Medication Overuse Headache

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Disclosures

- Advisory Boards: Allergan, Depomed, Teva

Learning objectives

- Participants will be able to diagnose medication overuse headache (MOH) and its various subtypes.
- Attendees will be able to describe the progression of episodic to chronic forms of headache via medication overuse.
- Participants will be able plan effective behavioral and pharmacological treatment strategies to better prevent and manage MOH.
- Attendees will be able to assess the complicated MOH patient with psychiatric comorbidities

Overview

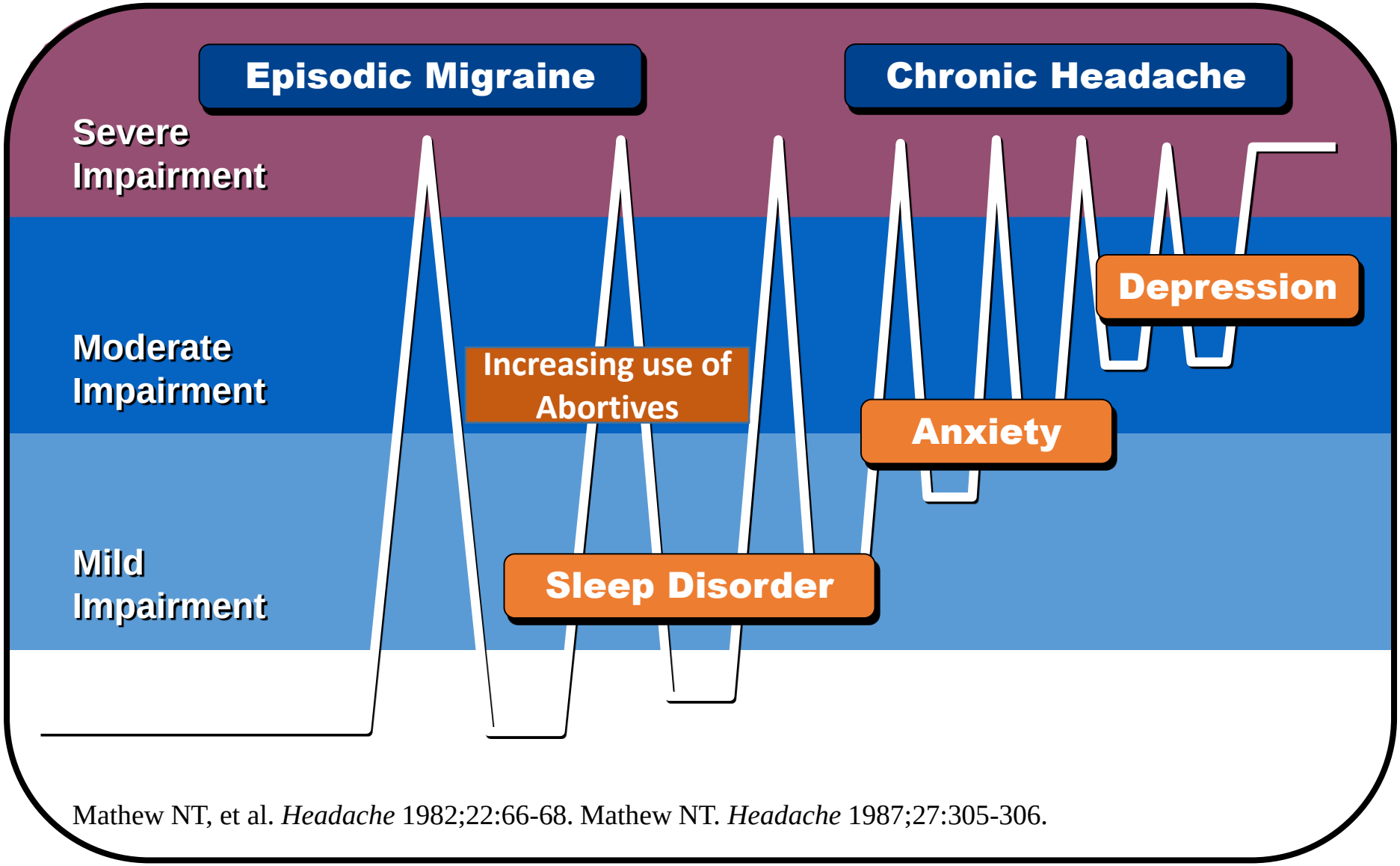
- History
- Clinical Features
- Classification and Diagnosis
- Epidemiology
- Progression to MOH
- Treatment of established MOH
- Summary and Conclusions

MOH: Early history

- Peters and Horton, 1951 reported withdrawal headaches with ergotamine tartrate.
- Kudrow, 1982- patients who were detoxified and placed on amitriptyline exhibited significantly better improvement (72%) than those not detoxified and placed on amitriptyline (30%).
- Mathew, 1982 found that majority of daily headaches are a continuum of episodic migraine, influenced and perpetuated by various factors such as neuroticism (abnormal MMPI 70% versus 12% episodic), excessive medication (52% vs. 6%) and stress related issues.
- Dichgans, Diener, et al 1984 showed withdrawal symptoms and at the end of the hospital stay chronic headache had completely disappeared or markedly improved in 77% of patients. Even after an average of 16 months of subsequent observation, chronic headache continued to be significantly improved in 70% of patients.

Peters GA, Horton BT. *Proc Staff Meet Mayo Clin*. 1951;26:153-161;
Kudrow L. *Adv Neurol 1982;* 33:335-341; Mathew NT, et al. *Headache* 1982;22:66-68.
Mathew NT. *Headache* 1987;27:305-306.; Dichgans, Diener, et al. *Dtsh Med Wochenschr* 1984 Mar 9;109(10):369-73.

Transformed Migraine



Mathew NT, et al. *Headache* 1982;22:66-68. Mathew NT. *Headache* 1987;27:305-306.

MOH: Clinical Features

- Most patients with MOH have a history of episodic migraine
- Features can change over time in the same patient and be quite different between patients but usually a gradual transformation with escalating frequency, intensity and medication usage which become refractory to acute care and preventive treatments. The quantity not quality of headaches informs the diagnosis.
- For many patient there is a self-sustaining rhythm of predictable and escalating medication use of q3-6 hours.
- Often have early morning headaches and significant neck pain that improve after discontinuation of offending agents.
- Medication withdrawal results in acute escalation of headache
- Episodic pattern may be restored after analgesic discontinuation with or without preventative treatment.
- Significant psychiatric comorbidity and sleep issues may also cloud diagnosis and often get treated without weaning.

Tepper SJ. *Continuum* 2012;18:807-22; Evers S, Marziniak M *Lancet Neurol*. 2010;9(4):391-401;
Saper JR, Da Silva AN. *CNS Drugs*. 2013;27(11):867-77

Medication Overuse Headache

- Patients with a pre-existing primary headache who, in association with medication overuse, develop a new type of headache or a marked worsening of their pre-existing headache that, in either case, meets the criteria for medication overuse headache (or one of its subtypes), should be given both this diagnosis and the diagnosis of the pre-existing headache. Patients who meet diagnostic criteria for both chronic migraine and medication overuse headache should be given both diagnoses.

Cephalalgia 2013;33(9):733-735.

ICHD-III-Beta Criteria for Medication Overuse Headache

A. Headache occurring on ≥ 15 days/month in a patient with a **pre-existing headache disorder**

B. Regular overuse for >3 months of ≥1 drugs that can be taken for acute treatment of headache

Still requires ≥ 10 days of use/month for ≥3 months of ergots, triptans, or combination analgesics but ≥ 15 days of use/month of analgesic monotherapy of NSAIDs, aspirin, or acetaminophen/paracetamol.

The old provision that the headache must revert to episodic with detoxification is gone

Cephalalgia 2013 33(9) 733-735

Epidemiology of MOH

- The prevalence rates of MOH are similar across different countries from 1-2% of the general population.
- The 6-month prevalence of MOH in Germany was 1.0% with a higher preponderance in women (74%) than men (26%) and a mean age of 53 years.
- In other countries, the prevalence rates were similar (average 1.1%), although different methods of diagnosis and different prevalence periods were used.
- The prevalence is much higher in tertiary care where up to 30% of headache patients in Europe and 50% in the USA have MOH.

Evers S, Marziniak M. *Lancet Neurol* 2010; 9: 391–401;
Stovner, et al. *Cephalalgia* 2007;27:193-210.

Risk Factors for CM/CDH Onset

Comorbidities

- Depression
- Anxiety
- Other pain disorders
- Obesity
- Asthma
- Snoring

Exogenous Factors

- Stressful life events
- Head/Neck injury
- Caffeine

Treatment-related

- Poor treatment efficacy
- **Medication overuse**

Headache Features

- Attack frequency (headache days)
- Persistent, frequent nausea with migraine
- Allodynia

AMPP; FRHE.

Incidence and Predictors for Chronicity of Headache in Patients with Episodic Migraine

- Clinic based study
- They followed 532 consecutive patients with episodic migraine for one year
- Sixty-four (14%) developed chronic daily headache
- Risk factors were high frequency at baseline and medication overuse
- The odds of developing CDH were 19.4 times higher in those overusing acute medication

Katsarava, Schneeweiss, et al *Neurology*, 2004

Progression to MOH/CM

- In a German Neurology clinic: **0-4** vs. **6-9 days/**month, Odds Ratio (OR) **6.2** for developing CM @ 1 year; **0-4** vs **10-14 days/**mo, OR **20.1** for CDH @ 1 year
- Population study confirms higher HA frequency at baseline predicts ↑HA frequency@ 1year
- AMPP surveyed 2005-2008 ("couplet") who had EM in the first year; N=11,453; Rate of new-onset CM in couplet year 2 was 3.1%; 16% for HFEM
- In AMPP, Bigal et al modeled probability of transition from EM in 2005 to MOH in 2006 in relation to medication use.
- **Any acute use at all of opiates and barbiturates is associated w/an overall increased risk of transformation to CDH**
- NSAIDs with <5-10 headache days/month reduces risk of CM transformation[4]
- NSAIDs ≥ 10-15 HA days/month associated with developing CM

Katsavara et al. *Neurology* 2004;62:788-790. Scher et al. *Pain* 2003;106:81-89; Bigal et al. *Headache* 2008;48:1157-68; Lipton et al. *Headache* 2013;53:1548-1563.

Adapted from Tepper
AHS, 2015 with permission

Acute medications and migraine progression

Abortive	Critical dosage	Comments
Opiates	8 days per month	men>women
Barbiturates	5 days per month	women>men
Triptans	Only in high frequency migraine	10-14 days/month
NSAIDS	Protective if HA< 10 M Induce progression in high frequency	

Bigal ME, Lipton RB: *Neurology* 2008; 71:742-746.

Poor Acute Care Associated with CM Risk

- AMPP study: N= 5,681 with EM in 2006; 3.1% progressed to CM in 2007
- Only 1.9% of the group with optimal acute treatment efficacy developed CM
- **The very poor acute treatment efficacy group had ≥2X increased risk of new onset CM (OR= 2.55) compared to the optimal treatment efficacy group**
- *Conclusion from AMPP*: Inadequate acute treatment efficacy was associated with an increased risk of new onset CM over the course of one year
- The hope is that optimal acute treatment might prevent progression (not yet proven)
- Clinical Management:

  1)Sustained pain-free response

  2) Behavioral approaches

  3) Daily prophylaxis to drive down # of headache days and # of treatment days

Adapted with permission from Tepper, AHS, 2015

Lipton et al. *Neurology* 2015;84:688-95.

Psychiatric Disorders in MOH

DSM-IV Dx	Precedes MOH	Follows MOH
First episode of MDD	76%	24%
Panic disorder	79%	21%
GAD	80%	20%
Social phobia	100%	0%
Substance abuse	89%	11%

Radat F et al *Cephalalgia* 2005;25:519-522

Pathophysiology

- Migraine is often associated with cutaneous allodynia which is related to central sensitization.
- Frequent use of immediate relief migraine medications leads to MOH that may share neuronal pathways with migraine.
- Sustained administration of triptans or opiates produced pronociceptive neuroadaptive changes.
- This may lead to hyperexcitability of the trigeminal system as well as engagement of descending facilitation.
- Enhanced descending facilitation is critical for allodynia and may mask the expression of diffuse noxious inhibitory controls.

De Felice M, Ossipov, MH, Porreca F. *Current Opinion in Neurology* 2011, 24; 193-196

Treatment options

- Patient Education
- Withdrawal therapy abrupt or tapered (barbiturates, opiates, benzodiazepines)
- Bridge therapy
- Preventative pharmacotherapy either immediately or wait to see if necessary after detoxification
- Behavioral treatment
- Address obesity and snoring
- Simple vs. complex patients
- Relapse prevention

Is Detoxification Necessary?

- Old evidence is that most patients did not improve without weaning them from overused immediate relief medications which also reduced effectiveness of preventive therapies.
- Evidence for CM with and without Medication Overuse (MO):
  - 2 topiramate studies for CM+MO, in one, TPM did not work in MOH, in the other it worked 50% less well than for CM without MOH
  - Subgroup analysis for OnabotulinumtoxinA in MOH at 24 weeks (after 2 cycles) reported benefit in reducing headache days −8.2 vs. −6.2 as well as secondary end points. Excluded continuous headache sufferers as well as most patients on opiates and barbiturates. The studies did not examine whether subjects would have done better if withdrawn first from overused agents.
- Recent COMOESTAS data used a consensus protocol of detoxification, prophylaxis for primary HA for majority of patients, led to removal of overuse in 2/3 of patients and 46% reverted to EM.
- Detoxification is the first consideration in patients overusing medications.

Tepper SJ. *Continuum* 2012;18:807-22; Tassorelli C, et al. *Cephalalgia* 2014;34(9):645-655;
Olesen J. *Cephalalgia* 2011; 32(5):420-422; Diener HC. *Cephalalgia* 2011; 32(5):423-427

Complex or Complicated MOH

- Diagnosis of co-existent, significant, and complicating medical illnesses.
- Current diagnosis of mood, anxiety, personality, eating or substance abuse disorder.
- Relapse after previous detoxification.
- Daily use of multiple doses of symptomatic meds
- Psycho-social and environmental problems.
- Better outcomes in simple MOH ($P<0.05$)
- Complicated MOH less likely to follow-up ($P<0.05$)

Rossi P, Faroni JV et al: *Eur J Neurol* 2011;18:396-401;
Saper JR, Hamel RL, Lake AE. *Cephalalgia* 2005; 25:545-546;
Saper JR, Da Silva AN, *CNS Drugs*. 2013 Nov;27(11):867-77.
Lake AE. *Headache* 2008; 48:26-31

Dependence-related behavior in MOH

- Recent studies in neuroimaging, suggest an overlap between the pathophysiological mechanisms of MOH and substance-related disorders.
- Compulsive drug seeking behavior in complex patients with some similarities to clinical OCD
- MOH patients had a more complex profile of psychiatric comorbidity with greater number of psychiatric diagnoses, moderate-severe anxiety and obsessive-compulsive traits as the major differentiation between MOH group and EM group.

Radat F, Lanteri-Minet M: *Rev Neurol* (Paris) 2011; 167(8-9):568-578;
Sarchielli P, Corbelli, et al. *Eur J Neurol.* 2015;0:1-7; doi: 10.1111/ene.12794;
Radat F, Lanteri-Minet M: *Headache* 2010;50(10):1597-1611;
Cupini LM, De Murtas M, et al. *Headach*e 2009; 49: 1005–1013
Fumal A, Laureys S, et al. *Brain* 2006; 129(Pt 2): 543–550.

Conclusions

- MOH is highly prevalent in a chronic headache population and almost all acute medications, if overused, will increase the frequency of headache.
- Use ICHD-3 Beta diagnostic criteria and be aware of the various clinical presentations.
- Withdrawal of offending agents will exacerbate headache but detoxification is the cornerstone of effective treatment. Strict limits on abortive agents.
- Optimize preventive pharmacological and behavioral therapies and prevent relapse
- Thorough behavioral/psychological assessment for complex MOH.