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Medical Therapies for Concussion

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Although concussion is a common sports injury, there are few published data on effective treatments. Many current recommendations are based on anecdotal evidence and consensus. Even when the search is expanded beyond the realm of sports, to include all forms of concussive brain injury, data remain scarce. The following article reviews the current recommendations for the management of sport-related concussion and some of the previously studied, potential therapies for the signs and symptoms of concussive brain injury in general. It is not an exhaustive review of all possible candidates for therapy, but rather a discussion of some of the more common recommendations, common therapies, and potential medications with the most published data available.

The terms concussion and mild traumatic brain injury are used interchangeably. However, concussions are not always mild. Exactly when a mild traumatic brain injury becomes moderate is unclear. Most often, the difference between mild, moderate, and severe traumatic brain injury is determined by the Glasgow Coma Scale at the time of injury.¹ However, the acute characteristics of concussion do not consistently predict recovery time. At some point, if symptoms and deficits in cognitive function persist, the patient originally believed to have mild traumatic brain injury should be considered to have more significant injury. This review discusses therapies investigated for the treatment of functional traumatic brain injury as a whole, not solely those initially labeled as mild.

PHYSICAL AND COGNITIVE REST

Current guidelines recommend physical and cognitive rest as the mainstays for treating sport-related concussion.² Physical rest is straightforward and understood by most athletes. To achieve physical rest, athletes are removed, not only from activities that place them at risk of further contact to the head but also from other strenuous aerobic activities and resistance training, such as running, ice skating, weight lifting, and so forth. Once athletes are symptom free at rest, they are returned to play in a graded, stepwise fashion. If they develop symptoms as they progress through these return-to-play stages, they return to the previous level at which they were symptom free for a period of time before attempting to

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progress again.³ This recommendation is based mainly on anecdotal evidence and consensus. However, some investigators have begun to study the role of physical activity during recovery, starting with the safety of light exercise on a treadmill.⁴

Cognitive rest is more difficult. To achieve cognitive rest, athletes minimize activities that require concentration and attention, such as reading, schoolwork, video games, text messaging, working online, and playing games that require concentration, such as Scrabble or chess. For some athletes, school attendance and academic workloads need to be adjusted.³ Again, this recommendation is based on mostly anecdotal evidence and consensus.

Studies have revealed that athletes who sustain sport-related concussions have quantitative deficits in their cognitive function compared with their preseason, base-line function.⁵⁻⁸ Young scholar-athletes' academic performance depends largely on memory and processing speed. As a result, their grades are likely to be affected during recovery. Therefore, academic accommodations should be considered during recovery from a concussion.⁹ This may help injured athletes preserve their grades, in addition to facilitating cognitive rest during the academic year.

Majerske and colleagues¹⁰ studied the effect of overall activity, combining both physical and cognitive activity, on symptoms and neurocognitive performance during concussion recovery. Their results suggest that high levels of overall activity may interfere with recovery, whereas more moderate levels may be acceptable, or even beneficial. However, the investigators point out that the retrospective nature of the study leaves it vulnerable to a confounder: athletes with milder injuries may have been more likely to engage in activity than those with major injuries. Thus, those engaging in moderate activity may have started with a less severe injury than those engaging in minimal activity. Nevertheless, their findings indicate the need for further investigation into the effects of activity on concussion recovery.

EDUCATION

Unlike a fracture, laceration, or other structural injury, concussion can be difficult to recognize both by the athlete^{11,12} and by the athlete's family members, friends, teammates, classmates, work colleagues, schoolteachers, employers, and so forth.¹³ The signs, symptoms, cognitive sequelae, and time course of recovery after a concussion are often unfamiliar to the patient. Moreover, because concussed athletes have no cast, or scar, or other visible signs of injury, the legitimacy of their injury is often questioned by those around them. Thus, education regarding the typical recovery process of concussive brain injury is one of the main functions of clinicians caring for athletes with sport-related concussions. This education has been shown to improve symptoms.¹⁴⁻¹⁶ Ponsford and colleagues¹⁷ studied 202 adults after mild traumatic brain injury. Patients were separated into 2 groups. The intervention group, seen 1 week after injury, underwent neuropsychological assessment, and was given a booklet of information about the symptoms of concussion, the likely time course of recovery, and suggested coping strategies. This group underwent follow-up evaluation at 3 months after the injury. The nonintervention group was given the standard emergency department information and treatment, and was also evaluated at 3 months after the injury. The intervention group reported fewer symptoms at their 3 month follow-up than the nonintervention group. A similar study by many of the same investigators was performed in pediatric patients. Again the intervention group reported fewer symptoms at the 3-month follow-up.¹⁸

MEDICATIONS

Most athletes who sustain a sport-related concussion have spontaneous resolution of their symptoms, recovery of their balance, and return of their cognitive function in a period of days to weeks.^{3,19–21} However, some people who sustain concussive brain injury have a prolonged recovery.³ The following interventions might be considered for these patients.

The evidence for many of the medications discussed in this article is equivocal.^{14,22} Many of the data are of low quality, without large, double-blind, randomized controlled trials.²³ Many of the studies include patients with more severe injuries than are typically seen in sports. Each therapy is associated with potential adverse effects. In many cases, the therapies described are off-label. It is the author's firm belief that pharmacologic treatment of sport-related concussions should be considered only if the following 3 conditions are met:

1. The athlete's symptoms have exceeded the typical recovery period for a sport-related concussion.
2. The symptoms are negatively affecting the patient's life to such a degree that the possible benefit of treatment outweighs the potential risks of the medication being considered.
3. The clinician caring for the athlete is knowledgeable and experienced in the assessment and management of sport-related concussion or concussive brain injury in general.

No effective pharmacologic treatment has been shown to speed recovery from traumatic brain injury.²⁴ As a result, no standard approach exists.^{25,26} The heterogeneity of injury forces, mechanisms, and postinjury signs and symptoms makes such a therapy a distant goal.²³ However, medications are used in treating the signs and symptoms of concussion.²⁷

Previous literature has grouped the symptoms after a sport-related concussion into 4 general categories²⁸:

1. Sleep disturbance
2. Somatic (mostly headache)
3. Emotional
4. Cognitive.

Because the medications chosen often depend on the symptoms experienced by the affected athlete, they are organized by those symptoms.

SLEEP DISTURBANCE

Complaints of sleep disturbance are common following concussion.^{29,30} The management of sleep disturbance should include, and perhaps start with, a discussion of sleep hygiene.^{13,31,32} Today's athletes are exposed to constant stimulation. Their bedrooms are often filled with televisions, stereos, video games, mobile phones, and computers. They are constantly bombarded with social messages online or via text messaging. Eliminating these distractions from the bedroom, and lying down to rest in a quiet, dark room, helps the athlete to fall asleep. Simply turning these stimuli off does not suffice, because the mere presence of a computer, or a to-do list, date book, or planner, can often trigger stress and anxiety regarding the tasks that lay ahead, particularly in athletes who are often competitive and highly motivated. In addition, those with sleep disturbance should be counseled to avoid, or at least minimize, caffeine, nicotine, and alcohol use, as well as daytime naps.³¹

Medications may also be helpful. Melatonin is an endogenous hormone produced primarily by the pineal gland from serotonin. Its production and secretion are increased during times of darkness, and maintained only at low levels during the daylight hours.³³ It is nontoxic and safe,^{34,35} making it an ideal candidate for assisting with sleep. In addition, there is some evidence that it may have other beneficial roles in recovery from traumatic brain injury.³⁵ It is the author's choice for first-line therapy for sleep disturbance following sport-related concussion. Trazodone, a serotonin reuptake inhibitor, is a commonly used agent to treat sleep disturbance after traumatic brain injury, and is sometimes mentioned as first-line therapy.¹³ Although benzodiazepines seem to be a logical choice, most experts recommend avoiding them because of their negative effects on arousal and cognition.¹³ Other therapies that may be considered include zolpidem, tricyclic antidepressants, psychotherapy, phototherapy, and chronotherapy.³¹

SOMATIC

Headaches are common after sustaining a concussion.^{13,30,36} Headache is the most common symptom reported after concussion,^{37,38} and sport-related concussion specifically.^{19,39} As every clinician who manages concussions can attest, postconcussive headaches can be difficult to treat. There seems to be an inverse relationship between the severity of head trauma and the occurrence of posttraumatic headaches.^{37,40–42} Although the use of analgesics, such as ibuprofen, may be beneficial in the short-term, rebound headaches are common and can complicate treatment and recovery.^{37,41,42} Therefore, their frequent use should be discouraged. Posttraumatic headaches are often categorized according to the International Headache Society classification system to tailor treatment.^{41–43} Most patients who develop headaches after trauma have tension-type headache or migraines.^{37,41,43,44}

Antidepressants are commonly used to treat posttraumatic headaches.²⁷ Amitriptyline has been studied specifically for treating posttraumatic headaches, and has shown some success.^{14,38,44–46} In a retrospective review of 23 patients treated with amitriptyline for headaches after sustaining a head injury, 90% made an excellent or good recovery.⁴⁵ However, not all investigators have seen such an effect.⁴⁷ Because amitriptyline can be used to treat tension-type headaches and migrainelike headaches, the most common forms of posttraumatic headaches,^{38,41,43} it is often an ideal choice. It has been recommended for posttraumatic headaches that are not otherwise categorized.⁴¹ Furthermore, its sedative effects can help those suffering from sleep disturbance after a concussion in addition to treating their headaches.⁴² Therefore, it is commonly used by the author to treat athletes with persistent headaches after sustaining a sport-related concussion.

β -Blockers, calcium channel blockers, valproic acid, topiramate, triptans, dihydroergotamine, and gabapentin, have all been discussed as potential medical therapies for persistent headaches after concussion and may make reasonable choices in the appropriate circumstances.^{41,42,44,48,49}

In addition to pharmacologic therapy, biofeedback, physical therapy, trigger point injections, and psychotherapy may also be considered, either as primary or adjunctive treatments, for persistent posttraumatic headaches.^{37,42,44}

Headaches after concussion can persist for months, years, or, in rare cases, never remit.⁴¹ It is often unclear in such cases, especially when all other signs and symptoms of concussion have resolved, whether a patient is still recovering from a concussion or has a new, daily, persistent headache, perhaps triggered at the time of injury.⁴¹ Such situations make return-to-play decisions difficult.

EMOTIONAL

Emotional symptoms are commonly reported after traumatic brain injury,³⁰ in particular depression.^{13,50} In athletes, the injury itself, as well as the restrictions placed on their physical and cognitive activity during the recovery phase, may lead to depression. Because the duration of symptoms from sport-related concussion is usually short, the author believes that depressive symptoms in these cases are best managed conservatively, with coping strategies, the support of family and friends, and counseling by a trained psychologist. However, there may be cases for which these interventions do not suffice and medical therapies should be considered. Tricyclic antidepressants and serotonin reuptake inhibitors are recommended as options in the treatment of traumatic brain injury–related depression.^{13,51,52} The prescription of these medications is best left to those providers with experience in managing depression.

Sertraline has been studied in the setting of traumatic brain injury and has been shown to not only treat depression, but perhaps offer cognitive benefits as well.^{22,53} In a study of patients with depression after traumatic brain injury, Fann and colleagues⁵³ conducted a single-blind placebo run-in trial of sertraline. They showed not only a significant change in depression scores but also improvements in psychomotor speed, memory, and general cognitive efficiency. Other serotonin reuptake inhibitors, such as citalopram and fluoxetine, have also been studied.^{22,54} Studies of amitriptyline suggest that, although it is useful in treating primary depression, it may be less effective in treating depression following traumatic brain injury.^{50,51}

COGNITIVE

Cognitive symptoms, such as difficulties with memory, difficulties with concentration, and slowed processing speed, are common complaints after concussive brain injury.^{30,51} The advent of computerized neuropsychological testing, and its spreading use among athletes who sustain sport-related concussions, have revealed quantitative deficits in cognitive function after injury.^{6–8} Certain strategies to help preserve cognitive function have been proposed.

Cognitive Rehabilitation

There is little evidence to suggest that cognitive rehabilitation is effective for treating the effects of a concussion.¹⁴ Given the short duration of signs and symptoms following sport-related concussions,^{3,19–21} the routine use of cognitive rehabilitation in the management of sport-related concussions is unnecessary and of doubtful benefit. However, there may be cases of prolonged recovery in which its use is considered. Although conflicting evidence exists, some studies suggest that certain aspects of cognitive performance may be enhanced by focused rehabilitation.^{55–57}

Medications

Medications are commonly used in treating the neurobehavioral sequelae of traumatic brain injury.⁵¹ As the effects of most sport-related concussions resolve quickly, the routine use of these medications is unnecessary. However, in cases of prolonged recovery, for which the main complaints are cognitive in nature, particularly if the athlete has quantifiable cognitive deficits, a trial of pharmacologic agents may be considered.

The role of methylphenidate after traumatic brain injury has been investigated more than most other cognitive agents.^{13,22,23,58–65} There is evidence, including randomized controlled trials, to support the use of methylphenidate in the setting of traumatic brain

injury.^{13,22,58–60,66} It is recommended to treat deficits in attention and speed of processing, and as an option for treating deficiencies in general cognitive functioning.⁵¹

In a randomized, double-blind, placebo-controlled trial, Whyte and colleagues⁵⁹ showed an improvement in the speed of performance on 5 attention tasks in patients given methylphenidate compared with controls given placebo. Plenger and colleagues⁵⁸ conducted a randomized, double-blind, placebo-controlled trial on 23 patients with complicated mild to moderately severe traumatic brain injury. They found that patients given methylphenidate scored significantly better on their disability rating scale and on tests of attention and motor performance at a 30 day follow-up appointment than subjects given placebo.

However, not all studies have shown such effects.²² Williams and colleagues⁶⁰ studied pediatric patients who sustained mild to severe traumatic brain injury in a double-blind, placebo-controlled trial and found no significant differences between patients taking methylphenidate and those taking placebo. However, this study included only 10 patients and may have been inadequately powered to detect any potential benefit. Some clinicians are reluctant to use methylphenidate after traumatic brain injury because of its potential for lowering seizure thresholds.²² As with all medications discussed in this review, the decision to start methylphenidate should be undertaken cautiously, after careful consideration of the individual athlete's sequelae, the possible benefits of medication, and the associated risks of medication.

Amantadine is a dopaminergic agent with possible *N*-methyl-D-aspartate antagonist effects.⁶⁷ The role of amantadine after traumatic brain injury has been investigated,^{22,23,51,65–69} with several studies suggesting that amantadine is safe in this setting and may improve aspects of cognitive function.^{23,65,68–71} In a study of 22 patients with mild, moderate, and severe traumatic brain injury, Kraus and colleagues⁶⁸ showed improvements in executive function as well as an increase in glucose metabolism in the prefrontal cortex on positron emission tomography in patients taking amantadine. However, results are mixed. In a randomized, double-blind, placebo-controlled trial, Schneider and colleagues⁷² found no significant difference on neuropsychological measurements between subjects taking amantadine and those taking placebo. However, the investigators acknowledge that, given their small sample size, the study may not have been powered adequately.

Amantadine has shown some efficacy in pediatric patients.^{23,73,74} In a retrospective, case-controlled study of 54 pediatric patients, Green and colleagues⁷³ concluded that amantadine was safe and well-tolerated after traumatic brain injury and lead to subjective improvement as well as significant increases in Ranchos Los Amigos scores. Similarly, Beers and colleagues⁷⁴ studied the effects of amantadine in pediatric patients after traumatic brain injury and concluded that the medication was safe in this setting. Their results suggested that cognition may be improved with amantadine, but differences were not statistically significant.

To a lesser extent, several other medications have been investigated as potential therapies for the cognitive sequelae of traumatic brain injury. These medications include dofenpezil,^{75–80} rivastigmine,^{52,81} cytidine diphosphoryl choline,⁸² fluoxetine,⁸³ sertraline,⁵³ pramiracetam,⁵¹ bromocriptine,⁵¹ and atomoxetine.²²

Most patients with sport-related concussions recover quickly. Therefore, the potential benefits of many of the therapies discussed earlier are outweighed by the potential risks. However, in patients whose recoveries are prolonged and are associated with significant, negative effects on their quality of life, medical therapies should be considered. Sport-related concussions are distinct, in some respects, from other forms of traumatic brain

injury. They generally involve low-force mechanisms. They occur in athletes whose personality traits, overall health, and moods likely differ from the general population. They are often recurrent, because athletes are usually anxious to return to the high-risk activity during which the injury was sustained. Further research conducted specifically in patients who sustain sport-related concussions would provide guidance on how these patients are best managed.

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