Medical Treatment of Persistent Post Concussive Symptoms

The 12th Annual Sports Concussion, Traumatic Brain and Spine Injury Conference
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Objectives

• Discuss Clinical Symptoms
• Discuss Quick Practical Management Points
• Understand Mechanism and Pathophysiology
• Focus on Headaches and Discuss Abortive and Preventative Pharmacological Treatment
• Briefly Review Non-Pharmacological Treatment
• Review Future Direction for Treatment
Symptom Clusters

Somatic
- Headaches
- Visual Problems
- Dizziness
- Noise/Light Sensitivity
- Nausea

Emotional
- Labile Mood
- Sadness
- Anxiety
- Irritability

Cognitive
- Attention Problems
- Memory Dysfunction
- Mental Fogginess
- Fatigue
- Cognitive Slowing

Sleep Disturbance
Quick Management

• Quick recognition of concussion symptoms is vital
• Quick removal from play
• Quick symptoms evaluation
• Quick evaluation of balance, neurological examination, look for focal signs
• Quick evaluation of cognitive function
Red Flags

- Focal Neurological Signs
- Vomiting that persists
- Waking up at night with a headache
- Headache that worsens with sneezing, coughing or change in position
- Seizure like symptoms
- Hallucination, suicidal ideation, severe depression
Pathogenesis of Post Traumatic Headaches

- Diffuse Axonal Injury
- Neurometabolic Cascade
- Muscle and Soft Tissue Injury
- Joint and bone mechanical injury
- Genetic Predisposition to Headaches
- Psychopathology and anticipation of symptoms
- Post-traumatic sleep disturbances
- Post-traumatic mood disorders and stress due to loss of school or work or litigation
- Overuse of abortive medications
Mechanism of Traumatic Brain Injury

- Calcium Influx
- Mitochondrial failure and Energy Crisis
- Glutamate/NMDA activation
- Cerebral Blood Flow
- Free Radicals
- Calpain Activation and proteolysis
- BBB disruption + activation of trigeminovascular system
- Cholinergic activation
Management/Treatment

- Physical rest (1-7 days) (not until symptoms resolve)
- Cognitive rest (1-7 days)
- Removal from contact sports
- Evaluate by PCP or medical provider
- Academic accommodations
- Return to Play stages
- “More evidence is emerging to restrict rest to a maximum of 3 days and resume modified activities after that”
- The challenge: Achieve a balance between: modifying activities \textit{and} avoiding deconditioning and reinforcing the sick role
General Headaches Management

1. Identify Headache type
2. Educate and Manage Expectations
3. Identify Headache Triggers and Relievers
4. Review Sleep, Hydration, Diet, Exercise recommendations
5. Avoid OTC medication overuse 1-3 times per week
6. Educate about Relaxation Techniques, CBT and Coping Strategies
### Coping Strategies


<table>
<thead>
<tr>
<th>Coping strategies Inventory</th>
<th>Subscales</th>
<th>Example items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem-focused engagement</td>
<td>Problem-solving</td>
<td>“I made a plan of action and followed it.”</td>
</tr>
<tr>
<td></td>
<td>Cognitive restructuring</td>
<td>“I convinced myself that things are not quite as bad as they seem.”</td>
</tr>
<tr>
<td>Emotion-focused engagement</td>
<td>Express emotions</td>
<td>“I let out my feelings to reduce my stress.”</td>
</tr>
<tr>
<td></td>
<td>Social contact</td>
<td>“I found somebody who was a good listener.”</td>
</tr>
<tr>
<td>Problem-focused disengagement</td>
<td>Problem avoidance</td>
<td>“I went along as if nothing were happening.”</td>
</tr>
<tr>
<td></td>
<td>Wishful thinking</td>
<td>“I hoped a miracle would happen.”</td>
</tr>
<tr>
<td>Emotion-focused disengagement</td>
<td>Self-criticism</td>
<td>“I blamed myself.”</td>
</tr>
<tr>
<td></td>
<td>Social withdrawal</td>
<td>“I spent more time alone.”</td>
</tr>
</tbody>
</table>
# Post-Traumatic Headache: (no specific type)

<table>
<thead>
<tr>
<th>Quality</th>
<th>Tension</th>
<th>Migraine</th>
<th>Cervicogenic</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bilateral, Moderate</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Severe unilateral throbbing +</td>
</tr>
<tr>
<td></td>
<td>Dull, pressure or squeezing</td>
<td>Severe</td>
<td>Mild-severe</td>
<td>autonomic activation:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Throbbing</td>
<td>Aching</td>
<td>lacrimation, rhinorrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea/Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Photo-/phonophobia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Vary</td>
<td>Vary</td>
<td>Focal/neck</td>
<td>Retro-/peri-orbital</td>
</tr>
<tr>
<td>Triggers</td>
<td>Tension/reading</td>
<td>Exercise</td>
<td>Neck movement/</td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Sustained poor posture</td>
<td>Lights and sounds</td>
<td>history of whiplash</td>
<td></td>
</tr>
</tbody>
</table>

**Post-Traumatic Headache:**

- **Quality:**
  - Tension: Bilateral, Moderate Dull, pressure or squeezing
  - Migraine: Unilateral Severe Throbbing Nausea/Vomiting Photo-/phonophobia Sensory Vision
  - Cervicogenic: Unilateral Mild-severe Aching
  - Cluster: Severe unilateral throbbing + autonomic activation: lacrimation, rhinorrhea

- **Location:**
  - Vary

- **Triggers:**
  - Tension/reading Sustained poor posture
  - Exercise Lights and sounds
  - Neck movement/history of whiplash
  - Alcohol
# Post-Traumatic Headache

**International Classification of Headache Disorders 3rd edition**

<table>
<thead>
<tr>
<th>Acute (less than 3 months)</th>
<th>Persistent (more than 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributed to mild TBI or/ Moderate to Severe TBI</td>
<td>Attributed to mild TBI or/Moderate to Severe TBI</td>
</tr>
<tr>
<td>Attributed to WHIPLASH injury</td>
<td>Attributed to WHIPLASH injury</td>
</tr>
<tr>
<td>Attributed to Craniotomy</td>
<td>Attributed to Craniotomy</td>
</tr>
</tbody>
</table>

- Headache developed within 7 days of TBI
- No specific feature for post-traumatic headache (migraine/tension/cluster/cervicogenic)
- Isolated or part of a group of post concussion symptoms
- >3 month → Headaches + other symptoms = Post-Concussion Syndrome
Medication-Overuse Headaches Management

E. Pinchefsky et al./Pediatric Neurology 52 (2015)

- Weaning or stopping of the overused abortive medications
- Starting preventative medications or other interventions once problem is identified
- Bridge therapy with a new acute medication (Indomethacin or Steroids)
- Establish treatment limits on use
- Patient education
- Consider steroid treatment or occipital block
## Abortive Medications

**Medication** | **Side Effects**
---|---
Acetaminophen | Liver Dysfunction
Ibuprofen | Gastritis, CI: Intracranial Hemorrhage
Naproxen | Gastritis, CI: ICH, Renal or Liver Disease
Ketorolac | GI bleeding, bronchospasm, CI: Asthma, ICH
Metoclopramide | Extrapyramidal signs, Sedation
Triptans | CI: ischemic heart disease, hypertension, basilar or hemiplegic migraine features S.E: numbness, tingling
Dihydroergotamine | Not w Triptans. CI: hypertension, hemiplegic migraine, pregnancy, CVS disease
**OPIOIDS** | MOH and dependence

*Different references*
## Classification of Migraine Preventive Therapies

### Evidence Based Guideline update (AAN and American Headache Society) April 2012

<table>
<thead>
<tr>
<th>Level A: Established Efficacy (≥2 Class I trials)</th>
<th>Level B: Probably effective (1 Class I or 2 Class II studies)</th>
<th>Level C: Possibly effective (1 Class II study)</th>
<th>Level U: Inadequate or conflicting data to support or refute use</th>
<th>Other: Medication that are established as possibly or probably ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal preps, vitamins, minerals</td>
<td>NSAIDs</td>
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<td>NSAIDs</td>
<td>Leukotriene receptor antagonist</td>
</tr>
<tr>
<td>Petasites (butterbur)</td>
<td>Fenoprofen</td>
<td>Flurbiprofen</td>
<td>Aspirin</td>
<td>Montelukast (singulair)</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Mefenamic acid</td>
<td>Indomethacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>Co-Q10</td>
<td>Omega-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>Estrogen</td>
<td>Hyperbaric Oxygen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herbal Preparations, vitamins, minerals and others</td>
<td>Herbal Preparations, vitamins, minerals and others</td>
<td>Herbal Preparations, vitamins, minerals and others</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium MIG-99 Feverfew, Riboflavin Histamine SC</td>
<td>Antihistamine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Preventative Medications

• Start 2-4 weeks in the presence of persistent severe symptoms

• Start with a small dose and adjust according to response, side effects and efficacy

• Choose medication according to nature of symptoms, side effects profile and patient profile
## Preventative Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline &amp; Nortriptyline: TCA</td>
<td>Sedation, appetite increase, mood changes, suicidal ideation, palpitation, dizziness (most studied with positive outcomes in small series). Nortriptyline: less sedating and less appetite increase</td>
</tr>
<tr>
<td>Cyproheptadine: Antihistamine</td>
<td>Suitable for children less than 10. Increases appetite and it is sedating</td>
</tr>
<tr>
<td>Gabapentin: AED</td>
<td>Mostly well tolerated but can cause dizziness and intense sedation (no studies)</td>
</tr>
<tr>
<td>Topiramate: AED</td>
<td>Word finding difficulties/cognitive side effects/paresthesia/Suitable in over weight patients with no cognitive concerns</td>
</tr>
<tr>
<td>Propranolol: Antihypertensive</td>
<td>CI: Asthma. Worsens depression and dizziness. Use with anxiety</td>
</tr>
<tr>
<td>Verapamil: Calcium channel blocker</td>
<td>Established migraine treatment</td>
</tr>
<tr>
<td>Valproic acid/Tegretol</td>
<td>No studies</td>
</tr>
</tbody>
</table>
# Preventative Supplements

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Side effects/comments</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium (400 mg/day)</td>
<td>Diarrhea&lt;br&gt;Mixed results: in doses that were effective 600 mg and higher, more side effects&lt;br&gt;Mg Oxide is chelated, absorbed better with less diarrhea&lt;br&gt;CI: ulcerative colitis, renal disease, etc.</td>
<td>Free Mg+2 level is low after brain injury&lt;br&gt;Mg: decrease platelet aggregation, nitric oxide production and release of substance P</td>
</tr>
<tr>
<td>Butterbur (25 mg 2 tab BID)</td>
<td>CI: Pregnancy and breast feeding</td>
<td>Petasin + Isopetasin: strong vasodilators + inhibit leukotriene synthesis + reduce inflammation + reduce smooth muscle spasms</td>
</tr>
<tr>
<td>Riboflavin/B2 (200 mg BID)</td>
<td>Discoloration of urine</td>
<td>Increases mitochondrial efficiency</td>
</tr>
<tr>
<td>Melatonin (up to 10 mg)</td>
<td>High doses were found to treat headaches + help insomnia</td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>GI irritability</td>
<td></td>
</tr>
<tr>
<td>Feverfew 50 mg-150 mg (0.2% of parthenolide is active ingredient)</td>
<td>Reasonable evidence in migraine studies/&lt;br&gt;Inconsistent preparations&lt;br&gt;Check PT and PTT&lt;br&gt;Stop 2 weeks prior to any surgery&lt;br&gt;CI: pregnancy and babies under 2</td>
<td>? Anti-inflammatory and antiplatelet aggregation</td>
</tr>
</tbody>
</table>
Preventative Supplements

- Promising due to perceived improvement BUT:
- FDA approval not available
- Concerns regarding dosing, additives, standardization of active ingredients
- More studies are needed
Pharmacological Treatment

Occipital Nerve Blocks

Indicated when there is:

• Occipital cephalgias with or without occipital tenderness
• Cervicogenic headaches
• Localized Neck Tenderness
• 64% of pediatric patients with high headache burden>15/month reported significant improvement (Barlow KM J of Pediatric Neurology 2014).
Sleep

Sleep/Wake Disturbances

- 40%-60% of our concussion patients in the neurology clinic (30 d) present with trouble falling asleep or excessive sleepiness
- S/W d affect headaches, mood, fatigue, cognitive function especially executive function (prefrontal cortex benefits the most from sleep)

TREATMENT

- Sleep Hygiene
- Melatonin, Zinc, Magnesium
- Acupuncture, exercise, relaxation technique
- Pharmacological Management: TCA, Trazadone, Mirtazapine
Cognitive Symptoms

• Symptoms
  Inattention
  Decreased Processing Speed

• Treatment
  Amantadine?
  Stimulants
  Omega 3 FA
  Improve sleep and treat headaches
Neuroprotection

Glutamate Network Dysfunction Following TBI is studied well in CCI models and epilepsy

*Glutamate and GABA Imbalance Following TBI*

Guerriero et al.

Decrease Glutamate Acute Toxicity by:

- NMDA blockage
- Remove glutamate from the synapse by scavengers like pyruvate and oxalacetate
- Upregulate glutamate transporters by: ? Ceftriaxone or Dehydroepiandrosterone
- Neuromodulation: anodal transcranial direct current stimulation $\rightarrow$ GABA reduction in motor cortex and improved memory (NOT TBI model)
96 Final Recommendations Comprise the Guidelines
Management of Concussion

Concussion SCAMP Decision Support

Abnormal neurological exam?
- Yes
   - Obtain MRI
   - MRI result?
     - Abnormal
       - Best Clinical Judgment
     - Normal
       - Concussion sustained for how many weeks?
         - < 4 weeks
           - Any symptoms?
             - Yes
               • Education
               • Physical and cognitive rest
               • Symptomatic treatment
               • 2 weeks video conference
               • Gradual return activity
               • Exit SCAMPs
             - No
               • Gradual return activity
               • Exit SCAMPs
         - ≥ 4 weeks
           - Any symptoms?
             - Yes
               • Education
               • Gradual return to activities (no impact, contact sports)
               • Academic accommodation
             - No
               • Gradual return activity
               • If patient is ≥12, use ImPACT to clear for sports
               • Exit SCAMPs

Primary symptom(s) ➔ Go to next page
SCAMPS

Headache Symptoms >4 weeks

- Number of headache occurrences per week?
  - < few times/wk
    - Alternative/Conservative Treatment*
    - Clinic follow-up within 2-8 weeks
      *Proceed to section A and C*
  - ≥ few times/wk
    - Headache score?
      - < 4
        - Alternative/Conservative Treatment*
        - Clinic follow-up within 2-8 weeks
          *Proceed to section A and C*
      - ≥ 4
        - Medication prescribed:
          - Amitriptyline
          - Topiramate
          - Gabapentin
          - Nortriptyline
          - Cyproheptadine
          - Propranolol
          - None
          - Other: ___________
          - Clinic follow-up within 2-8 weeks
          - Alternative/Conservative Treatment*
          *Proceed to section B and C*
SCAMP

Other Symptoms >4 weeks

Select primary symptom (please check one)

- Emotional
- Cognitive
- Fogginess
- Vestibular
- Seizures
- Sleep Disorder

Score?

- Low
- High

- <10
- ≥ 10

Cognitive Behavior Therapy
- Clinic follow-up within 2-8 weeks
- Additional Conservative/Alternative Treatment*

Proceed to B, D

Cognitive Behavior Therapy
- Psychiatry

Proceed to A, B, D

Neuropsych
- Amantadine

Proceed to A, B, C, D

Methylphenidate
- Neurpsych

Proceed to A, B, C, D

Amantadine
- Clinic follow-up within 2-8 weeks
- Conservative/Alternative Treatment*
- IEP, 504 plan

Proceed to A, B, C, D

Neuropsych
- Clinic follow-up within 2-8 weeks
- Conservative/Alternative Treatment*
- IEP, 504 plan

Proceed to A, B, C, D

Vestibular Therapy
- Clinic follow-up within 2-8 weeks
- Conservative/Alternative Treatment*
- IEP, 504 plan

Proceed to A, B, C, D

Vestibular Therapy
- Clinic follow-up within 2-8 weeks
- Refer to Balance Program
- Conservative/Alternative Treatment*

Proceed to A, B, C, D

EEG
- Neurology Referral
- Best Clinical Judgement

EEG
- Neurology Referral
- Best Clinical Judgement

Trouble falling asleep?

- Melatonin
- No nap
- Sleep hygiene
- Exercise per guidance
- Clinic follow 2-8 weeks
- Sleep clinic
- Sleep study

Proceed to A, D

Excessive Sleeping

- Sleep hygiene
- Exercise per guidance
- Clinic follow 2-8 weeks
- Sleep clinic
- Sleep study

Proceed to A, D

Red = SCAMP recommendations
Purple = Best Clinical Judgement