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Medication Overuse Headache

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Disclosures

- Speaker for Allergan, Pfizer and Zogenix
- “Off-label” use of medications and procedures for the treatment of medication overuse headache and migraine
- I have not yet hit it big in Vegas

Objectives

- Review classification of medication-overuse headache (MOH)
- Discuss who is at risk for development of this headache
- Pathophysiology behind the development of MOH
- Treatment strategies for the successful resolution of this headache type

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Classic History

- Pt w/ frequent, disabling migraines which were episodic at the start
- Medications taken to relieve symptoms, partial response, recurrence, repeat dosing → overuse
- Attacks increase in frequency to daily or near-daily
- Most likely w/ butalbital and opioids than with migraine-specific drugs
- Crossing the 15-day-per-month threshold changes everything for the patient

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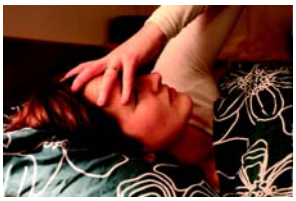
Key Points

- Medications need to be taken on only a modest number of days per month: 5 to 10, depending on the medication
- Common Symptoms:
  - morning HA
  - neck pain
  - non-restorative sleep
  - vasomotor instability



- Co-morbid depression and anxiety are common
- Prevention of MOH is always better than treating it after it occurs!

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8.2 Medication-overuse headache

- 8.2.1 Ergotamine-overuse headache
- 8.2.2 Triptan-overuse headache
- 8.2.3 Analgesic-overuse headache
- 8.2.4 Opioid-overuse headache
- 8.2.5 Combination analgesic-overuse headache*
- 8.2.6 Medication-overuse headache attributed to combination of acute medications
- 8.2.7 Headache attributed to other medication overus
- 8.2.8 Probable medication-overuse headache

*ICHD-2R eliminates MOH with differing *characteristics* by different medications

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8.2 Medication-overuse headache

A. Headache present on ≥15 d/mo fulfilling criteria C and D

B. Regular overuse for >3 mo of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

C. Headache has developed or markedly worsened during medication overuse

D. Headache resolves or reverts to its previous pattern within 2 mo after discontinuation of overused medication*

- *ICHD-2R eliminates this requirement

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Cephalalgia 2004;24: Suppl 1: 1-160. *Cephalalgia* 2005; 25: 460-465.

Medication-Overuse Headache (MOH)

- Prevalence: 1-2%
- Tertiary care: 15-70% of pts
- 2.5% pts with episodic migraine had “transformed migraine” 1 year later (Bigal 2008)
- Severe effects on quality of life
- Preventive and migraine specific acute medications are less effective, and patients need far more complex interventions

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•Bigal ME et al. Headache 2008; 48:1157–1168

•Straube A. Cephalgia 2009

Prevalence Rates and Demographic Features of MOH

	Period	Prevalence (%)	Female sex (%)	Mean age (years)
Taiwan[7]	1 year	1·1	62	45±15
Norway[8]	..	0·9	66	..
Spain[9]	..	1·4	92	45
Netherlands[10]	1 year	0·7	72	43±8
Norway[11]	1 year	1·7	76	..
Germany[6]	6 months	1·0	74	53

..=data not available.

Table 1: Prevalence rates and demographic features of medication-overuse headache in population-based studies

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Evers S. ***Lancet Neurol*** **2010; 9: 391–401**

Who is the patient who gets MOH?

In general, patients with MOH are more likely:

- Females
- Lower educational level
- Married
- Unemployed
- Hx of migraine remission during pregnancy
- Menopausal
- Have a higher number of comorbid diseases
- Not use oral contraceptives
- Higher use of health-care resources
- Polypharmacy

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Medication-overuse Headache

- Why?
- At risk: episodic migraineurs
- Only ~10% of severely affected migraineurs develop MOH
- Role: functional and structural changes in the brain
- Pts with MOH have a negative attitude towards analgesics but believe they cannot cope without them
- Relapse rate: 25-30% within 1 year
- Higher relapse rates in patients who overused combination analgesics containing codeine or barbiturates

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Flawed Coping Strategies?

Dual Process Model of Coping

- **Assimilative coping mode:** aimed at solving pain
  - Higher perceived need for medication
  - Higher concerns for tolerance and withdrawal symptoms
  - Heightened attention to pain
  - Concerns about unfavorable scrutiny by others
  - Related to medication overuse
- **Accommodative coping mode:** disengage from persistent attempts to solve pain
  - re-engage in the pursuit of life goals that are less affected by pain
  - Accept there is no solution and pain will last longer

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Lauwerier E et al. Pain 2011 152:1334-1339
Brandtstadter J, Renner G. Psychol Aging 1990:5:58-67

MOH: Addiction?

- ✓Tolerance
- ✓Withdrawal symptoms
- ✓Use of med in a larger amount or for a longer period of time than intended
- ✓Unsuccessful efforts to cut down or control the use despite harmful consequences
- ✓High priority give to drug use
- X Associated with a progressive increase of time in obtaining or taking the drug
- X Increased recovery from the effects of the drug
- X Progressive neglect of alternative pleasures or interests

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Calabresi P, Cupini LM. Medication overuse headache; similarities with drug addiction. Trends Pharmacol Sci 2005; 26: 62–8.

Risk of transformation

Frequency of headache:

Katsarava et al followed pts for 1 yr: compared with pts with 0-4 HA/mo

- 6 to 9 HA d/mo: 6.2 x more likely to develop CDH
- 10 to 14 HA d/mo: 20 x more likely to develop CDH.

Hierarchy of acute med days and risk for MOH

- **Butalbital:** as little as 5 days per month
- **Opioids:** as little as 8 days per month
- **Triptans, NSAIDS and analgesics:** as few as 10 days per month

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Katsarava Z, et al. Neurology 2004; 62:788–790
Bigal ME, et al. Headache 2008;48:1157-1168

Why does migraine become chronic?

- A yo-yo effect of repeated migrainous pain processes, followed by repeated medication, results in structural changes
- Propagate central sensitization with a lowered threshold for activation of head pain.
- This set of disturbances may occur due to under-treatment of migraine pain
- With inadequate pain control, headaches recur, and the process repeats until damage occurs
- Evidence for this is seen in up-regulation of excitatory serotonin receptors when analgesics are repetitively given to laboratory animals

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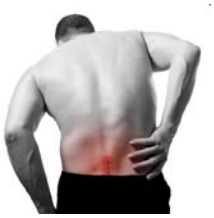
A pure withdrawal phenomenon?

- Is it that medication overuse headache is just a complex dependence-and-withdrawal phenomenon
- Arguing against this being a pure withdrawal phenomenon is that daily use of analgesics or opioids generally does not cause daily headache in non-migraineurs





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Pathophysiological abnormalities

- Increased pain after electrical forearm stimulation favoring central sensitization
- Low serotonin levels with receptor up-regulation
- NMDA receptor dysfunction
- Low beta-endorphin and opioid levels
- Increased norepinephrine turnover
- Increased inositolphosphate production in platelets suggesting abnormal signal transduction

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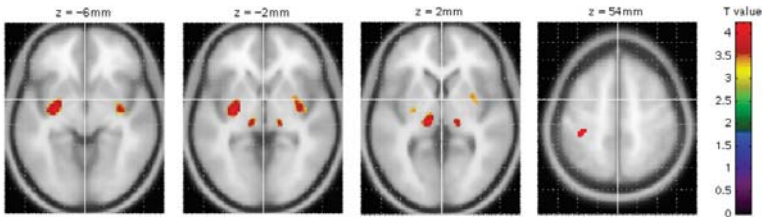
FDG-PET in migraine patients with longstanding MOH and compared the results of healthy volunteers



Before withdrawal:
Hypometabolic: bilateral thalamus, orbitofrontal cortex (OFC), anterior cingulate gyrus, insula/ventral striatum and right inferior parietal lobule

Fumal A et al. Brain (2006), 129, 543–550

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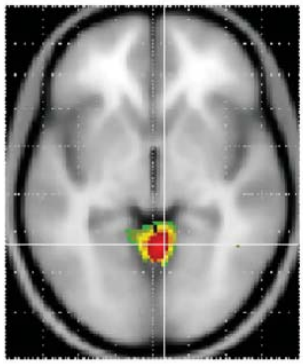
FDG-PET in migraine patients with longstanding MOH and compared the results of healthy volunteers

Before analgesic withdrawal

Hypermetabolic: cerebellar vermis.



Fumal A et al. Brain (2006), 129, 543–550

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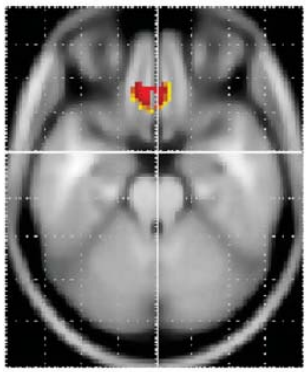
FDG-PET: 3 Weeks After Analgesic Withdrawal

- Glucose hypometabolism in the medial orbitofrontal cortex
  - Region which may be related to dependence on drugs and the high recurrence rate associated with MOH
- Orbitofrontal hypometabolism was significantly more pronounced in combination analgesic overusers vs non-narcotic analgesic overusers



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Risk of medication-overuse

- Headache
- Potential medical consequences:
  - gastrointestinal bleeds, analgesic nephropathy, barbiturate-worsened depression, etc.
- MOH causes ongoing conflict with the care provider over prescriptive scheduled medications, interfering with therapeutic alliance
- Risk of addiction and misuse by patient and others

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Resolution of MOH

- Improvement is the rule in the majority of patients after medication withdrawal
- Time to onset or time to resolution after withdrawal varies between triptans, ergotamine or analgesics
- Return to an episodic headache pattern
- In a minority (20%) the headache does not improve within 2 weeks

Diener HC Neurology 1989; 236: 9–14
Pini LA.. Cephalalgia 2001; 21: 878–83.

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Treatment

- 1st Step: Withdrawal of medication
- Education- habituated inadvertently
- Cognitive behavioral therapy
  - increasing problem-solving skills
  - changing the functional approach to pain in order to cope more effectively with disability, discomfort and distress
- "A willingness to experience continuing pain without needing to reduce, avoid or otherwise change it"
- Effective preventative migraine medications

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Always wean patients from rebound

- Wean alone can work in re-establishing EM, even with no prophylaxis
- Patients weaned, with prophylaxis and behavioral treatment, do better than with any one of these interventions alone, or no interventions
- Detoxification restores effectiveness of prevention and migraine-specific acute drugs

Kudrow. *Adv Neurol.* 1982;33:335-341; Mathew et al. Headache 1990;30:634-638; Linton-Dahlof et al. Cephalalgia 2000;20:658-662.

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Withdrawal – What to expect

- Main withdrawal symptoms:
  - worsening of the headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness
- Duration: typically 2 and 10 days (up to 4 weeks)
- Duration of withdrawal headache:
  - triptans (mean 1-4 days)
  - ergotamine (mean 6-7 days)
  - NSAIDs (mean 5-9 days)

Treatment

- Bridge Therapy-daily for 5 to 7 days or until the patient is headache-free for 24 hours
  - Corticosteroids
  - NSAIDS
  - Triptans
  - Dihydroergotamine
- After wean: provide acute medications (triptans or dihydroergotamine) for severe migraine no more than 2 days per week, fewer than 10 days/month
- Headache diary

Detoxification or Wean

- Most wean can be done outpatient slowly or with an infusion suite
- Those that will require inpatient infusion and multidisciplinary medical model offered by a structured headache program
  - High dose of narcotics or barbiturates
  - Comorbid medical illnesses that limit acute and preventative Rx
  - Severe and complicating comorbid psychiatric illnesses

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Four Levels of Weaning Patients in MOH

1. Conventional OP slow wean, slow addition of preventive medications and providing migraine-specific acute rx with strict limits
2. Conventional OP quick discontinuation with bridging medications, and quick addition of preventive medications
3. Medical model: Infusions as the bridge and quick addition of preventive medications either in infusion suite or inpatient
4. Multidisciplinary program: Day-hospital or Inpatient wean using infusions as the bridge and quick addition of preventive medications with psychology, skilled nursing, education, PT, dietary, etc

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Why admit?

- Patient doing poorly
- Emergency (suicidal, dehydrated)
- Failed outpatient therapy
- Patient desperate
- Family desperate
- Doctor desperate
- Not getting better

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Inpatient therapy: Medical Model

- Outpatient strategies work best for highly motivated patients who are competent and capable
- Reasons for admission: failed outpatient attempts
- Urgent complications: e.g. ergotism, angina, dehydration/pregnancy, psychiatric decompensation
- Patients “stuck” on narcotics (comorbid back pain)
  - Narcotics leave glutamate in the synapse, may render other treatments ineffective
- Excessive comorbid medical & psychiatric disorders
- Dangerous withdrawal
- Pearl: Check QTc prior to admission if on methadone

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Before admitting…

- Chose a goal, a “therapeutic target” that you and the patient agree upon
- If this cannot be achieved as an outpatient in a reasonable amount of time, admission may be appropriate

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Options

- Raskin protocol: repetitive dihydroergotamine [IV DHE])
- IV neurolpetics: chlorpromazine, metoclopramide
- IV valproate
- IV magnesium
- Occipital nerve blocks
- IV lidocaine
- IV ketorolac
- IV 5-HT3 antagonists
- IV steroids
- IV antihistamines: diphenhydramine
- Others

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Raskin protocol

- Repetitive IV DHE given tid, titrated to the effective sub-nauseating dose (up to 1 mg IV tid)
  - Typically 3 days
- Antiemetic 25 minutes prior:
  - Metoclopramide 10mg or prochlorperazine 10 mg or ondansetron 8 mg
- Can precede with diphenhydramine 25mg IV or po or benztropine mesylate 1-2mg (for dystonic reactions) or prn if needed
- Stop other analgesics
- Avoid in CAD, pregnancy
- Side effects respond to dose reduction: leg cramps, diarrhea
- There is a continuous infusion and SQ infusion protocol and patients can inject DHE1 mg SQ q 8 hours until headache free 24 hours

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Raskin NH.. Neurology 1986; 36: 995-997.
Ford RG, Ford KT. Headache 1997; 37: 129-136.

IV chlorpromazine

- Goal: sleep. Could use other neuroleptics
- Risks: QTc prolongation (daily EKGs), orthostatic hypotension, hypotension
- Start with 10mg IV tid. Might add oral clonazepam
- Pearl: neuroleptics suppress narcotic withdrawal symptoms nicely
- About 3 days

•Ashkenazi A, Levin M, Ward TN. Treatment of chronic daily headache with intravenous chlorpromazine (abstract S135). Presented at the 44th Annual Scientific Meeting of the American Headache Society. Seattle, Washington, June 2002

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IV valproate

- 500mg run in rapidly (≤ 5 minutes)
- Can be repeated
- Excellent choice if cardiac issues, bipolar
- Risk: encephalopathy due to hyperammonemia

Mathew NT, et al. Intravenous valproate sodium (Depacon®) aborts migraine rapidly: a preliminary report. Headache 2000; 40(9):720-723.
Krusz JC, et al. Intravenous Valproate for Treatment of Status Migrainosus in the Headache Clinic: A Retrospective Look. Headache and Pain 2006; 17(3): 121-13.

IV magnesium

- Unproven therapy
- Migraineurs have low brain magnesium
- Magnesium is an inhibitory ion, plugs calcium channels
- Safe in pregnancy
- Dose is 1-2 grams IV over 10-20 minutes. May repeat BID
- Ionized magnesium levels not generally available, ? RBC magnesium (send out lab)
- Bigal et al found it worked better in migraine with aura patients

Bigal et al. *Cephalalgia.* 2002;22:345-53

More

- Occipital nerve blockade
- IV ketorolac 30mg tid-qid for up to 5 days
- Lidocaine patches for back/neck pain up to 12 hours daily
- 100mg butalbital = 30 mg phenobarbital
- IV propofol and lidocaine

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Outpatient MOH Protocol for slow wean and addition of prevention

1. Slow taper of overused medications/caffeine over about 4-6 weeks
2. Add preventive medications slowly over 4-6 weeks

- Level 1 evidence categories:
- *Tricyclics* (eg, amitriptyline; nortriptyline and doxepin): Consensus
  -10 mg at night; increase by 10 mg per week to target dose of ~ 50 mg qhs.
- *Beta-blockers* (eg, propranolol, nadolol or metoprolol) Level 2
  -For nadolol, begin with 40 mg and increase by 40 mg/wk to 80 mg
- *Anti-epilepsy drugs*
  - Topiramate -25 mg qhs, increase by 25 mg/ week to target dose of 100 mg qhs
  - Valproate -250 mg ER qhs, increase by 250 mg to target dose of 500 mg-1 g qhs
- Onabotulinum toxinA (FDA approved for CM): Give & taper

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Outpatient MOH Protocol for slow wean and addition of prophylaxis

3. Set a quit date, generally, in week 4

   - should not longer treat low level headaches with the previously overused rebound medication or the newly provided acute migraine specific medication

4. Provide migraine-specific acute treatment for severe migraines, maximum 2 days/week

   -Never use the same medication that is being weaned, and if possible, change classes of acute medication

5. In difficult weans, a steroid course “can put a patient over the hump”

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Outpatient MOH alternative: the cold-turkey plus bridge and prophylaxis

1. Day 1: Cold turkey abrupt termination of acute rebound meds
2. Day 1: Initiate a therapeutic bridge therapy for 7–10 days

- The following bridges have been described or used by clinicians
  - NSAIDs can be used repetitively and in a scheduled manner:
  - Nabumetone: 750 mg per day
  - Naproxen: 500 mg bid
  - Steroids can be used, such as:
  - Dexamethasone 4 mg bid. for 4 days, qd for 4 day
  - Prednisone: 60 mg daily x 2 days and then taper by 20 mg/2d

Krymchantowski and Moreira. *Cephalalgia* 2003;23:982-993;
Ribeiro et al. *Cephalalgia* 2008; 28:999-1000.
Evans and Mariniak. Lancet Neurol 2010;9:391-401

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MOH Bridges, continued

Triptans can be used repetitively and in a scheduled manner:

- Sumatriptan: 25 mg tid for 10 days or until the patient is 24 hrs headache-free, whichever comes first
- Naratriptan 2.5 bid for one week
- Ergots:
  - –DHE nasal spray b.i.d. or t.i.d. for 7–10 days
  - –Methylergonovine 0.2 mg b.i.d. or t.i.d. for 7-10 days

Drucker and Tepper. *Headache*. 1998; 38:687 – 690 .
Krymchantowski and Moreira. *Cephalalgia* 2003;23:982-993.
Saper et al. *Headache* 2006;46(Suppl 4):S212-220.
Graff-Radford and Bittar. *Headache* 1993;33:390-393.

Outpatient MOH Cold Turkey protocol, continued

3. Beginning on Day 1:Start daily prophylaxis over 2 days, limited by tolerability

- Onabotulinum toxinA
- Tricyclics:
  - – Doxepin or Nortriptyline 25 mg qhs (day 1), 50 mg qhs (day 2)
- Beta blockers:
  - – Metoprolol 25 mg day 1; 50 mg day 2
  - – Nadolol 40 mg qd day 1, 80 mg day 2
- AED: rapid taper not recommended

4. At the end of the bridge, provide migraine-specific treatment such as a triptan with strict limits, maximum 2 days per week

- If the patient has difficulty, an additional steroid run can sometimes put the patient over the hump

Clinical Pearls on the Cold Turkey Protocol

- Potentially dangerous in patients on ≥ 3 tabs/day of butalbital
- May precipitate withdrawal in patients on opioids ≥ 3 tablets/day

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Multidisciplinary Program

- Involve multiple medical subspecialties:
  - psychology, skilled nursing, infusions, PT, dietary, etc
- Pain management specialist to help with management of other pain disorders: back pain, fibromyalgia, etc.
- Narcotics will require special detoxification
- Utilize non-habituating daily preventative medications
- The patient will learn strategies to limit usage of acute medications

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Response to treatment

- Success: ≥50% reduction in HA index from baseline
- Clinically meaningful: ≥25% reduction in HA index
- Monitor relapse rate

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Prognosis

- 72%–85% of patients improve
- >1/2 of patients who underwent treatment for MOH remained better and had an episodic pattern of headache 5 years later
- Preventable relapse occur

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Summary: Key Points

- Medications need to be taken on only a modest number of days per month: 5 to 10, depending on the type
- HA on ≥15 days per month, ≥ 4 hours for at least 3 months
- Co-morbid depression and anxiety are common
- Treatment options are effective
  - OP/IP/ cold turkey/slow wean
- Psychological therapy is essential
- Prognosis is good

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Four Simple Rules to Prevent Rebound

1. Use migraine-specific treatments (triptans, DHE)
   -NSAIDS can be added for synergy
2. Keep acute treatment days to <2 days per week.
3. Add daily prophylaxis at 10 HA d/mo. Or > 2 acute treatment days per week. Consider if HA frequency is climbing and frequency is 6-10 d/mo range
4. Do not use butalbital or opioids as acute treatment for migraine. Period.

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