Pharmacological Management of Concussion

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Disclosure

I have no conflicts to declare regarding the current presentation, however, I have had funding during the past 12 months for concussion research from:

Objectives

After this presentation participants will be able to:

1. Discuss a symptom-based approach to pharmacological management of concussion.

2. Analyze preliminary evidence for efficacy of amantadine as a targeted treatment for cognitive concussion symptoms.

3. Apply an evolving clinical trajectory and targeted therapy approach to concussion management.
Concussion is highly individualized

Most Commonly Reported Symptoms
1-7 Days Following Concussion
High School and College Athletes (N= 1,438)

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Headache</td>
<td>75 %</td>
</tr>
</tbody>
</table>
| #2 Difficulty
  Concentrating     | 57 %|
| #3 Fatigue           | 52 %|
| #4 Drowsiness        | 51 %|
| #5 Dizziness         | 49 %|
| #6 Foggy             | 47 %|
| #7 Feeling
  Slowed Down       | 46 %|
| #8 Light Sensitivity | 45 %|
| #9 Balance
  Problems         | 39 %|
| #10 Difficulty
  with Memory      | 38 %|

Kontos, Elbin, Schatz, Covassin, Heney, Pardini, Collins; AJSM, 2012
Focus on cognitive and physical rest and accommodations (as needed) in first week post-injury, but...

...avoid the “dark room”/shut-down approach.
Symptoms at 1+ week Post-injury

- NEUROPSYCHIATRIC SX
  - More emotional
  - Sadness
  - Irritability

- SOMATIC SYMPTOMS
  - Headaches
  - Visual Problems
  - Stiffness
  - Noise/Light Sensitivity

- COGNITIVE SYMPTOMS
  - Attention Problems
  - Memory dysfunction
  - "Foggy"
  - Fatigue
  - Cognitive slowing

- SLEEP DYSREGULATION
  - Difficulty falling asleep
  - Waking less than usual

Timeline for Progressive Treatment

- CONSERVATIVE
  - Cognitive & Physical Rest
  - Behavioral Mgt.
  - Sleep hygiene
  - Accommodations...

- MODERATE
  - Vestibular therapy
  - Physical therapy
  - Vision training
  - Melatonin...

- AGGRESSIVE
  - Meds for: cognitive, somatic, affective, and sleep

Progressive Symptom Cluster Approach to Pharmacological Treatment

- Conservative, Moderate, Aggressive progression
- 80% of sport-related concussions will resolve within 21-30 days of injury with proper management (McCory et al., 2009)
- Match symptom clusters with targeted pharmacological treatment
- Factors to consider:
  - Time since injury
  - Chronic (>3 months) present the greatest challenge to treatment
  - Do we treat early? How early? Is there evidence?
  - Age
  - Lower or no dose options for younger Pts
  - Current meds...

Sleep Dysregulation: Etiology

- Issues:
  - Difficulty with sleep initiation or maintenance
  - Too much/ too little sleep
- Possible etiologies:
  - Pre-existing sleep disorders
  - Neurophysiologic injury
  - Pain (headache)
  - Environmental stimuli
  - TV, texting, music...
  - Pharmacologic effects
  - Mood changes
  - Activity level changes

Sleep Dysregulation: Secondary Effects

- Decreased quality of life
- Difficulty concentrating
- Higher risk of accidents
- Higher rates of chronic pain
- Mood changes
- Risk factor for poor physical and mental health
Sleep Dysregulation: Conservative Treatment

- Sleep hygiene
  - no TV, computer, phone, iPad/iPod at bedtime
- Sleep consistency
  - 7-9 hours, no naps
- Nutrition, caffeine, alcohol
- Relaxation and behavior therapies

Sleep Dysregulation: Pharmacological Treatment

- Melatonin agonists
  - 3mg, 5mg, Reg vs. XR
- Anti-depressants
  - Amitriptyline- 25mg (titrate)
  - Trazodone- 100mg (monitor SE, men: priapism)
- Non-benzodiazepine hypnotics
  - Ambien- 5 or 10mg, 12.5mg XR
  - Lunesta- 3mg
- Anti-histamines
  - Vistaril 50-100mg (start 12.5 or 25mg for kids)

Somatic Symptoms

- Headache
- Nausea
- Light/Noise Sensitivity
- Dizziness...
- Predictive of protracted recovery
Role of Dizziness in Predicting Recovery


Study Overview

- 87 Male HS Football Players (Mean Age = 16.2 years) with a concussion
- 13 on-field signs/symptoms
  - Determined by ATCs/Sports Med Physicians
  - Combination of testing, observation, and self-report
- Players divided into 2 recovery groups:
  - Rapid (≤ 7 days)= 56 players
  - Protracted (≥ 21 days)= 31 players

Dizziness Predicted Protracted Recovery

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wald $\chi^2$</th>
<th>OR</th>
<th>p</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>5.44</td>
<td>6.34</td>
<td>0.02</td>
<td>1.34 - 29.91</td>
</tr>
<tr>
<td>LOC</td>
<td>3.53</td>
<td>0.27</td>
<td>0.11</td>
<td>0.54 - 1.35</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.45</td>
<td>0.42</td>
<td>0.23</td>
<td>0.10 - 1.72</td>
</tr>
</tbody>
</table>

Direct LR with 3 predictors: $\chi^2 (3, 94) = 11.77, p = .008$

Predictors reliably distinguish between rapid and protracted recovery groups

Dizziness Needs to be Identified and Treated

- On-field dizziness is best predictor of recovery
- Which kind of dizziness...
  - Migraine variant?
  - Central vestibular dysfunction?
  - Peripheral vestibular dysfunction?
  - Cervico-genic?
- Regardless of its cause, dizziness needs to be treated following injury


Somatic Symptoms: Post-traumatic Headaches

- Most commonly reported symptom of concussion (Kontos et al., 2012)
- Up to 75% of concussed athletes (Kontos et al., 2012)
- May not develop immediately after injury
- May worsen with exertion

Etiology of Post-traumatic Headache

- Musculoskeletal (myofascial/tension)
- Cervicogenic
- Rebound headaches (medication induced)
- Nerve injury (occipital nerves)
- Fatigue-related headaches
- Post-traumatic migraine
Role of Post-traumatic Migraine in Predicting Recovery and Outcomes

Post-traumatic Migraine (PTM)
- Post-traumatic Migraine
  - Headache, nausea, AND sensitivity to light OR noise (Int'l Headache Society)
- Determined using symptoms at 1-7 days

Study Overview
- 174 high school athletes with a concussion:
  1. 138 athletes had ImPACT composite and concussion symptom scores at:
     - Baseline-9-1-7 days-9-8-14 days
     - Divide into:
       - PTM (32), Headache (45), or No PTM/Headache (20) groups
  2. 97 athletes met Rapid or Protracted Criteria for Recovery Time:
     - Rapid (≤7 days): 61
     - Protracted (≥21 days): 36

Post-traumatic Migraine Predicted Protracted (>21 days) Recovery from Sports Concussion (N= 97)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald</th>
<th>p</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTM v. No Headache/PTM</td>
<td>7.60</td>
<td>.006</td>
<td>7.29</td>
<td>1.80-29.91</td>
</tr>
<tr>
<td>Headache v. No Headache/PTM</td>
<td>2.20</td>
<td>.14</td>
<td>2.83</td>
<td>0.72-11.20</td>
</tr>
<tr>
<td>PTM v. Headache</td>
<td>3.93</td>
<td>.04</td>
<td>2.57</td>
<td>1.10-6.54</td>
</tr>
</tbody>
</table>

Kontos AP, Elbin RJ, Lau B, Simensky S, Freund B, French J, & Collins MW; AJSM, in press.

Comparison of Visual Memory scores for PTM, Headache, and No PTM or Headache groups (λ = .88, F = 4.54, p = .002, η² = .06, n = 138)*
*PTM significantly different than both groups at 1-7 and 8-14 days

Kontos AP, Elbin RJ, Lau B, Simensky S, Freund B, French J, & Collins MW; AJSM, in press.

Comparison of Reaction Time scores for PTM, Headache, and No PTM or Headache groups (λ = .87, F = 4.16, p = .001, η² = .07)
*PTM significantly different than both groups at 1-7 and 8-14 days

Kontos AP, Elbin RJ, Lau B, Simensky S, Freund B, French J, & Collins MW; AJSM, in press.
It’s more than just a headache!

- Athletes with PTM are more likely to have a longer recovery than those without.
- It’s more than just headache.
  - Athletes with PTM were more likely to have a longer recovery, and more substantial and lingering cognitive deficits than those with just headache.
- We need to monitor and treat headache, nausea, and sensitivity to light/noise symptoms following concussion.
  - Also look for migraine Hx - personal and family.


Rebound Headache

- Medication overuse (Dodick et al., 2006)
  - Most common: opioids, butalbital-containing combination analgesics, and aspirin/acetaminophen/caffeine combinations.
- Opiates (Bigal et al., 2008)
  - Risk of transformation from episodic HA to chronic.
  - Increased risk in men.
  - Risk with 8 days a month.
- Acetaminophen greater risk than NSAIDs, triptans.
- Significant incidence in patients with chronic PTH.

Somatic/Headaches: Conservative Treatment

For Musculoskeletal/Myofascial/Tension HA:
- Physical Therapy
  - ROM, modalities, massage, TENS...
- Analgesics/Anti-inflammatories/Muscle relaxants
- Trigger Point Injections
- Nerve block (GON)
- Relaxation, Biofeedback, Acupuncture

Supplements for PTM:
- Magnesium, ALA, B6, Coenzyme Q10:
  - Decrease migraine frequency w/chronic supplementation.
Somatic/Headaches: Pharmacological Treatment

- **Antidepressants**
  - Amitriptyline (30-50mg)
  - Venlafaxine
  - Escitalopram
  - Sertraline

- **Anticonvulsants**
  - Topiramate
    - 25mg PO 1wk, then 25mg BID, then increase by 25mg/day/wk
  - Valproic acid
  - Gabapentin* (Start 300mg/d, increase to TID)

*Non-FDA approved indication

Headaches: Treatment (cont.)

- **Beta-blockers**
  - Propranolol

- **Migraine Abortives**
  - Triptans
    - Imitrex - 25-100mg/dose
    - Maxalt - 5-10mg/dose

Cognitive Symptoms

- Fogginess
- Difficulty concentrating/focusing
- Memory impairment
- Cognitive fatigue (slowed thinking/processing)
- Accompanied by headache- chronic fatigue headache (CFH)
Cognitive Symptoms: Conservative Treatment

- Accommodations
  - Academic, work
  - Testing, reading, additional time
- Environment
- Tutors, note takers, assistance
- Transportation...

Cognitive Sx (i.e., CFH): Treatment with Neurostimulants*

- Neurostimulants that enhance the dopaminergic system may help to (Goldstein, 2003):
  - Facilitate recovery
  - Improve quality of life
- Amantadine
  - 100mg breakfast 5 day, then 100mg BID breakfast & lunch

*Non-FDA approved

Efficacy of Amantadine treatment on symptoms and neurocognitive performance among adolescents following sports-related concussion.

Camiolo-Reddy, Collins, Lovell, Cantor, J Head Trauma Res, 2012
Study Overview

Subjects:
1. TREATMENT- 100 mg amantadine 2x/day (200 mg total)
   - 25 male (n=11) and female (n=14) adolescents, and
2. CONTROLS- treated conservatively without meds
   - 25 male (n=11) and female (n=14) age-, sex-, and concussion Hx-matched controls
   - Not recovered within 3 weeks of conservative management (physical, cognitive rest, accommodations)
3. Pre- and post-treatment (3-4 weeks) neurocognitive and symptom assessments

Camiolo-Reddy, Collins, Lovell, Kontos, JHTR, 2012

Comparison of SYMPTOMS from pre- to post-treatment for the amantadine (n=25) treatment and matched control (n=25) subjects (p<.05).

Comparison of REACTION TIME* scores from pre- to post-treatment for the amantadine (n=25) treatment and matched control (n=25) subjects (p<.05).*-Lower score= faster reaction time

Comparison of VERBAL MEMORY scores from pre- to post-treatment for the amantadine \((n = 25)\) treatment and matched control \((n = 25)\) subjects \((p < .05)\).

\[
\begin{array}{c|c|c}
\text{Pre-treatment} & \text{Post-treatment} \\
\hline
\text{Control} & 65 & 72 \\
\text{Amantadine} & 63 & 87 \\
\end{array}
\]


**Conclusion**

- Findings provide initial support for the efficacy of amantadine \((200\text{mg/day})\) as a pharmacological treatment for patients with protracted recovery \((i.e., >21\text{ days})\) following concussion
- Cognitive/Attention-specific effects
- We need a double-blind randomized control trial of the efficacy of amantadine following concussion in a sufficiently large sample to corroborate the current study's preliminary findings

Camiolo-Reddy, Collins, Lovell, Kontos, JHTR, in press

**Cognitive Sx (i.e., CFH): Treatment with Neurostimulants* (cont.)**

- Adderall
  - 5mg QID 5 day, then BID, increase by 5mg/d/wk. Max: 40mg/d
- Atomoxetine (Strattera)
  - 40mg 3d, then 80mg
- Methylphenidate (Ritalin/Concerta)
  - 5mg daily 5d, then BID, increase by 5mg/d/wk. Max: 60mg/day

*Non-FDA approved
Efficacy of Methylphenidate

- Whyte et al. (2004) conducted a double blind, placebo-controlled crossover trial of methylphenidate
- 34 moderate to severe TBI outpatients

Key Findings
- Primary benefit on impaired processing speed
- May also improve attention, memory, and higher demand cognitive tasks

Neuropsychiatric symptoms

- Mood disturbances occur following concussion (Kontos et al., 2012)
  - Nervousness, irritability, nausea, sleep disturbances, sadness, emotional
  - Sense of loss of control, fear about the future, removed from social experiences, removed from sport or fitness activity, family stressors
- Sub-clinical
- Clinical Anxiety/PTSD/Depression

Neuropsychiatric Symptoms: Etiology

- Pre-existing disorder
- Concussion-related
  - Neurophysiologic
  - Frustration, isolation
- Development of disorder concurrently with injury, but unrelated to injury
Neuropsychiatric: Treatment

- Psychotherapy and Support/Coping
  - Concurrent with meds
  - Expand social support
  - Enhance coping (Covassin et al., in press; Kontos et al., in press)

- Anti-depressants*
  - Selective Serotonin Reuptake Inhibitors (SSRI)
    - Sertraline
  - Tricyclic Antidepressant (TCA)
    - Amitriptyline
  - If headache/sleep component
  - Serotonin Norepinephrine Reuptake Inhibitor (SNRI)
    - Venlafaxine
  - If NA-only component

*Note - follow FDA dosage guidelines

Neuropsychiatric Treatment (cont.)

- Benzodiazepines
  - There are strong benefits from short term use, but limit use
  - Dosage
    - Ativan 0.5mg
    - Klonopin 0.25mg
  - Klonopin 0.25mg BID has been shown to:
    - Decrease vestibular symptoms
    - Improve vestibular-related anxiety (crowded environments, travel, mod-severe dizziness)
    - Supplemented with vestibular therapy
  - Side-effects can be problematic

Unintended (Side) Effects

- Neurostimulants
  - Adderall
    - Anxiety, hyper-vigilance, sleep disruption, dizziness, headache...

- Benzodiazepines
  - Klonopin
    - Anxiety, panic attacks, sleep disturbance...

- The above effects are often difficult to separate from concussion-related symptoms

- Need to monitor dosing, effects and potential overuse closely especially in children
**UpMC Sports Medicine Concussion Program Pharmacological Protocol Summary**

**Neuropsychiatric Sx**
- Psychotherapy
- Antidepressants: SSRIs, TCAs, SNRIs
- Benzodiazepines

**Cognitive Sx**
- Accommodations
- Neurostimulants:
  - Amantadine*
  - Adderall*
  - Methylphenidate*
  - Atomoxetine*

**Somatic Sx**
- Vestibular and physical therapy, supplements
- Meds (for HA):
  - Anticonvulsants
  - Antidepressants
  - Beta-blockers
  - Sipranes

**Sleep Disturbance**
- Sleep hygiene
- Meds:
  - Melatonin
  - Zolpidem
  - Amitriptyline
  - Ambien

**NOTE:**
- Off-label non-FDA approved use

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**Moving Forward**

**Looking Back...Epic fail?!**
- To date, 28 sponsored clinical drug trials for TBI and mTBI/concussion have resulted in exactly ZERO successful treatments (USAMRMC. 2013)
- The problem is less with the treatments and more with our approach to treating this injury
- The assumption is that EVERYONE with concussion will respond to a drug treatment in a similar manner
- The problem is we are dealing with a highly individualized injury to the most complex organ in the human body...the brain
We need a new model of treatment!
Using Concussion Clinical Trajectories to Inform Targeted Treatment Pathways

Risk Factors

Previous Concussions
Migraine
LD/ADHD
Sex
Age

Motion sensitivity, Ocular Hx...

Concussion
Concussion Clinical Trajectories
Treatment and Rehab Pathways

Targeted Treatment to Match Clinical Trajectory

- Identify primary clinical trajectory:
  - Cognitive - with attention-focus issues
  - Assessment - NCT, symptoms...
- Target with appropriate pharmacological treatment
  - Amantadine, Methyphenidate
  - Also, cognitive, vestibular, ocular...as needed
- Assess recovery/efficacy - NCT, symptoms...
- Possible early, more aggressive and targeted intervention to mitigate recovery times - ?
  - We need more research here

Conclusion and Implications

- Progressive approach - conservative...aggressive
- Need to
- Symptom clusters drive current treatment approach
- Moving Forward: Targeted treatments for specific clinical trajectories
- Anecdote is nice, but we need more research on the efficacy of pharmacological treatments