WELCOME

Post-traumatic Headaches in the Military Population: Initial Management and Alternate Approaches

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Overview

More than 262,000 U.S. service members have been diagnosed with traumatic brain injury (TBI) since 2000. Of those cases, more than 75 percent were classified as a mild TBI/concussion. Headache is one of the most common symptoms after a concussion and may persist for months to years after injury.

There are no FDA-approved medications for post-traumatic headache and only two — Botox and Topamax — are approved for chronic migraine. The majority of service members who have chronic post-traumatic headache/post-traumatic stress disorder (PTSD) are already on numerous medications for pain, sleep and mood, and are reluctant to add more. Physicians also are concerned about the possibility of drug interactions and/or side effects.

Service members with mTBI/PTSD almost always have numerous co-morbid medical, psychological, social, cultural and spiritual issues that must be addressed for treatment to be successful. In this webinar, we will discuss the multi-disciplinary approach we use to address post-traumatic headaches, as well as specific complementary treatments, such as acupuncture, Qi Gong and mind-body skills.
Dr. John L. Rigg

John L. Rigg, MD, FAAPMR, is actively involved in research and his current projects include investigating the effectiveness of hyperbaric oxygen to improve function after brain injury, developing a method of obtaining objective sleep data, and the use of omega-3 fatty acids to accelerate and improve recovery.

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Headache Treatment in an mTBI Clinic

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Disclosures

• The views expressed in this presentation represent the views of the speaker and not those of the U.S. Army or Department of Defense

• I do not have a relevant financial relationship to disclose nor do I intend to discuss an off-label/investigative use of a commercial product.
Objectives

• Discuss the presentation of headache as one of the post-concussion symptoms that also include sleep disturbance, memory/cognitive problems, mood issues

• Review the unique affiliation of headache with post-combat stress in service members

• Discuss a multi-disciplinary approach to treatment not only of the symptoms, but also the cause
Discovery consists of seeing what everybody has seen and thinking what nobody has thought.

Albert Szent-Györgyi von Nagyrapolt – Hungarian-American biochemist, 1893-1986, awarded the Nobel Prize for Medicine in 1937 for his investigation of biological oxidation processes and of the action of ascorbic acid (vitamin C)
Typical Initial Presenting Symptoms of mTBI May Have Multiple Etiologies

• Headache

• Sleep disturbance

• Memory/cognitive problems

• Mood issues
mTBI + Post-traumatic Stress

• Both TBI and Post-traumatic Stress (PTS) are physiological injuries which need to be treated within the larger context of symptoms including insomnia, pain, mood issues, etc.
  – The perspective of PTS as a psychological injury versus TBI as a physical injury should be avoided
• Most effective treatment is multi-disciplinary and multimodal
• Effective treatment demands a holistic approach – looking at the entire body and not treating only one symptom
• Effectiveness of treatment may be improved by addressing multiple comorbid medical, psychological, social, cultural and spiritual issues
Initial Headache Treatment

• Pharmacological
  – Abortives
  – Prophylactic

• Relaxation/Stress Reduction
  – Referrals to Physical Therapists, Occupational Therapists, Recreational Therapists
Current Pharmacological Treatments

• Provide symptomatic treatment

• Do not “cure” the problems!

• Concern about the possibility of drug interactions and side effects

• What can be done to actually “heal” the injury?
Typical Medical Treatment Model

• Drugs/Surgery
• Psychosocial approach
• Complementary/alternative medicine
Team Approach

The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated.

Plato
Multi-disciplinary Approach for mTBI

• Self-care
• Therapies that stimulate capacity for self healing
  – Physical Therapy, Occupational Therapy, Speech Language/Cognitive Therapy, counseling/cognitive-behavioral therapy, group support, diet, exercise, recreation, vocational rehabilitation
• Drugs/surgery
Create Realistic Expectations
Common Sense

“Thinking outside the box”
Stress

• Treatment and alleviation of stress will result in:
  – Improved sleep
  – Decreased headaches
  – Improved memory
  – Mood stabilization
Treatment of Post-combat Stress

• Mind/body skills
• Counseling to help patients recognize and relieve stress
• Cognitive Processing Therapy
• Empowerment
• Possible meds
Techniques Used in Mind-Body Medicine

• Deep-breathing exercises
• Muscle-stretching exercises
• Progressive muscle relaxation
• Physical exercise and movement
• Mental/guided imagery
• Meditation
• Spiritual practices
• Mindful and healthful eating
• Biofeedback
Placebo Effect

• Utilize it to benefit treatment
• Researchers from the University of Lincoln, Harvard Medical School and University of Connecticut conducted a meta-analysis of data from clinical trials of Z-drugs (non-benzodiazepine hypnotics) comparing drug effects with placebo effects
• 13 clinical trials containing 65 different comparisons and more than 4,300 participants
• Once the placebo effect is discounted, the drug effect is of “questionable clinical importance”
• Psychological treatments for insomnia can work as effectively as sleeping tablets in the short term and better in the long term

Placebo Effect

A meta-analysis of antidepressant clinical trials indicating that for most patients, difference between drug and placebo was not clinically significant


The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. For patients with very severe depression, the benefit of medications over placebo is substantial.

Treatment
CONCLUSIONS

• Petasites (a purified extract from the butterbur plant) is established as effective for migraine prevention (2 Class I studies)
• Riboflavin is probably effective for migraine prevention (1 Class I trial and 1 imprecise Class II study)
• Co-Q10 is possibly effective for migraine prevention (1 Class II study)
• A combination of soy isoflavones (60 mg), dong quai (100 mg), and black cohosh (50 mg) is possibly effective for migraine prevention (1 Class II study). Percutaneous estradiol is possibly effective for migraine prevention (1 Class II study); however, there is an increased risk of migraine recurring after estradiol patch discontinuation
• Magnesium is probably effective for migraine prevention (multiple Class II trials). MIG-99 (feverfew) is probably effective for migraine prevention (1 Class I study, 1 positive Class II study, and 1 underpowered negative Class II study)
• The efficacy of hyperbaric oxygen (HBO) for migraine prevention is unclear (1 imprecise negative Class II study)
• The efficacy of omega-3 for migraine prevention is unclear (1 imprecise Class I study)

Neurology 2012;78;1346

RECOMMENDATIONS

Level A
• The following therapy is established as effective and should be offered for migraine prevention:
  – Petasites (butterbur)

Level B
• The following therapies are probably effective and should be considered for migraine prevention:
  – NSAIDS: fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium
  – Herbal therapies, vitamins, and minerals: riboflavin, magnesium, MIG-99 (feverfew)
  – Histamines: histamine SC

Level C
• The following therapies are possibly effective and may be considered for migraine prevention:
  – NSAIDS: flurbiprofen, mefenamic acid
  – Herbal therapies, vitamins, and minerals: Co-Q10, estrogen
  – Antihistamines: cyproheptadine

Level U
• Evidence is inadequate or conflicting to support or refute the use of the following therapies for migraine prevention:
  – NSAIDs: aspirin, indomethacin
  – Herbal therapies, vitamins, and minerals: omega-3
  – Other: HBO
A Study Comprising 81 Migraineurs Showed a Significant Improvement with Magnesium (Mg)

- Attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group
- The active treatment group received 600 mg of trimagnesium dicitrate in a water-soluble granular powder taken every morning

Mg

- Koseoglu et al studied the prophylactic effects of 600 mg/day of oral magnesium citrate supplementation in patients with migraine without aura and found that active treatment resulted in a significant decrease in migraine attack frequency and severity.

Mg

• Another randomized controlled trial (RCT) showed no effect of oral magnesium on migraine likely because of the use of a poorly absorbed magnesium salt, as diarrhea occurred in almost half of patients in the treatment group
Headache – Prophylactic Treatment

- Mg gluconate 400 mg qhs
**Butterbur (Petasites hybridus)**

- A perennial shrub found throughout Europe and parts of Asia
- Used for many centuries as a remedy for pain, fever, spasms, and wound healing
- Mechanism of action is not fully understood
- Likely acts through calcium channel regulation and inhibition of peptide leukotriene biosynthesis, thus influencing the inflammatory cascade associated with migraine
Butterbur (Petasites hybridus)

- The pharmacologically active compounds in butterbur are sesquiterpenes such as petasin and isopetasin.

- Also contains pyrrolizidine alkaloids, which are hepatotoxic and carcinogenic, these substances are removed in the commercially available preparations, such as those manufactured by Weber & Weber (Inning am Ammersee, Germany; Petadolex® and others).

- Nonetheless, patients should be advised to use only butterbur products that are certified and labeled “PA-free”.
Butterbur (*Petasites hybridus*)

- In the first RCT, 50 mg of Petadolex® twice daily showed a significantly reduced number of migraine attacks and migraine days per month compared to placebo

- An independent reanalysis of efficacy criteria was subsequently performed because of flawed statistical analyses in the original study, and confirmed the superiority of the butterbur extract over placebo for all primary variables of efficacy
Butterbur (Petasites hybridus)

- A three-arm, parallel-group RCT of 245 patients comparing Petasites extract 75 mg twice daily, Petasites extract 50 mg twice daily, and placebo twice daily.
- Results showed that Petasites extract 75 mg twice daily was more effective than placebo in decreasing the number of monthly migraine attacks.
- Maximum response was achieved after three months, resulting in an attack reduction of 58% with the higher dose of Petadolex®, compared to the placebo response of 28%.
- Petadolex® was well tolerated in these studies, and no serious adverse events occurred.

Butterbur (Petasites hybridus)

- The most frequently reported adverse reactions were mild gastrointestinal events, especially eructation (burping)
- Petasites, like most other herbal preparations, should not be taken by pregnant women
Headache – Prophylactic Treatment with CoQ10 150 mg daily

- Two small studies thus far have shown some benefit of CoQ10 in migraine treatment
- In the first, an open-label study of 31 migraineurs who used 150 mg daily of CoQ10 for three months, 61% had at least a 50% reduction in migraine days
- Notably, supplementation was effective within the first month of treatment
- No significant adverse effects were noted
Prophylactic Treatment with CoQ10

• The second study, a small RCT (n = 42) assessing the efficacy of 100 mg of CoQ10 three times daily, found that CoQ10 significantly decreased attack frequency, headache days, and days with nausea
Prophylactic Treatment with Riboflavin

• Riboflavin, vitamin B2, is a component of two coenzymes (flavin adenine dinucleotide and flavin mononucleotide) that are cofactors in the electron transport chain of the Krebs cycle

• It plays a vital role in membrane stability and the maintenance of energy-related cellular functions
Prophylactic Treatment with Riboflavin

• One well-designed RCT found that it is beneficial in migraine prophylaxis
• Daily use of 400 mg riboflavin for three months resulted in a 50% reduction in attacks in 59% of patients, compared to 15% for placebo
• Two minor adverse reactions, diarrhea and polyuria, were reported in the treatment group
Prophylactic Treatment with Riboflavin

• In a small study investigating the effects of different treatments on auditory evoked cortical potentials in migraineurs, riboflavin and beta blockers were shown to act on two distinct aspects of migraine pathophysiology.
• The authors thus suggested that combining these treatments might increase their efficacy without concurrently increasing central nervous system side effects.
Prophylactic Treatment with Riboflavin

- Another pharmacogenetic study demonstrated that riboflavin may be more effective in the treatment of migraine patients with non-H mitochondrial DNA haplotypes
Prophylactic Treatment with Riboflavin

- As riboflavin is effective in deficiencies of the electron transport chain complex I but not in mitochondriopathies related to an isolated complex IV deficiency, the authors suggested that mitochondrial haplogroups differentially influence the activity of the various complexes.
- These results may have ethnic implications in that haplogroup H is predominantly found in the European population.

Feverfew

- Used to prevent or stop a migraine headache
  - 100-300 mg, up to four times daily, standardized to contain 0.2-0.4% parthenolides
  - Feverfew supplements may also be carbon dioxide extracted and dosed as follows: 6.25 mg, three times daily, for up to 16 weeks
Feverfew

- An herbal preparation used for centuries in the treatment of fevers, headache, infertility, toothaches, inflammation and arthritis
- Originally native to the Balkan mountains in Eastern Europe, now grows throughout Europe, North America, and South America
- Commercially available as the dried leaves of the weed plant *Tanacetum parthenium*, and its anti-migraine action is probably related to the parthenolides within these leaves
Feverfew

- Feverfew may act in migraine prophylaxis by inhibiting platelet aggregation as well as the release of serotonin from platelets and white blood cells
- It may also act as an anti-inflammatory agent through the inhibition of prostaglandin synthesis and phospholipase A
Feverfew

• The efficacy of feverfew in migraine prophylaxis has been controversial, as many RCTs conducted in the past three decades have yielded contradictory results.
• In addition, a 2004 Cochrane review of double-blind RCTs assessing the clinical efficacy and safety of feverfew in migraine prevention concluded that there was insufficient evidence to suggest that feverfew is more effective than placebo in migraine prophylaxis.
Feverfew

• No major safety or tolerability issues were identified, although side effects reported in the RCTs included gastrointestinal disturbances, mouth ulcers, and a “post-feverfew syndrome” of joint aches
• Inconsistent results from the above studies were attributed to wide variations in the strength of the parthenolides and differences in the stability of feverfew preparations
Feverfew

• Subsequently, a new, more stable feverfew extract (MIG-99) was created
• In an initial RCT involving 147 patients, none of the MIG-99 doses were significant for the primary endpoint, although a subset of high-frequency migraineurs appeared to benefit from treatment
Feverfew

- In a follow-up multicenter RCT with 170 subjects randomized to 6.25 mg t.i.d. of MIG-99 or placebo, a statistically significant and clinically relevant reduction in migraine frequency in the MIG-99 group compared to placebo was reported
Feverfew

- Feverfew should not be used by pregnant women as it may cause uterine contractions resulting in miscarriage or preterm labor
- It can also cause allergic reactions; patients with allergies to other members of the daisy family, including ragweed and chrysanthemums, are more likely to be allergic to feverfew
Exercise –
A Positive Effect on Migraine

• Pilot study developed a training program suitable for 16 migraine patients
  – Eight migraine patients completed a 10-week aerobic running exercise program consisting of three workouts per week. The program was developed by sports scientists especially to increase the fitness level
  – Control group of eight patients without any special physical training
Exercise – A Positive Effect on Migraine

• Migraine patients of the exercise group showed both a reduction in the number of migraine days per month (p=0.048) and the intensity of the attacks (p=0.028). An increase in fitness level resulted in a lowered stress level
Our lives are not determined by what happens to us, but by how we react to what happens; not by what life brings to us, but by the attitude we bring to life.

Anonymous
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References

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• Teicher, MH. et al. The Neurobiological Consequences of Early Stress and Childhood Maltreatment. *Neurosci Biobehav Rev.* 2003; 27(1-2); 33-44.


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• Henneicke-von Zepelin HH. Feverfew for migraine prophylaxis. Headache. 2006;46(3):531
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Questions?

Please submit your questions for the presenters using the Q&A box located on your screen. Our presenters will answer questions following the second presentation.
Marc S. Husid, MD is a board-certified neurologist with 30 years of neurological experience, and was among the first physicians to attain board certification in headache management. The experience gained from seeing hundreds of service members with post-traumatic headaches, post-traumatic stress, and related comorbidities made it apparent that the traditional western approach to these patients had many limitations, and Dr. Husid began studying alternate approaches.
Headache Management

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• I have no relevant financial relationships. As there are no FDA-approved medications for post-traumatic headache and only two medications approved for the treatment of chronic migraine (Topiramate and Onabotulinum toxin A), any other medications mentioned reflect my personal practice and that of recognized headache specialists around the country.
International Headache Society Criteria for Migraine

Migraine is an Episodic Headache lasting 4-72 hours with:

Any 2 of:
- Unilateral
- Throbbing
- Worsened by or causing avoidance of movement
- Moderate or severe

Any 1 of:
- Nausea or vomiting
- Photophobia and phonophobia

2+1 = Migraine
Keys to Treatment Success

- Doctor-patient relationship
- Headache diary
- Realistic expectations
- Education
  - Biologic nature of migraine and triggers

Nonpharmacologic Therapies

- Trigger and risk factor avoidance
- Proper diet, exercise, and sleep hygiene
- Use headache calendars – *essential*
- Biofeedback and stress management
- Cognitive therapy and psychotherapy
- Physical therapy, manipulation, acupuncture, reflexology)
- Vitamins, minerals, supplements, herbs:
  (Vitamin B-2, magnesium, feverfew, petasites, melatonin and coenzyme Q10)
Optimizing Acute Treatment of Migraine Attacks

- Use effective doses
- Treat early in the attack (mild pain)
- Avoid medications with high medication overuse headache potential (AAC, butalbital, opioids)
- Choose appropriate route of delivery
- Review headache diary at each visit to monitor response to treatment

Lipton RB et al. *Neurology*. 2001;56:S35-S42
When To Consider Prevention?

• Significant interference with patient’s daily routine despite acute treatment (infrequent, but profound disability)
• Frequency attacks (>2/week) with risk of developing medication overuse
• Failure, contraindication to, or troublesome side effects from, acute medications

When To Consider Prevention?

• Patient preference (i.e., desire to have as few attacks as possible)
• Presence of uncommon migraine conditions with risk of permanent neurologic injury:
  – Hemiplegic/basilar migraine, migraine with prolonged aura, migrainous infarction

Principles of Preventive Treatment

• Start low, go slow, don’t give up
• Give each treatment an adequate trial
• Avoid interfering, overused, and contraindicated drugs
• Be sure women of childbearing potential are aware of risks; pick medication least likely to have adverse effect on fetus (folate)
Principles of Preventive Treatment

- Involve patients in their care
- Take patient preferences into account
- Discuss rationale for a particular treatment, when and how to use it, possible side effects
- Address patient expectations – expected benefits of treatment and how long it will take to get there
- Consider comorbidity
- Periodically reassess and modify treatment
Botox Injection Sites

Botox slides used with permission of Allergan, manufacturer of Botox (Onabotulinumtoxin A)
Botox slides used with permission of Allergan, manufacturer of Botox (Onabotulinumtoxin A)
Botox slides used with permission of Allergan, manufacturer of Botox (Onabotulinumtoxin A)
Summary

• Recurrent disabling headache = migraine
• Migraine should be managed like any other chronic disease
• Understanding basic mechanism helps understand symptoms and rationale behind treatment
• Early treatment following onset of pain will improve response to treatment
• An ounce of prevention…
Questions?

If you have questions at this time, please submit them via the Q and A box located on the screen. Our speakers will address as many questions as time permits.
For additional TBI information and resources, visit dvbic.org
DVBIC Resources
www.dvbic.org
Signs and Symptoms Fact Sheet

This two-sided sheet, intended for all audiences, presents major physical, cognitive and emotional symptoms of concussion on the front, and coping and recovery tips on the back. Besides English, it is available in Spanish (pdf and hard copy), Estonian (pdf only), French (pdf only), Georgian (pdf only), German (pdf only), Italian (pdf only), Polish (pdf only), and Romanian (pdf only).

1-page handout, double-sided, 8.5"x11". For any audience.
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DCoE Products

Welcome to the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) resources section. Here you will find a central list of products and resources produced by DCoE, organized by topic. We encourage you to explore the broad range of resources we have available and, of course, to share with all who may find them useful.

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- mTBI Pocket Guide Mobile Application
- Assessment and Management of Dizziness Associated with Mild TBI Clinical Recommendation
- TBI Web-Based Case Studies Flyer
- Military TBI Case Management Newsletter 4
- DoD ICD-9 Coding Guidance for TBI Fact Sheet
- DCoE DVBIC Cognitive Rehabilitation Report
- Five Things You Need To Know About Concussion
This presentation with audio will be available online at

http://www.dvbic.org/online-education

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