

Neurology Update Migraine Headaches

Ralph T. Dunnigan, M.D.
Mid Dakota Clinic
Bismarck ND

Disclosure Statement

- DISCLOSURE OF CONFLICT OF INTEREST
- A commercial interest is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.
- Neither I, nor an immediate family member (parent, sibling, spouse, partner, or child), has any financial relationship with or interest in any commercial interest connected with this presentation.
- The content of my presentation WILL NOT include discussion of unapproved or investigational uses of products or devices.

Objectives

- Discuss Diagnosis of Migraine
- Review present standard of care treatment of acute migraine treatment
- Review present standard of care treatment for prevention of migraines

Diagnosis of Migraine

Criteria for diagnosis of "migraine without aura"	
International Headache Society Diagnostic Criteria ¹	STUDIO 54 Mnemonic
A At least 2 of the following characteristics	A At least 2 of
1 Moderate or severe intensity	Severe
2 Pulsating quality	Throbbing
3 Unilateral location	Unilateral
4 Inhibits or prohibits daily activities	Disabling
B At least 1 of the following symptoms	B At least 1 of
1 Nausea or vomiting	Intestinal symptoms
2 Photophobia and phonophobia	Orophobia/photophobia
C Attacks have occurred	C Both of
At least 5 times,	5 Attacks
Lasting 4-72 h each	4- To 72 h duration

Acute Migraine Treatment

- Goal is to reduce disability caused by migraine
 - Shortening the attack
 - Reducing the severity
- Treatment Approaches
 - Stratified Approach
 - Medication chosen based on migraine severity and the resulting disability
 - Best medication first approach
 - Step Care Across Attack Approach
 - Less expensive/safer medications used first, working up the ladder
 - Step Care Within Attack Approach
 - May work in selected patients with graduated headaches, but need to monitor effectiveness as time delay in taking stronger medication may result in prolonged morbidity and headache

Acute Migraine Treatment

- Early treatment is important
- Ongoing dialogue is important as sometimes medications don't work
- May need more than one type of treatment for more than one type of migraine in the same patient
- Medication choice based on many factors (comorbid conditions, presence of nausea/vomiting ect.)
- Two or more medications can be combined if necessary
 - sumatriptan and naproxen
 - triptan plus medication for nausea

Acute Migraine Treatment

- Overuse of Acute medications for migraine needs to be avoided
 - Use of NSAIDs or acetaminophen > 15 days per month
 - Use of combination analgesics, opioids, ergots, or triptans 10 days per month
- Opiates generally should be avoided except in certain circumstance
 - Usually less effective than other medications
 - Lead to escalation of acute migraine treatment, thought to alter receptors and ultimately make headaches more refractory over time
 - Lead to medication overuse

Acute Migraine Treatment APAP and NSAIDs

- Acetaminophen – may be suitable for mild migraines, but less effective than NSAIDs
 - 1000 mg per dose, short half life
- Ibuprofen
 - Studies showed that dose greater than 400 mg no more effective for migraine than the 400 mg dose
- naproxen sodium
 - Slower onset but longer lasting
 - Dose 550 or 650 mg (naproxen sodium), maximum dose 1375 mg per day
- diclofenac potassium – Only FDA approved NSAID for migraine
 - Not as good, avoid dose 50 mg, up to 150 mg per day can be used
 - Powder version (Cambia) 50 mg
- ASA – effective as a fast acting, effective as sumatriptan 50 mg
 - Dose 975 to 1000 mg
- Oral ketorolac not proven effective although IV form has been

Acute Migraine Treatment Triptans

- Should be considered first line in patients with severe headaches
- There is no preferred triptan, all have strong evidence for efficacy
 - Decisions based on
 - Patient preference
 - Cost
 - Delivery method (nausea ect)
 - Type of migraine (menstrual prevention)
 - Recent meta-analysis found eletriptan 40 mg (Relpax) and rizatriptan 10 mg (Maxalt) provided highest pain relief at two hours
 - Recent meta-analysis found eletriptan 40 mg (Relpax) highest 24 hour pain relief

Acute Migraine Treatment Triptans

- Headache recurrence within 24 hours treated with redosing, possibly adding naproxen sodium, or with a different triptan
- Frovatriptan (Frova) and naratriptan (Amerge) have slower onset of action and longer half life

Acute Migraine Treatments Rescue for Triptan Failures

- Ketorolac 30-60 mg IM, self injection at home
- Indomethacin 50-75 mg orally or suppository
- Dexamethasone (4mg tablets, disp#5, two now, two later today and if headache persists take additional one pill in the am)
- Tramadol with APAP
- Combination analgesics with opiates used sparingly

Acute Migraine Treatment Problem Medications

- Opioids/Opiates should generally be avoided
 - Thought to alter receptors and ultimately make headaches more refractory over time
- Butalbital compounds (Fioricet) – high risk for escalation and overuse
- Intranasal butorphanol (Stadol) – high potential for abuse

Acute Migraine Treatment

Antiemetics

- Promethazine (Phenergan)
 - Typically 25 to 50 mg orally or topically
- Metoclopramine (Reglan)
 - 10 mg up to four times per day
- Prochlorperazine (Compazine)
 - 10 mg up to four times per day orally
 - 10-25 mg suppository (maximum 50 mg per day)
- Ondansetron (Zofran) (5-HT3 receptor antagonist)
 - 4 mg to 8 mg QID up to every 4 hours
 - Warning about prolonged QT, Torsades de pointes
 - ECG monitoring recommended in some cases
 - May cause Serotonin Syndrome by itself
- May be used with other acute therapies

Preventative Migraine Treatment

- Recommended for recurring migraine attack that interfere with quality of life
- Frequent headaches (for or more per month or more than 8 headache days per month)
- Failure or contraindication, or overuse, or side effects from acute medications
- Patient preference
- Complicated migraine (hemiplegic, brainstem)

Preventative Migraine Treatment

- Need to manage expectations
- Success is considered reduction in frequency or days by 50% in 3 months
- Experts say prevention is underutilized in that only 13% of migraine patients on preventative medications

Preventative Migraine Treatment

- Choice based on best Proven Efficacy
- Choice based on Risk/benefit analysis
- General guidelines
 - Start low
 - Consider comorbid states and other medical factors
 - Adequate treatment trial up to 2-6 months
 - Realistic expectations
 - Reevaluate therapy
 - Always consider pregnancy risks in females
 - Involve patients in their care
 - Discuss side effects in advance

Preventative Migraine Treatment

- Goal initially is monotherapy
- Take into account comorbid conditions
 - Sometimes requires two medications (tricyclic at low dose for migraine, SSRI or SNRI for depression)
- Prevention goal are for 6-9 months of control then slow taper and reinstitution as necessary (but relapse rate is high)

Preventative Migraine Treatment

Beta Blockers

- Nonselective - propranolol
- B1 selective - metoprolol, atenolol, bisoprolol, nadolol, timolol
- Those with sympathomimetic activity not effective - pindolol (Visken), acebutolol (Sectral)
- Contraindicated in asthma, COPD, AV conduction defects, Raynaud's, PVD, severe DM
- Up to 50% effective

Preventative Migraine Treatment Antidepressants

- Efficacy is not thought to be related to treating underlying depression in most cases
- Amitriptyline is TCA used most commonly and only one for which data supports its use. We do sometimes try or substitute other with less side effects at times
 - Need to go slow due to side effects: dry mouth, constipation, dizziness, urinary retention, blurred vision
- SSRI, SNRI data is mixed, generally disappointing except with venlafaxine
 - Use with low dose tricyclics may be helpful in patients with comorbid depression

Preventative Migraine Treatment Calcium Channel Blockers

- Often used still but efficacy in real studies is lacking
- May be some benefit with brainstem migraines (anecdotal)
- No longer recommended

Preventative Migraine Treatment Antiepileptic Drugs

- Valproic Acid – 43-48% response at dose 500-1500 mg per day across studies.
 - ER preparation best tolerated doses up to 1000 mg per day
 - Caution in women
 - Needs monitoring
- Topiramate – comparable to amitriptyline in efficacy
 - Typical dose 25-100 mg per day
 - Common side effects: paresthesias, difficulty concentration and memory (dose related), fatigue
 - Rare angle closure glaucoma within 2 weeks of starting therapy, stop immediately if there is eye pain
 - Kidney stones 1.5%, 2.4 fold increase
 - All doses less than 200 mg per day thought generally not to interfere with Oca, but some argument about this.
 - Lab monitor for hyperchloremic non-anion gap metabolic acidosis (stop if bicarb/CO2 levels <18)
 - Reclassified as category D pregnancy in 2011 due to slightly higher cleft lip/palate
- Gabapentin – generally not effective

Preventative Migraine Treatment Antiepileptic Drugs

- Lamotrigine – limited data, may be effective in migraine with prolonged aura

Preventative Migraine Treatment Other Blood Pressure Medications

- ACE Inhibitors
 - Lisinopril – limited data but small controlled trial showed efficacy at 10-40 mg per day
- Angiotensin Receptor Antagonists (ARB)
 - Candesartan – limited data but small controlled trial showed efficacy at 16-32 mg per day

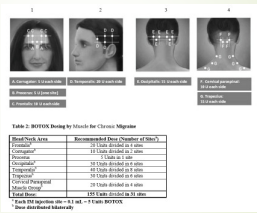
Preventative Migraine Treatment Antihistamines

- Cyproheptadine – H1, 5HT2 and muscarinic cholinergic receptor antagonist
 - Used widely in children for migraine prevention
 - Dose ranges from 12-36 mg per day
 - Shown in a single study to be as effective as propranolol 80 mg per day
 - May inhibit growth in children
 - Reduces efficacy of SSRIs
 - Side effects sedation, weight gain, dry mouth, lightheadness

Preventative Migraine Treatment Botox

- Approved for patients with 15 or more headache days per month with each headache lasting longer than 4 hours
- Efficacy in study resulting in FDA approval was 62 %
- Keeping a headache calendar for up to three months prior to injection required by some insurance companies
- 31 standard injections over the scalp for 150 units then 45 units used for 'follow the pain' protocol

Preventative Migraine Treatment Botox



Head/Neck Area	Recommended Dose/Number of Sites*
Forehead	75 Units divided as 3 sites
Crow's feet	75 Units divided as 3 sites
Between brows	75 Units as 3 sites
Chin/neck	45 Units divided as 3 sites
Neck/neck	45 Units divided as 3 sites
Submental	45 Units divided as 3 sites
Suboccipital	45 Units divided as 3 sites
Suboccipital	45 Units divided as 3 sites

* One 150 Unit vial of BOTOX contains 150 Units of BOTOX. Use 45 Unit vials.

Preventative Migraine Treatment Other considerations

- Women with migraine with aura that use estrogen based OCs are at 1.5 times the risk of stroke, and if they smoke and use OCs the risk is 5 times
- Women who smoke and have migraine with aura are at 2 times the risk of stroke, even without the use of OCs
- Migraine prevention in some studies has been shown to be much less effective in patients that smoke, the threshold seems to be 5 cigarettes per day

Preventative Migraine Treatment Other Considerations

- Lifestyle issues cannot be stressed enough to patients with migraines
- Treatment of migraines is a team sport, and if the patient isn't on the team, it usually results in a loss
- Headache calendars are very effective for getting patients involved in their headache management
- It is important to treat the comorbid issues, especially insomnia, anxiety and depression

Preventative Migraine Treatment Other Considerations Behavioral Management

- Relaxation Training, thermal biofeedback, EMG biofeedback and CBT have been shown helpful for migraine prevention (some studies average 32-49% reduction in headache scales)
- Helpful to minimize use of acute medications and in identifying triggers and relieving anxiety
- Recommended for pregnant and lactating women
- Emerging evidence that aerobic exercise reduces headache frequency

Nutraceuticals for Headache

- 80% of patients with headaches use complementary or alternative medications to manage headaches (supplements)
- Many patients prefer 'natural' treatments over prescription
- Using non-prescription medications that are proven often adds to the doctor/patient relationship as they respect your willingness to do something other than just prescribe the regulars
- Nutraceuticals many times complement and may augment a standard treatment protocol for migraines

Nutraceuticals for Headache Riboflavin

- Riboflavin (vitamin B2) – important role in mitochondrial energy production
- Riboflavin 400 mg per day in one study offered 59% of patients 50% or greater improvement in headaches as compared to 15% in placebo
- Another study compared combo of Feverfew 100 mg, Mg 300 mg and Riboflavin 400 mg vs Riboflavin 25 mg vs placebo and both treatment groups 40% of patients had 50% reduction in headaches
- AAN Guidelines: Riboflavin if probably effective for prevention of migraines
- Side effects diarrhea, polyuria rarely occur, causes bright yellow urine
- Recommended dose 400 mg per day

Nutraceuticals for Headache Coenzyme Q10

- Evidence that migraine is associated with mitochondrial energy depletions, CoQ10 is considered
- CoQ10 is an electron carrier in the electron transport chain, cofactor in maintaining mitochondrial energy stores
- Few studies
 - 48% of 42 patients had greater than 50% reduction in headaches (300 mg per day) vs 14% in placebo
 - Two pediatric studies at 1-3 mg/kg/day demonstrated statistically significant reduced migraine frequency
- AAN Guidelines: Possibly effective in treatment of migraines
- May be effective in children: lower quality of evidence
- Side effects <1% anorexia, dyspepsia, nausea, diarrhea
- Dose 100 mg TID for Adults

Nutraceuticals for Headache Magnesium

- Mg binds to and inhibits NMDA (glutamate) receptors
- Many studies demonstrate low Mg levels in migraine patients
- Data suggests Mg more effective in patient with aura
- Studies are mixed
- AAN has no recommendations on use of Mg
- Experts argue that trial of Mg for migraine with aura is reasonable in some cases, dose Mg Citrate 300 mg per day
- Side effects diarrhea, flushing, weakness

Nutraceuticals for Headache Butterbur (Petasites hybridus)

- Petasites has antihistamine properties, inhibits calcium channels
- Sold as Petadolex since 1988
- Studies are mixed and some experts raise concern about risk/benefit due to potential liver toxicity
- Dose: 100 mg once daily
- AAN recommends use of butterbur, but many experts argue against it for safety reasons
- Side effects mild GI discomfort, cholestatic hepatitis
- If patients do use this, need liver monitoring

Nutraceuticals for Headache Feverfew

- Tanacetum parthenium (chrysanthemum family)
- Mechanism mostly unknown
- AAN guidelines suggest possibly effective
- Average study dose 100 mg per day
- Well tolerated but 'post feverfew syndrome' reported with arthralgia and mouth ulcers

Nutraceuticals for Headache Melatonin

- Data is limited and conflicting
- AAN has no recommendations

References

- Continuum Lifelong Learning in Neurology, Aug 2015, Volume 21, Number 4
- Schoenen J, Jacqy J, Lanzaerts M. Effectiveness of high dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology*, 1998;50(2):466-470. doi:10.1212/WNL.50.2.2.466
- Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004;44(9): 885-890
- Sandor PS, DiClemente L, Coppola G, et al. A randomized controlled trial of coenzyme Q10 in migraine prophylaxis. *Neurology* 2005;64(4):713-715
- Koseoglu E, Talasiloglu A, Gomul AS, Kula M. The effects of magnesium prophylaxis in migraine without aura. *Magnes Res* 2008;21(2): 101—108

References

- Prietto JM: Update on the efficacy and safety of Petadolex, a butterbur extract for migraine prophylaxis. *Botanics Targets Ther* 2014;4:1-9
- <http://migraine.com/wp-content/uploads/2013/03/Botox-Injection-Sites-Migraine.pdf>

Thank You

