A Comprehensive Approach to Chronic Migraine:
Pragmatic Treatment Options

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Disclosures

- I pander indiscriminately on behalf of SHS
- Persona non grata with 2 triptan manufacturers (others)
- All suggested medication uses will be “off-label.”
The challenges of CM

- OnabotulinumtoxinA and topiramate are only treatments with RDBPCT evidence of efficacy
- Medication overuse is common
- Most patients complain of neck pain: cause or effect?
- There is high psychiatric co-morbidity: does it matter?
- Increasing number of interventional options: who should be referred?
- When is enough enough?
Because so many scientific theories from bygone eras have turned out to be wrong, we must assume that most of today’s theories will eventually prove incorrect as well.... No matter the domain of life, one generation’s verities so often become the next generation’s falsehoods that we might as well have a pessimistic meta-induction from the history of everything.
Hey, my migraine is gone.
Differential diagnosis of CM

- MOH
- New Daily Persistent Headache (NDPH)
  - ICHD-3 allows for migraine features
  - requires onset “clearly remembered”
  - consider thunderclap and non-TCH onset
- Hemicrania continua
  - “every patient with rCM deserves a trial of Indocin”
- IIH/SIH
  - “every patient with rCM should have an LP” vs “I try to find a reason not to do an LP.”
- Cervicogenic headache
Comprehensive Treatment Approach to CM

- Aggressively treat MOH
  - including caffeine
- Trial of DHE +/- ketorolac (self-administration)
- Usual preventives
- Consider the neck and TMJ
  - PT
  - GON blocks/TP injections
  - facet nerve blocks
- Hormonal therapy
- Address psychiatric/psychosocial issues/lifestyle
- Truly refractory options
  - Daily triptans
  - Opiates
  - Tramadol
  - referral/?inpatient unit
  - MAO-Is
Impact of continuing vs discontinuing symptomatic medication

Fig 1.—Headache Indices during the baseline period and 12 weeks of follow-up.

- **S.M.C.** Symptomatic Medications Continued
- **S.M.D.** Symptomatic Medications Discontinued
- **P.M.S.** Prophylactic Medications Continued
- **U** Unchanged
- **P.M.CH** Prophylactic Medications Changed

Which group would you like to be in?

- patients who did not stop their medicines
- patients who stopped and did nothing else
- patients who stopped and took additional preventive medicines
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Klapper JA, Stanton J. Clinical experience with patient administered subcutaneous dihydroergotamine mesylate in refractory headaches. Headache. 1992

- Telephone survey
- 43 patients with “CDH or Mw/oA”
- Results:
  - 46% ≥ 90% relief of pain
  - 77% ≥ 50% relief
  - ER use decreased in 83%
  - 80% preferred DHE to their previous therapy
  - No evidence for the development of MOH

- retrospective study of 51 patients
  - 21 EM
  - 27 CM
  - 3 CTTH
- Response:
  - 35% excellent
  - 18% good
  - 12% poor response but continued to use DHE
  - 35% had discontinued – primarily d/t side effects
  - nausea/vomiting, limb pain or numbness, chest or throat tightness, and soreness at the injection site
  - dramatic reduction ER and physician office utilization
Charles JA, von Dohln P.
Outpatient intravenous dihydroergotamine.
Headache. 2010

- 31 patients
  - 25 CM
  - 6 MOH
- Methods: continuous home IV DHE
  - days 1-2: 3 mg/24 hour
  - day 3: 1.5 mg
- Results:
  - mean headache reduction 83%
  - all but 1 converted to EM

Robbins. Headache. 1992
Methods:
- retro- and prospective studies
- 4 doses of DHE 1mg over 2 days
- Results:
  - 73% (71/97) - excellent response to DHE at two days
  - 43% (33/77) sustaining excellent or moderate relief at six weeks.

- ER populations
- 8 trials - 321 (141 ketorolac) patients
- Ketorolac ≈ meperidine at 60 minutes
- Ketorolac > IN sumatriptan
- Ketorolac = phenothiazines at 60 min
Two groups (n=14, each) migraine with alodynia

- Group 1 – *delayed* sumatriptan injection (6 mg) 4 hours after onset of attack
  - all patients continued to exhibit alodynia 2 hours after treatment
  - none of them became pain free.
  - ketorolac infusion (two 15-mg boluses) 2 hours later -> 71% pain-free

- Group 2 - ketorolac monotherapy 4 hours after onset of attack -> 64% pain-free

- Nonresponders from both groups, in contrast to the responders, had a history of opioid treatment.
Infusion of COX1/COX2 inhibitors:

- blocked sensitization in meningeal nociceptors
- suppressed ongoing sensitization in spinal trigeminovascular neurons.
- normalization of neuronal firing rate
- attenuation of neuronal responsiveness to:
  - mechanical stimulation of the dura
  - mechanical and thermal stimulation of the skin.
Common protocols for home use of DHE/ketorolac IM

- **MOH - detoxification**
  - DHE daily, or bid if needed
  - Ketorolac 60mg, with DHE, or for breakthrough pain

- **CM or prolonged attacks of migraine**
  - Use DHE if you need to take a triptan more than 2 days in a row

- **Acute migraine**
  - Ketorolac alone, or in combination with triptan

- **Menstrual migraine: DHE +/- ketorolac qd or bid prn**

- **In-office rescue:**
  - DHE 1mg + ketorolac 60 mg
  - If headache persists the next day, Decadron burst
Treatment of Chronic Migraine: A Three-Month Comparator Study of Naproxen Sodium vs. SumaRT/Nap Dexter et al. Cephalalgia 2013. IHSAbstracts

![Graph showing headache days per month](chart.png)

- **Baseline**: Group A: 18.9, Group B: 16.4
- **Month 1**: Group A: 14.4, Group B: 6.2
- **Month 2**: Group A: 18, Group B: 8.4
- **Month 3**: Group A: 16.9, Group B: 6.6

* = Group A vs. Group B p-value < 0.05
# = Month vs. Baseline p-value < 0.05
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Elimination of menstrual-related migraine beneficially impacts chronification and medication overuse.


- CM in 92%
  MOH 72%

- Strategies:
  - Low-dose OC with supplemental estrogen in menstrual week
  - Extended-cycle OC with supplemental estrogen in menstrual week
  - Natural menstrual cycle with perimenstrual application of estradiol patch

- Resolution of MRM in 81% of subjects who were compliant with HP
  - associated with:
    - reversion to episodic migraine (59% vs 18%, P < .001)
    - resolution of medication overuse (54% vs 20%, P < .001)
    - significant decreases in per capita consumption of triptans, opioids, all acute agents, and migraine preventive medications.
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Cervicogenic headache
ICHĐ-3 Beta definition

A. Any headache fulfilling criterion C
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache
C. Evidence of causation demonstrated by at least two of the following:
   • 1. headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
   • 2. headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
   • 3. cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
   • 4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply
D. Not better accounted for by another ICHĐ-3 diagnosis.
Cervicogenic headache

- ICHD-3 (beta) comment:
  It seems appropriate to add an Appendix diagnosis A11.2.5: 
  Headache attributed to cervical myofascial pain,
  and await evidence that this type of headache is more closely related to other cervicogenic headaches than to 2. Tension-type headache.
The prevalence of neck pain in migraine.

- Prospective observational study of:
  113 migraineurs/786 migraine attack days
- Regardless of the intensity of headache pain at time of treatment, neck pain was a more frequent accompaniment of migraine than was nausea (P< .0001).
- Prevalence of neck pain correlated with chronicity of headache as attacks moved from episodic to chronic daily headache.
“Field guide” for suspecting myofascial headache

- Significant ongoing neck pain in between headache episodes
- Neck pain or movement triggers or exacerbates headache
- Significant h/o neck trauma
- Clear h/o prolonged headache relief following cervical ESI or facet blocks
- TMD – pain in jaw area
150 patients with “cervicogenic” CM

- 37 – unilateral GON block
- 113 – bilateral GON block

52% w >50% reduction in headache days over next 30 days

- 60% “better”
- 30% “much better”
Open-label study of 218 patients with rCM w/o medication overuse of opiates or butalbital

Fixed-site protocol:

- 0.1 cc of 0.25% bupivicaine
- GON/LON – 10
- auriculotemporal/zygomaticotemporal – 5
- supraorbital/supratrochlear – 2

At 12 months, 53% patients had >50% reduction in headache days

Results:

• Of 2128 references, 3 RCT were included.
• The total sample was 205 subjects.
• The occlusal devices tested are stabilization, prefabricated, resilient and control appliances.
• Headache improvement ranges from 30-50% at the 12 months follow-up independent of device type.

Conclusions:
Despite these positive results, the evidence available is insufficient to support the use of occlusal devices in the management of headache associated with TMD.
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  - consider use of Clonazepam
  - office-based behavioral therapies
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Where is the lesion of chronic migraine?
CNS Activation During Migraine

Dysfunction of brain stem pain and vascular control centers

Pain Perception*
- Anterior cingulate cortex

"Migraine Generator"*
- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

*Areas of red indicate cerebral blood flow increases (P < 0.001).
(Weiller et al. 1995)
Cortical (limbic) structures which modulate pain
(with permission, from Tracy I. Nature Medicine 2010)
Neurolimbic model of migraine

- Migraine is a spectrum disorder
- Limbic influences constantly modulate pain pathways and are likely important in migraine
- The more chronic and/or refractory the headache, the more important the limbic influence
- Limbic influences include:
  - Axis I/II
  - Patient attitudes/behaviors/concerns
  - Stressors
  - Previous traumas
Psychiatric co-morbidity of CM

- Anxiety/depression
- Bipolar spectrum
- PTSD
- Personality disorders
- Somatization disorders
Does Psychiatry co-morbidity matter?

- Anxiety/depression
  - **no evidence (as yet) that treatment influences headache outcomes**
    - most of our patients are already on antidepressants
  - risk factors for transformation BUT do not reduce probability for remission
  - treatment of anxiety may offer significant improvement in headache control (personal observation)
  - improved mental health is its own reward

- Bipolar spectrum: ~8% of migraineurs
  - caution re ADs, steroids
  - impulsive pill takers → MOH
  - Mood-stabilizing AEDS are a good preventive choice (VPA > topiramate)

- PTSD/childhood abuse
  - “Touch the Pain”

- Personality disorders: 5.5% of 1000 migraineurs (Robbins)
  - pay attention to your own body “alarms”
  - consider personality disorder with “difficult patients”

- Somatization disorders – headache is not an isolated symptom
  - challenge of defining somatization in patients with chronic pain
Anxiety and Depression in Migraine

FRAMIG - 3 Lanteri-Minet et al. Pain 2005

Anxiety: 28%
Anxiety & Depression: 19%
Depression: 4%
Clonazepam as migraine preventive?

- US Headache Consortium rated clonazepam as “evidence of no efficacy”
- 1979 study: 38 patients -> 34 completed
  - clonazepam 1 mg -> 50% dec ha freq (p = .055)
  - clonazepam 2 mg -> 37% dec ha freq (p = .10)
  - placebo -> 8% dec in headache freq
  - not adequately powered
  - no correction for crossover effect
  - medication overuse headache not recognized
  - anxiety/depression not identified

Clonazepam for Refractory Headache: Three Cases Illustrative of Benefit and Risk. Maizels M. Headache. 2010

- 43 y/o mother with MA c RxO
  - headache 3-4d/wk, 30 butalbital q 2wks
  - mild fibromyalgia, subclinical anxiety
- PHQ9 – 8; GAD - 14
- d’c’d butalbital but did not improve w nortriptyline/meloxicam/rizatriptan
  - resumed butalbital
- Rx’d vnlfxn, dexa, nara; clonazepam for sleep
  - decided to take only clonazepam
- f/u 1 mo later – only 1 headache day
- f/u 3 mo later – 1 headache/mo (severe migraine → started butalbital, terminated w/ clonazepam)
Observations re clonazepam for migraine

- Clinical effect is rapid and appears independent of perceived change in mood
- Dose range is low (1 – 2 mg/d)
- Common themes of responders
  - Anxious or obsessive somatization
  - Associated symptoms
    - Paresthesias
    - Dizziness/vertigo
    - Insomnia
  - Patient often already using short-acting benzo’s, butalbital, or opiates
- Often effective as acute abortive agent
Concerns re benzodiazepines

- Escalation/habituation/withdrawal sx’s
- Psychological
  - sedation, paradoxical increase of anxiety, psychomotor impairment, memory disruption
- Physical
  - vertigo, ataxia/falls, risk of accidents
- “Downward spiral” - benzodiazepine use (but not opiate use) significantly associated with:
  - activity level (P<0.05)
  - medical visits (P<0.01)
  - domestic disability (P<0.01)
  - depression (P<0.01)
  - disability days (P<0.1).

Bizarre symptoms or beliefs

- “pseudo hemiplegic migraine”

Refusal to acknowledge mind-body connection

- either denies any stress or any possible connection between stress and headache
- “If you would just fix me . . . ”

River of symptoms

Alexithymia
Brief office-based behavioral interventions

- Provide a credible mind-body connection
- “Touch the pain”
  - ask about previous traumas
- Identify healthy aspects of the patient
  - “What were you like before pain took over your life?”
  - “What used to give you pleasure/meaning?”
- Encourage previously pleasurable behaviors
A mind-body message

The sorrow which has no vent in tears may later make other organs weep

Henry Maudsley, MD
(1835-1918)
Behavioral sleep modification may revert transformed migraine to episodic migraine.


- Sleep hygiene vs sham behavioral instructions improved:
  - Headache frequency (28.1% vs. –3.0%)
  - Intensity (39.4% vs. 12.1%)
  - 35% of the treatment group reverted to episodic headache by the 6th week of treatment compared to none of the controls
- Improvements in headache were proportionate to the number of sleep behaviors changed.
The five component sleep hygiene intervention

1. Schedule consistent bedtime that allows 8 hours in bed.
2. Eliminate watching television, reading, or listening to music in bed.
3. Use visualization technique to shorten time to sleep onset.
4. Move supper at least 4 hours before bedtime and limit fluids within 2 hours of bedtime.
5. Discontinue naps
Sometimes you need a “big gun”
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“Big Guns” for rCM

Robbins L. Refractory Chronic Migraine. Practical Pain Management 2010

- Daily triptans
- Chronic opiate therapy
- ???Psychostimulants
- MAO-Is
Daily use of triptans

- Retrospective study of 118 patients
- 90% averaged daily triptan use
- Duration of use: 6 months → > 6 years
- Hematologic and cardiac monitoring
  → “no adverse consequences over a prolonged period.”
CONCLUSION:
Only a select and very limited group (estimate of 10-20%) of refractory headache patients who meet criteria for COT respond with convincing headache reduction and functional improvement over the long-term.
Caveats for use of opiates in headache patients

- Treat non-opiate MOH
- There is no evidence that LAOs are superior to SAOs either for chronic pain or headache
- When initiating long-term therapy with opiates, instruct the patient that, once stabilized, opiate dose will never be increased in the future.
Hot Off the Press

- Omega-3 FA -> anti-nociceptive compounds
  - Resolvins
- Omega-6 Fas -> pro-nociceptive compounds
  - PGE2
- 56 randomized to:
  - High O3/ Low N6
  - Low N6
Omega 3/6 - Results

- **Biochemical markers**
  - Both interventions significantly increased n-3 EPA- and DHA-derived resolvin pathway precursors
  - significantly reduced pronociceptive precursors
  - H3-L6 intervention produced significantly more pronounced increases in 18-HEPE and 17-HDHA

- **Clinical Outcomes**
  - both groups showed statistically significant improvements in clinical outcomes (Headache Days, Severe Headache Days, Headache Hours HIT-6) compared to baseline
  - H3-L6 → significantly greater improvements in all 4 of these clinical outcomes:
    - HIT-6 score (7.5 vs 2.1; P < 0.001)
    - number of Headache Days per month (8.8 vs 4.0; P = 0.02), compared to the L6 group.
    - Probability of severe headache day: 66 -> 38% vs 68 -> 61%)
Hey, my migraine is gone.
Therapeutic Effect of Nasal Oxytocin in Chronic Migraine: Dependence on Cytokines. Yeomans et al.
Conclusion

- Treatment of MOH is the first step in treating CM.
- The more tools you have, the more people you will help.
- “It takes a village …”