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Continuing Education

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From Headache to Healing

Medication Management in Pediatric Concussion Care

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DEFINING WHAT MEDICINE MEANS.

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DEFINING WHAT MEDICINE MEANS.

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Objectives

- Discuss the role of medications in pediatric concussion management by identifying appropriate indications, contraindications, and potential side effects of medications commonly used in managing symptoms of pediatric concussion.
- Formulate treatment strategies/customize medication regimens for individual pediatric concussion patients, considering their symptom profiles and recovery goals.

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Concussion: Definition

- Traumatically induced *transient disturbance of brain function* that involves a *complex pathophysiological process*.
- A *subset of mild traumatic brain injury* which is classified based on acute injury characteristics at the less severe end of the brain injury spectrum.
- Clinical signs and symptoms of concussion cannot be otherwise explained by drug, alcohol, medication use, or other injuries (such as cervical injuries or peripheral vestibular dysfunction) or other comorbidities (psychological or medical conditions).

American Medical Society for Sports Medicine (AMSSM) position statement (2019)

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AMSSM AMERICAN MEDICAL SOCIETY FOR SPORTS MEDICINE

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Concussion: Definition

- Traumatic brain injury, a *pathophysiological process affecting the brain*, induced by *direct or indirect* biomechanical forces (*e.g.*, a blow to the head or body)
- Common features include the following:
  - Rapid onset of usually short-lived neurological impairment which typically resolves spontaneously
  - Acute signs and symptoms that reflect a *functional disturbance rather than structural injury*
  - A *range of clinical symptoms* that *may or may not involve loss of consciousness* (LOC)
  - *Routine neuroimaging studies* (*e.g.*, traditional computed tomography or magnetic resonance imaging [MRI]), if obtained are *normal*
  - Signs or symptoms that are not explained by other medical issues (*e.g.,* alcohol, drugs, medications, cervical spine injury, peripheral vestibular dysfunction, psychological disorder) or other comorbidities

American College of Sports Medicine (2021)

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Concussion: Epidemiology

- Where concussions occur
  - Organized sports – 53 .3%
    - Soccer – 12.9%
    - Football – 9.8%
  - School – 16.5%
    - School PE class – 10.6%
  - Recreational – 6.7%
  - Motor vehicle collisions – 6.6%
  - Home – 5.5%

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Concussion: Management

- Initial rest → gradual activity increase
- Cognitive modifications as needed
- Many concussions resolve within a few weeks without medication
- Limited research on pharmacotherapy
- Reasons to consider pharmacotherapy for concussion
  - Potential to shorten the course of the injury
  - Potential to lessen symptoms
  - Potential to improve long-term outcomes after concussion

Currently, there are no medications that have conclusive evidence to accomplish any of the proposed benefits of treatment with medication

and

Currently, there are no medications approved by the FDA for the treatment of concussion

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Medication Use Survey

- Survey of pediatricians
  - Pain Management
    - Acetaminophen 62%
    - NSAIDs 54%
  - Sleep support
    - Melatonin 20%
    - Tricyclic antidepressants (also pain management) 20%
  - Cognition/Stimulation
    - Amantadine 10%
    - Stimulants 8%
- Survey of pediatric emergency medicine physicians
  - 78% acetaminophen
  - 77% NSAIDs
  - 54% ondansetron

Pediatricians managing >16 concussions per year were more likely to use prescription medications and less likely to use NSAIDs

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Medication Overview

- Key Considerations for Medication Use
  - Mechanism of action
  - Indications
  - Contraindications
  - Dosing
  - Adverse effects

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Headaches

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Headache Medications

- Acetaminophen
- NSAIDs
- Topiramate
- Amitriptyline
- Nortriptyline
- Propranolol
- Gabapentin

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Headaches: Acetaminophen

- Mechanism
  - Unknown for pain, may be due to an inhibition of central prostaglandin synthesis (specifically COX-2) and an elevation of the pain threshold
- Indication
  - FDA: Pain
  - Non-FDA: Acute migraine
- Contraindication
  - Active/severe liver disease
  - Hypersensitivity
- Dosing
  - Oral < 60 kg
    - 10-15 mg/kg/dose q4-6 hours, max 1625 mg/day
  - Oral >60 kg
    - 650 mg q4-6 hours , max 3250 mg/day

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Headaches: NSAIDs

- Mechanism
  - Analgesic by inhibiting prostaglandin synthesis
- Indication
  - FDA: headache, migraine, pain
- Contraindication
  - Allergic-type reaction with Aspirin or NSAIDs
  - Hypersensitivity
  - CABG
- Dosing
  - Chewable tabs/suspension
    - 2-3 years, 24-35# 100 mg q6-8 hours
    - 4-5 years, 36-47# 150 mg q6-8 hours
    - 6-8 years, 48-59# 200 mg q6-8 hours
    - 9-10 years, 60-71# 250 mg q6-8 hours
    - 11 years, 72-95# 300 mg q6-8 hours
    - Max 4 doses/day
  - Tabs/capsules
    - 12+ years, 200 mg q4-6 hours
    - Max 1200 mg/day

No studies have suggested harmful effect of NSAID use (i.e. increased risk for intracranial bleed)

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Medication overuse headache (MOH) aka Rebound Headache

- Retrospective chart review
  - Adolescent patients treated in a headache clinic with chronic posttraumatic headaches
  - 70% met criteria for medication overuse headaches
  - After discontinuation of the over-the-counter medications, 68.5% of patients had resolution/ improvement of headaches
  - Suggests caution in chronic administration of over-the-counter analgesics in concussion headache management

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Medication overuse headache (MOH) aka Rebound Headache

- Causes changes in the central nervous system, specifically in pain processing and dependence networks, sensitization, and receptor density
- Patients with migraines or tension-like headaches more prone
- Functional and structural changes in the central nervous system (CNS)
  - Hippocampal periaqueductal gray area
  - Posterior cingulate cortex thalamus
  - Cerebellum
  - Orbitofrontal cortex
  - Mesocorticolimbic reward system
- Changes in the serotonergic neuromodulatory system
  - Upregulation of vasoactive and pro-inflammatory mediators
  - Increased susceptibility to cortical spreading depression
  - Central sensitization
  - Increase in nociceptive sensory fields

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Medication overuse headache (MOH) aka rebound headache

Diagnosis of Medication-overuse Headache (MOH) According to ICHD-3 Must Meet Criteria A-C for the Diagnosis of MOH

- Headache on 15 or more days per month AND a pre-existing headache disorder
- Overuse of acute and/or symptomatic headache drugs for over three months (Regular intake of drugs on greater than or equal to 10 days/month for ergotamines, triptans, opioids, and combination analgesics and on greater than or equal to 15 days per month for acetaminophen, ASA and NSAIDs)
- No better explanation by another ICHD-3 diagnosis

Medication Overuse Headache by Drug Class and Duration of Headache

- Ergotamine-->10 days/month for over 3 months
- Triptan-->10 days/month for over 3 months
- ASA-->15 days/month for over 3 months
- NSAIDs-->15 days/month for >3 months
- Acetaminophen/paracetamol-->15 days/month for over 3 months
- Opioids-->10 days/month for over 3 months
- Combination analgesics-->10 days/month for over 3 months
- Multiple drug classes-->10 days/month for over 3 months

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Headaches: Topiramate

- Mechanism: exact is unknown
  - Blockage of voltage-dependent sodium channels
  - Augmentation of gamma-aminobutyrate acid activity
  - Antagonism of AMPA/kainite subtype of the glutamate receptor
- Indications
  - FDA: migraine prophylaxis
- Contraindication
  - Not been determined
- Dosing
  - Immediate release (BID)
    - Week 1: No dose in the AM and 25 mg in the PM
    - Week 2: 25 mg in the AM and 25 mg in the PM
    - Week 3: 25 mg in the AM and 50 mg in the PM
    - Week 4: 50 mg in the AM and 50 mg in the PM
  - Extended release (once/day)
    - Week 1: 25 mg once a day
    - Week 2: 50 mg once a day
    - Week 3: 75 mg once a day
    - Week 4: 100 mg once a day
- Adverse effects
  - GI (abdominal pain, diarrhea, loss of appetite, nausea)
  - Neurologic (dizziness, parasthesias, somnolence)
  - Psych (nervousness)

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Headaches: Amitriptyline

- Mechanism:
  - Promotes neuronal activity by blocking reuptake of serotonin and norepinephrine
- Indications
  - Non-FDA use: headache prophylaxis
- Contraindication
  - Co-administration with MAOI (or within 14 days of MAOI) , hyperpyretic crisis, convulsions, death
  - Co-administration with cisapride, QT prolongation
  - Hypersensitivity
  - MI during acute recovery period
- Dosing
  - 9-12 years, 1 mg/kg/day in 3 doses, increase after 3 days to 1.5 mg/kg/day
  - 12+ years, 10 mg TID
  - Anecdotal: 10 mg qhs
- Adverse effects
  - Endocrine (weight gain)
  - GI (constipation)
  - Neurologic (dizziness, headache, somnolence)
  - Ophthalmic (blurry vision)

Headaches: Nortriptyline

- Mechanism
  - Inhibits reuptake of norepinephrine and serotonin
  - Antagonist of H1 and 5-HT2A receptors
  - Central anticholinergic effects
- Indications
  - Non-FDA use: headache prophylaxis
- Contraindication
  - Co-administration with MAOI (or within 14 days of MAOI) , hyperpyretic crisis, convulsions, death
  - Co-administration with Linezolid or methylene blue
  - Hypersensitivity
  - MI during acute recovery period
- Dosing
  - 12+ years old, 30-50 mg/day in divided doses or single daily dose
- Adverse effects
  - GI (constipation)

Headaches: Propranolol

- Mechanism
  - Nonselective beta-adrenergic blocker
  - Reduces portal pressure by producing splanchnic vasoconstriction thereby reducing portal blood flow
- Indications
  - FDA: migraine prophylaxis
- Contradictions
  - Hypersensitivity
  - Sinus bradycardia
  - Greater than 1st degree AVB
  - BP <50/30
  - Bronchial asthma, bronchospasm
  - Decompensated heart failure
- Dosing
  - Weight directed
    - 3+ years old, 0.5-3 mg/kg/day in 2-3 divided doses, max daily dose 120 mg/day
  - Fixed dose
    - 7+ years old, 10 mg daily, increase weekly by 10mg increments, range 10-40 mg TID, max 120 mg/day
  - Anecdotal: 10 mg BID start
- Adverse effects
  - GI (diarrhea, vomiting)
  - Neurologic (Dizziness, sleep disorder)
  - Other (fatigue)

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Headaches: Gabapentin

- Mechanism
  - Binds to voltage-gated calcium channels presynaptically
  - May modulate the release of excitatory neurotransmitters reducing neuronal excitability
- Indications
  - Non-FDA: headache prevention
- Contradictions
  - Hypersensitivity
- Dosing
  - Initial 5 mg/kg/dose at bedtime, maximum dose: 300 mg/dose
  - Day 2: Increase to 5 mg/kg/dose twice daily, maximum dose: 300 mg/dose
  - Day 3: Increase to 5 mg/kg/dose 3 times daily, maximum dose: 300 mg/dose
  - Further titrate with dosage increases (not frequency) to effect
  - Usual dosage range: 8 to 35 mg/kg/day divided into 3 doses daily; maximum daily dose: 3,600 mg/day
  - Anecdotal: 100-300 mg qhs
- Adverse effects
  - Cardiovascular (peripheral edema)
  - GI (nausea, vomiting)
  - Neurologic (ataxia, nystagmus)
  - Other (fatigue, fever)

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Muscle Relaxers

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Muscle Relaxers

- Cyclobenzaprine
- Tizanidine

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Muscle relaxer: Cyclobenzaprine

- Mechanism
  - Influences both gamma and alpha motor systems by reducing tonic somatic motor activity
- Indications
  - FDA: Skeletal muscle spasms in adolescents >15 years old
- Contradictions
  - Acute MI recovery period
  - Arrhythmias
  - Cardiac conduction disturbances
  - Coadministration with MAOI
  - Congestive heart failure
  - Heart block
  - Hyperthyroidism
  - Hypersensitivity
- Dosing
  - 5 mg TID, may increase to 10 mg TID
  - Not to exceed 2-3 weeks
  - Anecdotal: 5 mg qhs
- Adverse effects
  - GI (constipation, indigestion, nausea)
  - Neurologic (dizziness, somnolence)
  - Other (fatigue)

Muscle relaxer: Tizanidine

- Mechanism
  - Alpha$_2$-adrenergic agonist
  - Decreases spasticity by increasing presynaptic inhibition
- Indications
  - Non-FDA: headaches, muscle spasms/pain
- Contradictions
  - Coadministration with potent CYP1A1 inhibitors (i.e. Ciprofloxacin, Fluvoxamine)
  - Hypersensitivity
- Dosing
  - Initial 2-10 years old: 1 mg at bedtime, titrate PRN
  - Initial 10+ years old: 2 mg at bedtime, titrate PRN
  - Titration/maintenance: titrate initial dose to reported effective range of 0.3-0.5 mg/kg/day in 3-4 divided doses
  - Max daily dose 24 mg/day
- Adverse effects
  - Cardiovascular (hypotension)
  - GI (xerostomia)
  - Neurologic (dizziness, somnolence)

Stimulants

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Stimulants: Amantadine: Case-controlled study

- Amantadine
  - Retrospective, case-controlled study
    - Compared 25 athletes with concussion who were still symptomatic after 3 weeks of rest with 25 controls
    - Amantadine 100 mg BID for 3-4 weeks
    - Results: Those treated with the amantadine demonstrated statistically significant improvement in symptoms ($P < 0.005$) as well as performance on ImPACT test reaction time ($P < 0.05$) and verbal memory ($P < 0.009$) components
    - Prior to treatment, the amantadine group had statistically greater symptoms and worse performance on those test components
    - Ultimately, the treatment and control groups finished with essentially identical symptom reporting and performance on all 4 ImPACT components, which questions the conclusions of the potential benefits of amantadine suggested

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Stimulants: Amantadine, systematic review 1966-2007

- Mechanism
  - Both a dopamine agonist and antagonist.
  - Pre-synapse, it facilitates the release of dopamine and delays reuptake absorption
  - Post-synapse, it increases the number of dopamine receptors
  - Additionally as an antagonist of *N*-methyl-D-aspartate at glutamate receptors
- Indications
  - TBI: arousal, executive functioning
- Dosing
  - Ranged from 200-400 mg /day, BID to TID
- Adverse effects
  - GI distress (Nausea, vomiting, constipation)
  - Agitation
  - Psychotic symptoms (delusions, hallucinations)
  - All remitted once dose decreased or stopped
- Conclusion
  - Clinically beneficial for children who sustained head injuries for symptoms of alertness/arousal
  - Further research needed

Sleep Aids

Sleep Aids

- Melatonin
- Trazodone

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Sleep Aid: Melatonin

- Mechanism
  - Binds to MT1, MT2, and MT3 receptors which may contribute to sleep-promoting properties that regular circadian rhythm and sleep
- Indications
  - Not regulated by FDA
  - Insomnia
- Contradictions
  - Hypersensitivity
- Dosing
  - Preschool children 1 to 2 mg
  - School-aged children 1 to 3 mg
  - Adolescents 1 to 5 mg
  - 30 to 60 minutes before bedtime
  - Not be used infants 0-2 years
  - Begin at the lowest possible dose and be titrated on weekly basis as needed
- Adverse effects
  - Generally well tolerated, minimal side effects, and few to no significant adverse events in children

No published research exists regarding melatonin use for concussions

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Sleep Aid: Trazodone

- Mechanism
  - Inhibits reuptake of serotonin, $5HT_{2a}$ receptor antagonist, blocks histamine (H_1) and alpha1-adrenergic receptors
- Indications
  - Non-FDA: Insomnia
- Contradictions
  - Co-administration with MAOI (or within 14 days of MAOI) , Linezolid, IV Methylene blue
  - Co-administration with saquinavir/ritonavir
  - Hypersensitivity
- Dosing
  - 18 months-3 years
    - 1-2 mg/kg at bedtime, max 25 mg/dose
    - May increase 12.5-25 mg increments q2 weeks, not to exceed 100 mg/dose
  - 3-5 years
    - 1-2 mg/kg/dose at bedtime, max 50 mg/dose
    - May increase 12.5-25 mg increments q2 weeks, not to exceed 150 mg/dose
  - >5 years old
    - 25-50 mg at bedtime
    - May increase 12.5-25 mg increments q2 weeks, not to exceed 200 mg/dose
- Adverse effects
  - GI (diarrhea, constipation, nausea)
  - Neurologic (confusion, dizziness, headache, somnolence)
  - Ophthalmic (blurry vision)
  - Psychiatric (dream disorder, feeling nervous)
  - Other (fatigue)

No research studies have been published on the use of trazodone for sleep disturbances after pediatric concussion

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Conclusions

- No drugs specifically approved by the FDA for treatment of concussions
- Medication management should complement gradual return to physical and cognitive activity
- Children requiring medication to manage symptoms should not be cleared for full academic and physical activity
- Caution with OTC analgesics for risk of rebound headache

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Questions?

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