symptoms are gone (3–4 days post-concussion) before they demonstrate physical and cognitive homeostasis. During the period when the patient denies symptoms but metabolic changes are still in effect, symptoms may be induced by rigorous exercise. Therefore, team physicians use exercise as a "symptom stress test" to determine whether a player is ready to return to play [12••, Class III].

Although most concussed individuals will recover completely within the 7- to 10-day period, approximately 10% will display signs and symptoms of concussion past the usual period. After 3 weeks, patients begin to worry about when they will recover, and by 6 weeks, if symptoms persist, PCS can alter how individuals live their lives. PCS is defined by the DSM IV as 1) cognitive deficits in attention or memory, and 2) at least three or more of the following symptoms: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, apathy, or personality change [13••, Class II]. The DSM IV diagnostic criteria are quite conservative. Most patients with PCS have only a few symptoms, headache and fatigue being the most common. The fatigue is related to changes in cognitive function and is most demonstrable for students (related to learning demands) and employees in whom work places demands for attention and concentration. A recent study found that use of the broader definition of PCS (represented by the World Health Organization [WHO] International Classification of Disease [ICD] 10 clinical criteria—three or more of the following symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, or memory difficulty) was six times more sensitive for identifying PCS patients [13••, Class II].

In the model of brain injury and concussion presented in Figure 1, we suggest that patients with PCS have semipermanent brain injury and therefore move from a diagnosis of concussion to a diagnosis of mTBI. The assumption is that metabolic and structural changes in the brain of the concussed individual have not returned to homeostasis. The diagnosis of PCS is controversial. The symptoms of PCS, such as headache, fatigue, and depressive symptoms, are common in the general population. PCS is a common complaint of individuals involved in litigation after an injury. Individuals with PCS often appear as confused about their symptoms as are the practitioners treating them. Individuals with PCS are often depressed, whether from neurologic insult related to the concussion or in reaction to cognitive and somatic changes resulting from the concussion. Differential diagnosis is not straightforward.

Differential diagnosis is determined, in part, by careful history taking. Individuals with multiple concussions are more likely to sustain another concussion. Recent research suggests that a significant risk factor for the development of PCS is three or more prior concussions [14,15, Class II]. Other predictors of PCS are female gender, age (> 40 years), and prior history of affective disorder such as depression [16, Class II]. Predictors related to injury severity, such as length of posttraumatic amnesia and cognitive difficulties (as demonstrated on the digits forward and backward test), are clearly associated with symptoms at 1 month but less so at 6 months after injury [17, Class II].

The differential diagnosis of PCS includes factitious disorder, anxiety disorder, chronic fatigue syndrome, and chronic pain syndrome. In many instances, especially automobile crashes, one can see more than one condition in the same patient. Our advice is that if there is evidence for PCS, treat the PCS and then see if the depression or anxiety remains. We find that factitious disorder is quite rare, and such patients do not generally like to follow the recommended treatment plan for PCS described in the following text.

## PATHOPHYSIOLOGY OF CONCUSSION

Concussion is the result of rapid deceleration of the brain within the skull that imparts shearing or torsional forces to neural tissue followed by metabolic and mechanical changes [3••, Class III]. The mechanical changes are generally referred to as diffuse axonal injury. The vulnerable cellular structure is the axon and in particular the long axons, that is, axons involved with high-level associative functions. In more severe brain injury, diffuse axonal injury is visible on MRI because of eventual cell death. With concussion the effects are less obvious. Diffuse axonal injury is considered instrumental in causing cognitive sequelae such as memory difficulties and problems with concentration.

The forces that produce a concussion combined with the stretching of axons result in what has been called a cascade of neurochemical changes. In animal studies, this cascade occurs over a period of hours rather than minutes and thus explains why some signs and symptoms of concussion may be delayed [10, Class II]. The metabolic cascade is characterized by an initial depolarization of neuronal membranes and the release of excitatory amino acids, particularly glutamate, which produce fluxes of calcium and potassium ions across neural and vascular tissue resulting in at first a hypermetabolic glycolytic state as the neurons attempt to restore equilibrium. There follows a calcium ion–induced vasoconstriction that reduces cerebral blood flow and glucose delivery with a resultant state of "metabolic depression" as the brain energy demand is not met by the vascular energy supply, which may last from days in animals to weeks in humans [10, Class II]. This complex cascade has also been shown to render neural tissue more susceptible to further injury [7, Class II], which may explain the clinical observation that patients with a history of concussions are at greater risk for recurrent concussion and for the development of PCS. Recently, Korn et al. [18•, Class II] showed areas of focal cortical dysfunction in conjunction

**Table 1. Common acute symptoms of cerebral concussion**

| Somatic | Neurobehavioral | Cognitive |
|---|---|---|
| Headache | Drowsiness | Feeling "slowed down" |
| Nausea | Fatigue/lethargy | Feeling "in a fog" or "dazed" |
| Vomiting | Sadness/depression | Difficulty concentrating |
| Balance problems/dizziness | Nervousness/irritability | Difficulty remembering |
| Sensitivity to light/noise | Sleeping more than usual | |
| Numbness/tingling | Trouble falling asleep | |
| Blurred vision/diplopia/flashing lights | | |
| Tinnitus | | |

**Table 2. Common acute physical signs of cerebral concussion**

| |
|---|
| Impaired conscious state or brief loss of consciousness |
| Confusion |
| Vacant stare/glassy eyed |
| Amnesia: retrograde or anterograde |
| Slow to answer questions or follow directions; easily distracted/poor concentration |
| Poor coordination or balance; unsteady gait |
| Personality change; inappropriate emotion (laughing or crying) |
| Slurred speech |
| In athletes during competition, one may also observe: |
| Unaware of period, opposition, or game score |
| Inappropriate playing behavior, eg, running in the wrong direction |
| Significantly reduced playing ability |

with blood-brain barrier disruption and reduced regional cerebral blood flow in patients months to years after mTBI. Thus, the accumulating data suggest that the altered brain metabolic milieu after concussion can persist for a long time in some patients.

# Treatment

## Emergency department evaluation

### History

- The history should include a description of the mechanism and force of the head trauma and the number and severity of symptoms experienced by the patient. Table 1 presents common symptoms and Table 2 presents common physical signs observed acutely after concussion. Symptoms may be delayed for several hours or days after even a seemingly mild head injury [5, Class II]. The physician should ask about the presence and duration of loss of consciousness, any convulsive activity, and any balance problems. Although dramatic and a signal to perform neuroimaging, post-concussive seizures are usually benign [19].

### Physical examination and amnesia/cognitive tests

- The Sport Concussion Assessment Tool (SCAT) [12••, Class III] developed by the 2004 Prague International Conference on Concussion in Sport is a standardized tool for patient education and physician evaluation of concussion. The SCAT includes a graded symptom checklist, cognitive assessment drills, and a brief physical examination. The patient is asked to recall five words immediately and then again after performing concentration

drills of stating the months of the year in reverse and a series of digits backwards tests. The physical examination includes speech fluency, a cranial nerve examination, and pronator drift and gait assessment. The Romberg test and vestibular testing should also be performed because balance and vestibular deficits may persist for up to 10 days after concussion [20, Class II], with improvement correlating with recovery from concussion [21••, Class II]. Any focal neurologic deficits mandate rapid neuroimaging and neurosurgical consultation [3••, Class III].

## Risk factors for hemorrhage and neuroimaging decision

- Risk factors for hemorrhage reported in the literature include GCS < 15, amnesia, headache, vomiting, neurologic deficit, seizure, (older) age, race (black), mechanism of injury, drug/alcohol intoxication, and historical items (defined as pretrauma epilepsy, neurosurgeries, coagulation disorders, and shunted hydrocephalus) [22, Class I]. However, no single variable provides adequate positive prediction of the risk for intracranial lesions after mTBI. Two widely used clinical decision rules for the use of head CT in the emergency department are the Canadian Head CT Rule and the New Orleans Criteria. In a recent prospective comparison of these rules for predicting the need for neurosurgical intervention after mTBI [23], both were found to be 100% sensitive, but the Canadian rule was significantly more specific. Nevertheless, physicians were not comfortable using the rules in all cases. The application of clinical decision rules was influenced by clinician thresholds, the prevailing local emergency department practices, and the legal climate.

## Post-acute advice

- Wake-ups and rest
  - It has been recommended that the concussed patient be awakened every 3 to 4 hours during sleep to evaluate for signs of intracranial bleeding. No documented evidence suggests what severity of injury requires this approach, and there is debate as to whether this is necessary [24, Class III]. A good rule of thumb is if the patient has experienced loss of consciousness, prolonged amnesia, or is still experiencing significant symptoms, he or she should be awakened. The use of oral and written instructions increases the compliance rate for purposeful awakening during the night [25, Class III].
  - Evidence from basic animal research suggests that an initial period of physical and cognitive rest is therapeutic after concussive injury [10, Class II], but in a randomized human trial complete bed rest was ineffective in reducing symptoms [26, Class I]. The literature is in general agreement that relative rest (ie, avoiding studying and physical exertion but resuming normal activities of daily living as soon as possible [24, Class III]) for the first 2 to 5 days after concussion is important because strenuous cognitive and physical activity may exacerbate symptoms and delay recovery [12••, Class III].
- Medication
  - Acetaminophen is a logical choice for immediate treatment of post-concussion headache because there is a theoretical risk early after the injury (within 48–72 hours) of inducing or exacerbating cerebral hemorrhage with aspirin or other nonsteroidal anti-inflammatory drugs [24, Class III], although there are no controlled trials demonstrating this.

- Information
  - Many patients are discharged from the emergency department with no specific recommendations for follow-up [2, Class II]. Two randomized trials have shown that routine follow-up after mTBI reduces the number and severity of post-concussion symptoms [27, Class II; 28, Class I]. Thus, it is important that these patients receive specific instructions to see their primary physician or a neurologist after emergency department discharge. Several European neurological societies have developed clinical guidelines that recommend routine follow-up for these patients [2, Class II].
  - Although infrequent, the potential for neurologic deterioration after mTBI exists [29, Class II]. Caregivers should be given specific written instructions regarding signs and symptoms to watch for. Written instructions are superior to verbal explanations, in terms of compliance with instructions and for retaining the information, but there are only limited scientific studies that identify what variables are the most important to monitor.

## Initial physician visit

### Classification of concussion severity

- The 2004 Prague International Conference on Concussion in Sport classifies concussions as simple or complex [12••, Class III]. A simple concussion resolves within 7 to 10 days, with no residual deficits or complications, and does not require sophisticated imaging or testing. Simple concussions represent the most common form of this injury and can be managed by primary care physicians. A complex concussion is characterized by persistent post-concussion symptoms, signs, cognitive dysfunction, and complications (eg, convulsions). Patients with prolonged loss of consciousness (> 1 minute) or those who suffer multiple concussions over time or with progressively less impact force may also be included in this category. Formal neuropsychological testing and neural imaging should be considered for complex concussions, and management generally requires a multidisciplinary team (primary care/team physician, neurologist, neurosurgeon, and neuropsychologist).

### History and examination

- The progression of initial symptoms and the appearance of any new symptoms must be assessed, and a thorough neurologic examination must be performed, emphasizing memory, concentration, cranial nerves, and balance/vestibular function. The physician should elicit more detail about the number of prior concussions, the specific symptoms associated with each and time to resolution, any treatment, neuroimaging, and medication (prescription and nonprescription). Information about all prior head, face, or neck injuries is also relevant because patients often do not recognize that a concussion may have occurred on these occasions. Research on the significance of prior concussions indicates that subsequent concussions occur with decreasing levels of impact [12••, Class III].
- Because some patients may have persistent or worsening symptoms that may be associated with intracranial lesions or subdural bleeding, clinicians must decide whether neuroimaging is indicated. In most patients who have a simple concussion, conventional neuroimaging is normal [12••, Class III]. CT or MRI is recommended if the patient is clinically worsening, but what constitutes deterioration is a clinical judgment. Newer imaging

modalities such as positron emission tomography, single photon emission computed tomography (SPECT), and functional MRI promise greater utility for concussion assessment but await prospective studies of their sensitivity, specificity, and predictive value.

## Treatment

- Activity
  - Once the patient is asymptomatic at rest, he or she is advised to progress stepwise from light aerobic activity such as walking or stationary cycling up to sport or work-specific activities (see following text) [12••, Class III]. However, there is no evidence-based research to quantify specific activity type, intensity, and progression rate.
- Medication
  - The most common symptom for which medication is indicated is post-concussion headache [30, Class III]. As many as one third of patients report increased headaches 1 year after head trauma [31]. Generally the headache (eg, tension, migraine) is similar to the type of headache the patient typically had before the trauma [30, Class III], with most (85%) being described as steady, aching, tension-type headaches [32, Class III]. Migraine headaches with or without aura have been reported with less frequency after concussion [32, Class III]. Adolescents participating in sports with repetitive minor head trauma such as football, hockey, and boxing can develop "footballer's migraine" [32, Class III]. The headaches are thought to be attributed to myofascial injuries, intervertebral disc damage, facet joint injury, temporomandibular joint injury, and muscle spasms in the superior trapezius and semispinalis capitis muscles in the suboccipital region [30, Class III].
  - One study of depressed post-mTBI patients found that amitriptyline was ineffective [33, Class II], whereas in another study amitriptyline reduced headache symptoms in patients without depression [34]. Intravenous dihydroergotamine has been shown to improve headache and to reduce sleep disturbance and dizziness in post-mTBI patients [35, Class II]. A randomized trial showed that cervical spinal manual therapy reduced headache pain at 5 weeks after head injury, versus the application of cold packs to the neck, but did not reduce the use of analgesics [36, Class II]. As discussed in a recent systematic review of treatments for mTBI, there is insufficient scientific evidence to support the use of specific pharmacologic interventions in the treatment of post-concussion headache [37••, Class III].

## Return to activity

- Young athletes who return to competition before the symptoms of concussion have resolved may be at risk for catastrophic cerebral edema and death, known as the second impact syndrome [38, Class III]. Although earlier guidelines from the AAN allowed patients with a grade I concussion (symptoms that resolve within 15 minutes; no loss of consciousness or amnesia) to return to play that contest, more recent guidelines recommend that all athletes who demonstrate signs or symptoms of concussion be withheld from participation and see a physician before returning to play [12••, Class III]. During the initial 2 to 5 days of recovery, patients must avoid symptom-inducing physical and cognitive activity. A stepwise approach for returning athletes to sport after concussion is now

recommended [12••, Class III]. This stepwise approach allows athletes to proceed to increasing levels of activity if asymptomatic. If any symptoms occur, the patient returns to the previous asymptomatic level and tries to advance again after 24 hours. The advice to avoid at-risk situations that might produce symptoms (eg, strenuous exercise, flying, stress) should be provided to individuals injured in any circumstance.

## Treatment of PCS

### Diagnosis of PCS

- There is considerable controversy regarding PCS and whether these patients are experiencing depression, somatization, chronic fatigue syndrome, chronic pain, vestibular dysfunction, or some combination of these conditions. Patients often present with considerable insecurity as to why they are experiencing PCS symptoms, which typically include headache, fatigue, sleep disturbance, vertigo, irritability, anxiety, depression, apathy, and difficulty with concentration. Symptoms are often subtle and difficult to link directly to the head trauma. However, recent research has demonstrated that most individuals complaining of PCS symptoms have neurologic changes as demonstrated by abnormal functional neuroimaging (SPECT) [39, Class II], neurochemical imbalances (eg, S100B) [40, Class II], and electrophysiological indices of impairment [41; 42, Class II].
- Diagnosis of PCS and description of relevant signs and symptoms are best done using the WHO's ICD 10 criteria. The criteria require three or more of the symptoms described in the preceding paragraph. An interview format is available at no charge from the authors of an excellent review and investigation of the various criteria for diagnosis of PCS [13••, Class II]. We also recommend an assessment of postural stability using a procedure such as the Balance Error Scoring System [21••, Class II]. Postural instability is much more likely to be present when the other signs and symptoms are indeed the result of organic-based PCS. The overlap between symptoms of PCS and the competing diagnoses makes diagnosis difficult, but the best approach, in our opinion, is to assume that the individual has PCS unless there is 1) no response to treatment, or 2) compelling evidence to support an alternate diagnosis.

### Treatment strategies

- Neurocognitive rehabilitation therapy is the most widely used treatment for severely brain injured patients, but empirical investigations to date have not shown conclusive evidence of efficacy in improving outcome, and there are no published clinical trials of this treatment for mTBI or concussed patients. Nonetheless, research has demonstrated limited effectiveness of cognitive rehabilitation on cognitive functioning and activities of daily living using single-group design studies [43; 44, Class II]. A review indicates that neuropsychologists use the following intervention strategies with the greatest frequency: education of the patient regarding PCS, support and reassurance, graded increase in activity, and cognitive restructuring [45•, Class III]. Many neuropsychologists also recommended antidepressant medication.
- The most common medications prescribed by neurologists for PCS are antidepressants [45•, Class III]. The selective serotonin reuptake inhibitors (SSRIs) have become the primary treatment for head injury–associated depression because of perceived clinical efficacy and relatively few side effects. However, most of the evidence for their use comes from small, uncontrolled/open studies and case reports rather than large randomized

trials. With this caveat in mind, these studies suggest that SSRIs are efficacious in reducing depression and cognitive impairments. For example, in an 8-week, nonrandomized, single-blind trial of sertraline (starting at 25 mg/day and increasing stepwise up to 100–200 mg/day), Fann et al. [46, Class II] found that 87% of patients had significant reductions in depression symptoms accompanied by improvements in cognitive variables of psychomotor speed and recent verbal and visual memory [46, Class II; 47, Class III]. Thus, treating depression after mTBI may also improve the cognitive deficits that afflict these patients.

- Over the past decade, a new group of antidepressants with a mixture of effects on serotonin, norepinephrine, and dopamine has been developed. None of them has been scientifically evaluated for the treatment of PCS or post-concussion depression. Trazodone has been used in the brain-injured population to treat sleep disorders that can accompany head injury because it has been shown to be efficacious in depressed patients with insomnia [48, Class II]. However, it has anticholinergic and cardiovascular side effects, and priapism may limit its use.
- Cholinergic dysfunction is thought to underlie the memory impairment seen in patients with Alzheimer's disease (AD). Because the deficits in attention and memory for new information seen after head injury mimic those in AD [49, Class III], memory deficits in TBI might be responsive to cholinergic treatment. Physostigmine and donepezil are acetylcholinesterase inhibitors that temporarily increase brain acetylcholine levels, whereas lecithin and CDP-choline are precursors that increase brain acetylcholine levels. In controlled trials, physostigmine improved neuropsychological test performance when used alone [50, Class II] or in combination with lecithin [51, Class II] after TBI. However, its short half-life, non-oral route of administration, and problematic side effects limit its potential for human treatment. A 1-month placebo-controlled trial of CDP-choline [52, Class II] after mTBI showed improved neuropsychological test performance and reduced post-concussion symptoms, but the duration of improvement after medication termination was not reported.
- Donepezil, a longer-acting oral anticholinesterase inhibitor that is relatively well tolerated, has been shown to improve cognition in AD patients [53, Class I], and two recent open-label controlled trials in patients with severe head injury [54,55, Class II] demonstrated improvements in function [54] and in short- and long-term memory [54, Class II]. Donepezil also reduced measures of anxiety, depression, and apathy in some head-injured patients [54, Class II]. Thus, there is accumulating evidence that cholinergic agents may alleviate some of the cognitive deficits suffered by head-injured patients, but there is a need for large randomized trials of these agents in patients with concussion or mTBI.

## Emerging therapy for PCS

- Most athletic team physicians have been using graded increased activity as a standard procedure while monitoring the recovery of athletes with PCS. They discover that if the athlete returns to vigorous exercise too soon there is an immediate return of symptoms. In addition, because most athletes have learned to push themselves through pain, they often continue with the exercise until they become quite ill. Exercise-induced symptoms may last several days or even weeks, usually leaving the athlete quite discouraged (depressed).
- We have been monitoring athletes after concussion in a more systematic manner. The athlete with PCS performs graded stationary cycle exercise under close observation, attempting to reach a heart rate target of 85% of

age-predicted maximum. Blood pressure and perceived state of effort are measured every 2 minutes, and the athlete is instructed to stop the activity the moment he or she feels any symptoms of concussion. Typical symptoms at the threshold are localized headache, feeling pressure in the head or the eyes, visual disturbance, and foggy thinking. The symptom-free exercise duration and intensity become the threshold for symptom regeneration, and we have the athlete return to the laboratory to exercise at 15% below threshold for 2 or 3 weeks. The opportunity to exercise is perceived as a very positive activity (often leading to an immediate reduction in depressive symptoms). It is imperative that the athlete not go beyond the new exercise limit, which most athletes are keen to do. After the 2 or 3 weeks of subthreshold exercise, the athlete is reassessed to see if the threshold has changed. The exercise program is then realigned to be 15% less than the new threshold. In our experience thus far, symptoms disappear within several months. Regular subthreshold exercise should help the individual become better conditioned and may have a fairly immediate effect on fatigue level and mood. We hypothesize that controlled, graded symptom-free exercise may restore to normal the cerebral autoregulatory system responsible for maintaining cerebral blood flow during changing states of systemic blood pressure, which may be dysfunctional in concussed patients [56, Class II].

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