Pharmacology and Natural Therapies for Postconcussion Syndrome

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ABSTRACT

Despite the high prevalence of traumatic brain injury, and the subsequent occurrence of neuropsychiatric sequelae, our evidence-based treatment strategies are thus far confined to physical therapy and rehabilitation medicine. Further, there are no standardized medication or natural-based recommendations for patients with postconcussion syndrome (PCS). Yet, clinicians are often presented with patients who have PCS seeking relief and who are anxious about their futures. Prescription-based treatment has traditionally been limited to attempts at symptomatic relief, yet at least 20% of PCS patients will have persistent symptoms for more than 6 months, and a subset will face indefinite issues. Thus, clinicians should also be aware of neuroprotective strategies aimed at reducing the risk of prolonged deficits and future dementias as the result of multiple concussive injuries. Treatment of PCS should involve not only symptomatic relief, but also neuroprotective strategies, and both modalities should begin at initial patient encounters. This article reviews the pharmacotherapy aimed at ameliorating specific complaints, as well as the natural, neuroprotective strategies recommended for long-term use. **[*Psychiatr Ann*. 2017;47(2):83-87.]**

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Postconcussion syndrome (PCS) is a common neuropsychiatric sequelae of traumatic brain injury (TBI), affecting between 30% and 80% of patients with mild to moderate brain injury.[1] The wide range of occurrence is due to the diversity of patient populations studied and the variable nature of criteria used to make the diagnosis of PCS over time. Yet, even when there are standardized criteria, results may still vary widely within the same patient population.[1]

Most discussions of PCS are preceded by the caveats that issues of litigation, secondary gain, premorbid conditions, and somatization may also be reflected in diagnostic trends. For

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the purposes of this treatment discussion, patients will be assumed to have suffered a concussion resulting in sufficient neuronal injury that manifests as somatic and neuropsychiatric symptoms of a nonpsychogenic origin. (A full review of neuropsychological challenges in the evaluation and treatment of PCS patients is elaborated by Dr. John M. Goeke in this issue of *Psychiatric Annals*.)

PCS is a variable symptom complex that includes the possible combination of headache, tinnitus, dizziness or disequilibrium, light and noise sensitivity, and fatigue. Further, a variety of neuropsychiatric symptoms may also be present, such as depression, anxiety, irritability, tremors and movement disorders, sleep disorders, and memory and cognitive impairment.[2] A more comprehensive list of possible symptoms is presented in the article by Research Fellow Sydney T. Smith (*Psychiatric Annals*, this issue). Loss of consciousness does not have to occur for symptoms of PCS to develop. The syndrome is most commonly seen after mild TBI (mTBI), but it may also occur after moderate and severe TBI, and may also occur after whiplash injuries.

Sigurdardottir et al.[3] have indicated that overall the severity of a patient's injury does not necessarily correlate with the risk of developing PCS, nor the severity and duration of PCS symptoms. However, a history of one or more prior concussions is a risk factor for persistent postconcussive symptoms.

Along with vestibular rehabilitation, and when indicated, rest and/or physical therapy, there is also a role for pharmacology as well as natural-based therapies in PCS. Although some neuroprotective strategies discussed are presently theoretical and under investigation, their safety and potential value argue for early use and in some cases indefinite use (**Table 1**).

PART I: SYMPTOMATIC RELIEF

In the absence of well-established, evidence-based treatments, the standard medication approach to patients with PCS has been the targeting of specific complaints. The first principle for clinicians to be mindful of is that patients with a head injury are traditionally more sensitive to the central nervous system (CNS) side effects of psychotropic agents and/or any agent that crosses the blood-brain barrier. Secondly, as with many neuropsychiatric conditions, there are no guidelines for the duration of a successful therapy.

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Headache

Headache (HA) is accepted as the most common manifestation of PCS. Vascular constriction has been identified in soldiers who experience persistent HA after blast injuries[4] and in blast/concussive wave injury; the persistence of HA is seen as a marker for continued vascular-related pathology. Persistent vascular constriction may also contribute to, or cause, other ongoing symptoms, including memory deficits. The mechanism of mechanical (non-blast) postconcussive HA is thought to be multifactorial.

The earliest literature suggested the use of tricyclic antidepressants and/or beta blockers.[5] More recently, anticonvulsants and regimens identical to those for poststroke persistent HA have been used. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to have utility in the short term,[6] whereas opiates are not advised for ongoing treatment due to their addictive nature, and the potential for "medication overuse headache" or rebound HAs.

Clinicians will find that PCS HAs are highly variable in their response to particular agents, and it is not uncommon for a patient to try serial therapies without experiencing any relief, or that may even worsen HA.

Impact-Site Sequelae

A variety of dysesthesias, or the persistence of pain, numbness, tingling, temperature alteration, or touch sensitivity at the site of impact, are often conflated by patients into the single complaint of HA. They may understand and report these symptoms as synonymous with PCS-associated HA, rather than two separate complaints. Impact-site sequelae may respond to NSAIDs, and in more severe cases may be treated with second-generation anticonvulsants much like neuropathies. These symptoms tend to be slow to resolve, and often outlast many others during recovery. This symptom is often a contributor to insomnia, as patients report an inability to initiate or sustain sleep if the injury site contacts their pillow.

Dizziness and Related Symptoms

Complaints of vertigo, disequilibrium, and dizziness in PCS are common, and patients may have difficulty articulating exactly which of these they are experiencing. The dizziness and related complaints of PCS are not usually responsive to meclizine beyond the days immediately after injury, although the agent is often prescribed for persistent PCS.[7] These symptoms are best treated with vestibular rehabilitation, which is elaborated in the article by Physican Assistant Kristina Eilbacher (*Psychiatric Annals*, this issue). There is evidence to suggest that the presence and persistence of dizziness may indicate a prolonged recovery period.[8]

Tinnitus

Tinnitus may be intermittent or persistent after concussion. As with many symptoms, it is worsened with fatigue and insomnia. Interestingly, acamprosate may provide partial or full relief for patients with tinnitus,[9] although low-dose antipsychotics may be necessary in severe cases. Again, the symptom may be resistant to these pharmacotherapies, or patients may experience exaggerated CNS side effects.

Memory Deficits

Traditionally, patients with PCS have been prescribed a combination of an anticholinesterase inhibitor and memantine, ie, the regimen commonly used for Alzheimer's dementia. Relief is unpredictable, and the duration of therapy is not established.[10] Yet, memantine may prevent calcium influx into the intracellular space of damaged cells; thus, this strategy may offer some degree of neuroprotection,[11] and is often continued in head injury clinics despite lack of significant symptomatic relief.

Movement Disorders

There are no clinical trials to reference with regards to movement disorders and PCS. Not surprisingly, PCS-associated Parkinsonism and tremors are less responsive to traditional therapies, such as levodopa or ropinirole, yet for many sufferers a trial should be attempted. Anticholinergic strategies may also be useful but they risk worsening memory deficits.

Sleep Attacks and Disorders

PCS-associated narcolepsy and sleep attacks can be treated with modafinil or stimulants. A double-blind, placebo-controlled crossover trial of 400 mg per day of modafinil failed to show a "consistent and persistent clinically significant difference between treatment with modafinil and placebo," with respect to daytime sleepiness and fatigue.[12] The authors did elaborate that there were "sporadic statistically significant differences identified."[12] Again, this speaks to the tremendous variability of the patient profiles within this diagnosis, and their unique profiles of response and nonresponse to treatment. Thus, many patients with PCS may benefit from stimulant or modafinil therapy and many deserve an adequate trial.

Depression, Anxiety, Irritability, and "Personality Changes"

The most commonly prescribed agents for PCS are NSAIDs, yet the second and third most common are antidepressants and benzodiazepines.[13] Many patients and their family members report depression, irritability, anger outbursts, apathy, generalized anxiety, and "personality changes."[14] These complaints are common in at least 50% of people who suffer with PCS.[14] Serotonin reuptake inhibitor and serotonin and norepinephrine reuptake inhibitor therapy is traditionally used, once again with the understanding that no agent will be universally effective or well-tolerated. Many patients with PCS do receive ongoing benzodiazepine therapy, and clinicians need to be mindful of dependence and abuse potential.

In more resistant cases, mood stabilizers and antipsychotics can be beneficial, again with the expectation that CNS side effects may be exaggerated in patients with TBI.

PART II: NEUROPROTECTION

Neuronal injury from TBI is categorized as primary and secondary. Primary injury is mechanical: the compression and shearing of CNS tissue. Secondary injury describes the cascade of physiological events that begin moments after the trauma and continue for days, perhaps longer. The mechanisms of cell demise after concussive injury share many commonalities with those responsible for Parkinson's, Lou Gehrig's (amyotrophic lateral sclerosis), Alzheimer's, and Huntington's diseases. And new data indicate significant neurophysiological changes in the hippocampus in response to TBI that are key to the neuronal demise. [15]

The often severe and debilitating nature of postconcussive sequelae, and the risk of chronic traumatic encephalopathy with repeated injury, argue for aggressive neuroprotective strategies based on the known mechanisms of cell demise in neurodegenerative illness, particularly because these measures involve natural, low-risk agents.

TABLE 1.

Neuroprotective Protocol for Postconcussion Syndrome

- Prescription Enlyte[a] bid for 2 months followed by qd for a minimum of 6 months
- 400 mg of over-the-counter N-acetyl cysteine bid for 1 month followed by 400 mg qd for 5 months
- 700 mg qd docosahexaenoic acid and phosphatidylserine for 6 months

Abbreviations: bid, twice per day; qd, once per day.
[a] Enlyet is a gel-cap containing all B vitamins in their metabolized forms and all micronutrients needed to optimally metabolize homocysteine in the central nervous system.

Reduced B Vitamins

Proposed mechanisms of cell death in numerous neurodegenerative diseases involve elevated homocysteine (HCY) levels either at baseline and/or in response to organic, traumatic, or psychosocial stress.[16] HCY is a nondietary amino acid that is directly toxic to vasculature, DNA, membranes, and is a contributor to apoptosis—the programming of DNA for early cell death. HCY is also a form of oxidative stress and induces an inflamma-

tory response.[16] Lowering HCY in the CNS acutely and as an ongoing strategy may provide neuroprotection for patients with PCS, and theoretically shorten their course of illness and lower the risk of eventual chronic traumatic encephalopathy.

A recent study[17] of methylenetetrahydrofolate reductase (MTHFR)-positive patients demonstrated a 28% reduction in HCY levels compared to placebo using a cluster of reduced B vitamins. Vitamins B6, B9, and B12 in their reduced fully metabolized forms are coenzymes necessary for HCY metabolism. One would expect MTHFR-positive patients to be at higher risk for PCS as MTHFR status is the primary predictor of HCY levels; however, a patient need not be MTHFR positive to benefit from vitamin-based HCY lowering agents.

All patients in our Regional Psychiatric Clinic of the University of North Carolina Healthcare with concussive injuries are prescribed a gel-cap containing all reduced B vitamins and micronutrients necessary for optimal HCY reduction in the CNS, and this agent is continued for at least 6 months even if achieving an asymptomatic state prior to that time.

N-acetyl Cysteine

N-acetyl cysteine (NAC) is known to clinicians as the antidote to acetaminophen toxicity, as a mucolytic, and as an effective therapy for trichotillomania, dermatillomania, and obsessive-compulsive disorder, yet it is also known as a precursor to the CNS antioxidant glutathione.[18]

Studies[19-21] have demonstrated that NAC provides antioxidant and neurovascular-protective effects after mTBI. In animal models, NAC was found to reduce levels of cytosolic-free Ca2+ and reactive oxygen species, as well as decrease apoptosis in the hippocampus after TBI.[22]

In military personnel suffering blast-induced mTBI, NAC was shown in a randomized double-blind trial to improve multiple symptoms of mTBI. Patients received a 4-g loading dose, then 18 to 24 hours later, initiated on 2 g twice a day for 4 days, then 3 g daily (also in divided doses).[23] Outcome measures were the presence of dizziness, hearing loss, HA, memory loss, sleep disturbances, and/or neurocognitive dysfunction. Resolution of symptoms 7 days after blast injury was the main outcome measure.

Overall, NAC treatment was significantly better than placebo with regards to symptom resolution, and secondary analysis revealed patients receiving NAC within 24 hours of blast had an 86% chance of symptom resolution with no reported side effects versus 42% for those also seen and treated early, but with only placebo.[23]

TBI and PCS are associated with oxidative stress in the CNS. The recommendation of this natural precursor to a potent antioxidant that crosses the blood-brain barrier is another low-risk strategy that theoretically could offer neuroprotective value in addition to hastening recovery. It is available over the counter.

Omega-3 Fatty Acids

As with the other natural measures listed, there are limited data regarding the benefit of omega-3 fatty acids in patients with PCS; however, there is literature regarding cognitive impairment (pre- or nondementia related) that argue for therapeutic value.[24] The use of omega-3 fatty acids in PCS is another low-risk, potentially therapeutic and neuroprotective measure that may be continued for a period of time after a patient achieves an asymptomatic state.

Although limited to case reports in TBI, omega-3 fatty acids have the potential to ameliorate the inflammatory responses after TBI, and may further provide symptomatic relief. What is critical to this discussion is that they are accepted as a neuroprotective strategy for people with mild cognitive impairment, or otherwise at risk for dementia, and this understanding may serve patients with PCS as well, given the overlapping pathways of cell demise.

Lewis[25] recently argued for "aggressively adding substantial amounts" of omega-3 fatty acids to optimize the nutritional foundation of TBI, concussion, and PCS patients. Further, their use in a prophylactic manner, along with HCY-lowering B vitamins, may serve generations of people who are at risk of TBI.

DISCUSSION

Perhaps there is no other potentially debilitating and unpredictable disorder clinicians face in which there are no established or standard treatment options, coupled with such a paucity of direction from the literature. The physical rehabilitation for PCS is much more advanced and evidence based than the pharmacology and natural-based options.

A review of current studies of PCS registered online[26] indicates that only 6 of 62 trials involve pharmacology (ibuprofen/acetaminophen, sertraline, prazosin, ondansetron, metoclopramide, and sildenafil).

Because every head injury is unique in occurrence and each brain is unique with regards to its underlying vulnerabilities, each cluster of neuropsychiatric symptoms is uniquely derived. Understandably, a single set of treatment recommendations will always be elusive. However, the traditional approach of symptomatic targeting should be combined with neuroprotective strategies. Specifically, the use of NAC, HCY-lowering reduced B vitamins, and omega-3 fatty acids, not only postinju-

ry, but in future protocols as prophylactic measures for athletes, and anyone at occupational or recreational risk of TBI could, in my view, eliminate or reduce future disability in countless patients.

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