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For more information visit: www.pcss-o.org
For questions email: pcss-o@aaap.org

Twitter: @PCSSProjects

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Opioid Use in Headache Medicine

Laszlo Mechtler, MD, FAAN
and
Jennifer W McVige, MD

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Laszlo Mechtler MD, FAAN
Professor of Neurology and Oncology
Dent Neurologic Institute
Roswell Park Cancer Institute
Director of Headache Center
UCNS certified in Headache, Neuro-Oncology and Neuroimaging

Jennifer W McVige, MD
Pediatric Neurology, Adult and Pediatric Headache Medicine
Director of Concussion Clinic
Dent Neurologic Institute
UCNS certified in Headache and Neuroimaging
Opioid Use in Headache

• Define opioid.
• Review the mechanism and benefits of opioid medications.
• Discuss the adverse effects of opioid medications.
• Review the evidence for opioid use in the treatment of headache.
• Discuss hyperalgesia and medication overuse headaches.
• Review alternate treatments for chronic headache
Definitions

• **Opium**
  - fluid extracted from the poppy plant

• **Opiate**
  - a “natural” alkaloid derived from opium

• **Opioid**
  - Semi-synthetic or fully-synthetic substances with morphine-like actions, but not derived directly from the poppy plant
How Do Opioids Work?

**Bind to opioid receptors**

- **Increase dopamine** in pleasure centers (ventral tegmental area → nucleus accumbens)

- **Decrease noradrenalin** in the fight or flight centers (locus coeruleus and amygdala) - calming

- **Affects brainstem** (from respiratory deprivation)

- Can produce dysphoria, sedation, impaired judgment, constipation, weight gain, erectile dysfunction (from **decreased testosterone**).

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Taylor et al; Unifying Perspectives of the Mechanisms Underlying the Development of Tolerance and Physical Dependence to Opioids, JPET APRIL 1, 2001 VOL. 297 NO. 1 11-18

Mechanisms of Opioid Actions:

• Activate mu (μ), delta (δ), or kappa (κ) opioid receptors
  ▪ Therapeutic opioids are selective for mu receptors

• Opioid receptors are members of the 7TM, G protein-coupled receptor superfamily

• Activation of opioid receptors inhibits neuronal activity
  ▪ Increases potassium conductance
  ▪ Decreases calcium conductance
  ▪ Inhibits neurotransmitter release
Opioid Types

- **Pure mu agonists:**
  - **Natural or semi synthetic:** morphine, codeine, hydrocodone, oxycodone, hydromorphone
  - **Synthetic:** fentanyl, methadone, propoxyphene

- **Partial mu agonists:**
  - Buprenorphine, tramadol (weak)

- **Kappa agonist/mu antagonists:**
  - Pentazocine, butorphanol, nalbuphine (*a partial list)*
Opioid Medications

Oral, transdermal, transmucosal and parenteral forms

**Therapeutic Actions:**
- Analgesia through stimulation of central and peripheral opioid receptors
- Inhibit intestinal motility
- Suppressive cough reflex
- Euphoria, sense of well being
- Mild sedative, induce sleep

**Side Effects:**
- Constipation
- Respiratory depression
- Sedation, cognitive blurring
- Sweating, meiosis,
- Urinary retention
- Tolerance, physical dependence
- Hyperalgesia

Opioid Withdrawal

• Flu-like syndrome: muscle aches, joint pains, sweating, stomach cramping, diarrhea
• Irritability, arousal, wakefulness
• Mild increase blood pressure and heart rate
• Mydriasis
• Piloerection (gooseflesh)
Studies show the risk of opioids are likely greater than their benefits when used for non-cancer chronic conditions including back pain, HEADACHES, and fibromyalgia.

Opioid Use in Migraine/Headache Patients
American Migraine Prevalence and Prevention (AMPP) study

- Sample of 5796 migraineurs
- 798 (13.8%) previous opioid users
- 922 (15.9%) current opioid users
- 30% reported use of opioids for headache treatment in the past 4 years
- 153 (16.6%) met criteria for probable dependence

AMPP study

Opioid use for migraine was associated with:

- more severe headache related disability (MIDIAS scores)
- more severe symptomatology
- more comorbidities (depression, anxiety, cardiovascular disease and events)
- greater health care resource utilization for headache (ER, Immediate Care)

Examined reasons for discontinuing meds:

- Opioid use was associated with increased risk of medication discontinuation.

- Common reasons included:
  - return of migraine pain
  - drug interaction concerns
  - stomach upset

- MIDAS scores were decreased in triptan users compared to opioid users.

AMPP study

- 120,000 people followed over 5 years
- 8,219 had episodic migraine
- 2.5% developed transformational migraine – to chronic daily headache

Stats were adjusted for other variables but result showed 8 days or more/month use of OPIOIDS was a risk factor to progress to medication overuse headaches.

This campaign advocates for avoidance of the use of opioid or butalbital treatment for migraine; except as a last resort.

Opioid and butalbital treatment for migraine should be avoided because more effective, migraine-specific treatments are available. Frequent use of opioid and butalbital treatment can worsen headaches. Opioids should be reserved for those with medical conditions precluding the use of migraine-specific treatments or for those who fail these treatments.
Saper and Colleagues 5 yr study

• ↑ # patients violated contractual agreements, used meds inappropriately, multi-sourced prescriptions, tried to fill scripts early, or claimed to lose them and requested more.

• Many patients who reported improvement in pain control with opioids did NOT return to work or demonstrate improvement in measures of disability (MIDAS).

• More than half required escalating doses during the 5 years.

Opioids in the ER

• Opioids remain the most widely used medication class for acute migraine treatment in North American emergency rooms (ERs)

• Canadian study 500 patients with migraine presenting to 5 Canadian ERs, 59.6% received opioids for headache.
Acute Headache Treatments in Patients With Health Care Coverage: What Prescriptions Are Doctors Writing?

STEWART J. TEPPER, MD et al,

Figure 2 – This graph shows the pattern of acute headache pain medication use among persons with diagnosed migraine/nonmigraine headaches who had prescription coverage in 2003.

**Source of Opioids for Nonmedical Use Reported by Users**

- **Friend/Relative**: 59.8%
- **One Doctor**: 16.8%
- **Dealer/Stranger**: 4.3%
- **Internet**: 0.8%

*Source of drugs for the most recent nonmedical use of pain relievers reported by persons aged 12 or older in the United States 2005.

Why is this important?

• Drug overdose is the leading cause of death in US
  - 47,055 lethal drug overdose in 2014
    - 18,893 related to prescription pain relievers
    - 10,574 involving heroin
  - In 2012, 259 million prescriptions were written for opioids which equals every American adult with their own bottle of pills
  - 4 in 5 heroin users started by misusing prescription painkillers. This leads to the increase in rate of heroin overdose deaths four times from 2000 to 2013.
Identification of Prescription Opioid Abusers

- Deterioration in home/work
- Resistance to changes in therapy
- Use of drug by injection or nasal route
- Early refills
- Lost/stolen prescriptions
- Doctor shopping

- Prescription forgery
- Abuse of other substances
- Frequent ED visits
- Unauthorized dose increases
- Nonmedical use
- Refuses UDS/referral to specialist
Why Opioids are not effective in Headache?

- **Drug Opposite Responses**
  - Increased pain: Opioid induced and/or enhanced hyperalgesia
  - Deleterious effects on mood

- **Neuroplastic changes**
  - Upregulation of CCK in Rostral Ventromedial Medulla with more descending pain facilitation
  - Increased CGRP and, as a result, activated NMDA glutamate receptor
  - Central sensitization and inflammatory changes

- **Neurotoxicity**
  - NMDA Glutamate Receptor-induced cell death

- **Medication overuse headache**

Tepper (2012) 52;S1:30-34 (see subsequent slides for specific citations)
Drug-Opposite Response

• **Opioid-induced hyperalgesia**
  - Decrease pain threshold
  - Increase pain sensitivity

• **Opposite effects:**
  - Headache worsens
  - Episodic migraines transform to chronic migraines
  - Chronic daily headaches become worse with chronic opioid use

Tepper SJ. *Headache.* 2012;52;S1:30-34
Drug-Opposite Response

• “Episodic opioids can cause euphoria and reduction of emotional distress, but chronic methadone maintenance participants and heroin users show significant negative mood disturbance relative to controls.”

Neuroplastic Changes

During chronic exposure of opioids

Cholecystokinin (CCK) is upregulated in the rostral ventromedial medulla (RVM)
- CCK activates descending RVM pain facilitation

Leading to hyperalgesia

Increase peripheral expression of calcitonin-gene related peptide (CGRP) in primary afferent neurons
- Activate NMDA glutamate receptors

Also causes central sensitization in spinal trigeminal nucleus

Neuroplastic Changes

• **CGRP** is a peptide implicated in migraine associated with vasodilation and inflammation.

• **Increased CGRP levels** can result in *Inflammation* and peripheral and central sensitization (migraine).

• Chronic opioid use and migraine processes are similar – causing **increased CGRP and Inflammation**

• This can lead to **medication overuse headache (MOH)**
Neuroplastic Changes

- Chronic opioid use = central sensitization and Medication Overuse Headaches (MOH).
- The reversal of central sensitization with appropriate migraine treatment is inhibited by chronic opioid use.
- Patients with prolonged migraine were treated with sumatriptan with ketorolac infusion
- 71% free of pain in one hour pain and allodynia-free.
- Nonresponders - had received opioids.

Neurotoxicity

- Chronic opioid use increases spinal cord Dynorphin
- Dynorphin enhances nociception
- Can release of excitatory amino acids such as CGRP from primary afferent nociceptors
- Dynorphin activates NMDA/glutamate receptors

Neurotoxicity

• Activation of NMDA-glu increases opioid tolerance

• Activation of NMDA-glu receptors also increases neurotoxicity by neuronal apoptotic cell death and damage

Conceptual Framework for Transitions in Migraine

No Migraine → Low frequency episodic migraine → High frequency episodic migraine → Chronic MIGRAINE

Not Readily Modifiable
1. Age
2. Low socio-economic status
3. Head injury

Modifiable
1. Attack frequency
2. Obesity
3. Medication (OTC, butabital, opioids)
4. Stress
5. Sleep


CHD-2 Criteria for Headache Attributed to Medication Overuse

A. Headache present on >15 days/month

B. Regular overuse for >3 months of one or more acute/symptomatic treatment drugs as defined under subforms of 8.2.
   1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month on a regular basis for >3 months
   2. Simple analgesics or any combination of ergotamine, triptans, analgesics opioids on ≥15 days/month on a regular basis for >3 months without overuse of any single class alone

C. Headache has developed or markedly worsened during medication overuse

Diff Dx: Type of Chronic Daily Headaches

- **Chronic (transformed) migraine (CM):** Headache fulfilling criteria C and D for Migraine without aura on ≥15 days/month for >3 months

- **Chronic tension-type headache (CTTH):** Low-grade daily or almost-daily chronic headache without migrainous features

- **New daily persistent headache (NDPH):** Abrupt onset of unremitting new CDH, may be complicated by drug overuse; no history of evolutive migraine or ETTH

- **Hemicrania continua (HC):** rare, indomethacin-responsive headache disorder; continuous, unilateral, fluctuating, moderate-severe pain

Headache Classification Subcommittee of the International Headache Society. *Cephalalgia.* 2004
Treatment of Medication Overuse Headache

MEDICATION OVERUSE

PREVENTIVE THERAPY

DETOXIFICATION

FAIL

FAIL

Bigal RB, Lipton RB. Neurology. 2008; 71; 1821-8
Diener HC Limmorth V. Lancet Neurol 2004; 3 ;475-83
Hagen K. et al. Cephalgia 2009; 29; 221-32
Medication Overuse Withdrawal

- Use a daily preventative agent
  Amitriptyline, Propranolol, Valproic Acid, Topmamax; doses modestly adjusted upward
- Triptan given for acute headaches
- Chlorproomazine suppositories can be used for nausea & pain
- Use long acting NSAIDS – eg Naproxen BID
- Cognitive behavioral therapy

Terminating the Headache Pattern

Some medications are effective in terminating the headache cycle. These can be given via IV repeatedly.

- Dihydroergotamine
- Neuroleptics: prochlorperazine, chlorpromazine, droperidol
- Corticosteroids
- Valproate sodium
- Magnesium
- Ketorolac

Justification for Hospitalization

- Intractable symptoms are intense and disabling often requiring hospitalization
  - Specially for patients with headache accompanied by drug overuse or toxicity
- Presence of neuropsychiatric and behavioral comorbidity renders outpatient treatment ineffective
- Confounding medical illness
- Treatment urgency of clinically desperate patient
Possible Non-pharmacological Pain Management

- Patient support groups
- Physical Therapy
- Chiropractic
- Massage
- Acupuncture
- Complementary therapies
- Nutritional evaluation
- Pain psychologist
Alternative Injection Treatments

• Trigger point injections
• Nerve blocks (occipital, supraorbital)
• Sphenopalantine ganglion block
• Botox

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncement/s/ucm229782.htm - Botox approved
Neuromodulation and Headache Outline

• **FDA APPROVED:**
  - Transcranial magnetic stimulator (TMS) for acute treatment of migraine with aura (Spring TMS) – phase 4 in selected centres
  - Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEPHALY) – available

• **NOT FDA APPROVED:**
  - Non-invasive Vagal Nerve Stimulator (nVNS, Gammacore)
  - Sphenopalatine Ganglion stimulation (SPG, PULSANTE)
  - Occipital Nerve Stimulation (ONS)
  - Deep Brain Stimulation (DBS)
If Opioids are indicated health care providers can:

Discuss pain treatment options, including ones that do not involve prescription drugs.

Follow guidelines for responsible painkiller prescribing, including:

- Screening and monitoring for substance abuse and mental health problems.
- Prescribing only the quantity needed based on appropriate pain diagnosis.
- Using patient-provider agreements combined with urine drug tests for people using prescription painkillers long term.
- Avoiding combinations of prescription painkillers and benzodiazepines (such as Xanax and Valium) unless there is a specific medical indication.
- Use prescription drug monitoring programs (PDMPs)—electronic databases that track all controlled substance prescriptions in the state—to identify patients who may be improperly using prescription painkillers and other drugs.

http://www.cdc.gov/vitalsigns/PrescriptionPainkillerOverdoses/index.html
In Summary

• The use of opioids in headache medicine should **not** be considered for first line therapy in an acute or chronic situation.

• The evidence shows that there are several alternatives in the form of medications, injections and alternative therapies, that should be considered first.

• All providers should have an awareness of the potential risks and benefits of opioids and use caution in prescribing.
Questions?
THANK YOU!

For questions or feedback, please e-mail hplanalp@aan.com