Preventive treatment of migraine

Elizabeth Loder, MD, MPH
Chief, Division of Headache
Department of Neurology
Brigham and Women’s and
Brigham and Women’s Faulkner Hospitals
Boston, MA
Disclosures

• No financial connections with drug or device companies
• Immediate past president of the American Headache Society, which created and endorsed guidelines I will discuss
• Salary support from the British Medical Journal
• Many preventive treatments are not FDA-approved
Objectives

• Recognize clinical situations in which preventive treatment for migraine should be used
• List four treatment principles that increase the likelihood of successful preventive migraine treatment
• Identify, based on guidelines, four top tier migraine preventive medications and some which should not be used
Definition

“…designed to keep something undesirable such as illness, harm, or accidents from occurring”

Something to emphasize to patients: preventive treatment is taken every day, even when you do not have a headache.

http://www.oxforddictionaries.com/us/definition/american_english/preventive
Definitions

- There is substantial overlap between abortive and preventive treatments
- Examples:
  - Nonsteroidal anti-inflammatory drugs
  - Triptans
  - Beta blockers
  - Biofeedback and other relaxation strategies
• They don’t always work
• They don’t always work well
• They have side effects
A small thing at the level of the patient, but a BIG thing nonetheless

© Primary Care Network
Prevention is underappreciated

- Preventive headache treatments belong to “a distinguished group of underappreciated preventive medical interventions”
  - Shortcomings loom large
  - “Headaches that never happen” may not be noticed

Headache Prevention Timeline

- 1962: Methysergide
- 1960s and 70s: Tricyclic antidepressants
- Late 60s and 1970s: Beta adrenergic blockers
- 1980s: Calcium antagonists
- Late 80s, 1990s: Valproate
- Late 90s, 2000s: Topiramate
- 2000s: Onabotulinum toxin A
“It was quite astonishing how this drug changed physicians’ thinking about the nature of migraine. This drug’s ability to antagonize certain actions of serotonin abruptly transformed migraine from a psychological problem to a scientific one.”

When should prevention be considered?

- Frequent headaches
- Failure, contraindication to, or troublesome side-effects from acute medications
- Overuse of acute medications

Special situations

  e.g. headaches with profound disability or consequences

Preventive treatment goals

Decrease attack frequency, intensity, duration

Improve responsiveness to acute treatment

Improve function

Reduce need for acute treatment
Treatment principles

“Start low, go slow”

Adequate treatment duration and dose
Choose treatments based on comorbidity and side effects: think about reproductive toxicity

Quantify treatment effects

Reevaluate treatment at regular intervals

Classes of Migraine Preventives

• Antiepileptic drugs
• Antidepressants
• Beta-adrenergic blockers
• Calcium channel antagonists
• Serotonin (5-HT) antagonists
• Neurotoxins (eg, onabotulinumtoxinA)
• ACEI/ARBs
• Vitamins, herbs, minerals
Guidelines and Evidence Reviews

- EFNS (2011)
- Canadian Headache Society (2012)
- AHRQ evidence-based report (2013)

<table>
<thead>
<tr>
<th></th>
<th>AAN/AHS</th>
<th>Canadian</th>
<th>EFNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Search dates</strong></td>
<td>Through 5/09</td>
<td>Through 6/11</td>
<td>Through 1/09</td>
</tr>
<tr>
<td><strong>Planned update</strong></td>
<td>Not reported</td>
<td>“at least every 2 years”</td>
<td>“should be done every 3 years”</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>“…randomized adult patients with migraine to agent under study or comparator”</td>
<td>“prospective, randomized, controlled trials…”</td>
<td>“Papers published in English or German..a review book..the German treatment recommendations…”</td>
</tr>
<tr>
<td><strong>Methods of classification</strong></td>
<td>Level A, B, C, U  A: established efficacy, should be offered; B: Probably effective, should be considered; C: Possibly effective, may be considered. U: uncertain, insufficient</td>
<td>Level of evidence rated high, moderate, low or very low; then graded strong or weak based on balance of benefits and harms</td>
<td>Grade A, B, C (drugs of first choice, drugs of second choice, drugs of third choice)</td>
</tr>
</tbody>
</table>
Do guidelines agree?

Highest level in AHS/AAN and Canadian guidelines:

– Divalproex
– Metoprolol
– Propranolol
– Topiramate

2012 AAN/AHS Guidelines
Level A Drugs: “should be offered”

- $\geq$ 2 RCTs showing efficacy. 6 drugs
- Beta-blockers:
  - metoprolol, propranololol and timolol
- AEDs:
  - topiramate and divalproex/sodium valproate
- Butterbur
2012 AAN/AHS Guidelines
Level B Drugs: “should be considered”

• 1 RCT or ≥ 2 less rigorous studies. 10 drugs
• Includes amitriptyline, feverfew, several NSAIDs, riboflavin (Vit B2) and venlafaxine
2012 AAN/AHS Guidelines
Level C Drugs: “may be considered”

- A single less rigorous study. 11 drugs
- **New**: lisinopril and candesartan
- Includes Clonidine, carbamazepine, coenzyme Q10
2012 AAN/AHS Guidelines
Level U Drugs

• “Insufficient data to support or refute…” i.e. methodologic shortcomings or conflicting study results

• 14 drugs

• Includes: gabapentin, verapamil, indomethacin, fluoxetine, proprtriptyline and acetazolamide.
2012 AAN/AHS Guidelines
Ineffective: “should not be offered or considered”

• “possibly or probably ineffective”

• Includes: lamotrigine, montelukast, oxcarbazepine and telmisartan.
# NSAIDs For Prevention

<table>
<thead>
<tr>
<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoprofen</td>
<td>Flurbiprofen</td>
<td>Asprin</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Mefenamic Acid</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman, E. Evidence-Based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Neurology 2012;78;1346-1353
Complementary Preventives

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petasites (50mg-75mg BID)</td>
<td>Magnesium (400-1200mg/d)</td>
<td>CoQ10 150mg BID</td>
</tr>
<tr>
<td>MIG-99 (feverfew) 6.25mgTID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin 400mg/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman, E. Evidence-Based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Neurology 2012;78;1346-1353
A different perspective...

• AHRQ review reached different conclusions
• They emphasize the overall benefits of ACEIs and ARBS...mostly driven by quality scores for individual studies and benign side effect profile

“All approved drugs, 4 off-label beta blockers, 2 angiotensin-converting enzyme inhibitors and 1 angiotensin receptor blocker outperformed placebo in reducing monthly migraine frequency by ≥50% in 200-400 patients per 1,000 treated.”

“...there were no statistically significant differences in benefits between approved drugs. Off-label angiotensin-inhibiting drugs and beta-blockers were most effective and tolerable for episodic migraine prevention.”
Figure B. Bayesian network meta-analysis of clinical response to drugs versus placebo (66 RCTs of 14,774 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults

<table>
<thead>
<tr>
<th>Active drug (RCTs in network meta-analysis/subjects in the analyses)</th>
<th>Median Bayesian Odds ratio (2.5%; 97.5 CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
</tr>
<tr>
<td>Topiramate (16/1,812)</td>
<td>2.48 (1.69, 3.60)</td>
</tr>
<tr>
<td>Divalproex (8/419)</td>
<td>3.24 (1.97, 5.61)</td>
</tr>
<tr>
<td>Propranolol (24/1,172)</td>
<td>2.87 (2.04, 4.15)</td>
</tr>
<tr>
<td><strong>Off label</strong></td>
<td></td>
</tr>
<tr>
<td>Angiotensin inhibiting drugs (5/180)</td>
<td>5.85 (2.53, 14.65)</td>
</tr>
<tr>
<td>NSAID (9/11,442)</td>
<td>2.54 (1.42, 4.66)</td>
</tr>
<tr>
<td>Beta-blockers (17/714)</td>
<td>3.37 (2.31, 5.30)</td>
</tr>
<tr>
<td>Antidepressant (10/595)</td>
<td>2.12 (1.33, 3.59)</td>
</tr>
<tr>
<td>Antiepileptic (9/457)</td>
<td>2.16 (1.32, 3.52)</td>
</tr>
<tr>
<td>Ergot alkaloids (2/259)</td>
<td>1.50 (0.63, 3.74)</td>
</tr>
<tr>
<td>Clonidine (7/271)</td>
<td>3.66 (2.04, 6.49)</td>
</tr>
<tr>
<td>Ca++ blockers (4/136)</td>
<td>2.77 (0.99, 6.30)</td>
</tr>
</tbody>
</table>

CrI = credible intervals; NSAID = nonsteroidal anti-inflammatory drugs
Clinical response was defined as ≥50% reduction in monthly migraine attacks or perceived clinically important treatment success. We used heterogeneous random effects model that assumes correlation within study (rho = 0.5) and heterogeneous between studies (WinBUG codes are in Appendix B).
A healthy 24 year old woman with migraine has used 32 tablets of sumatriptan in the last month. When questioned, she says the drug works well. She uses it 2-3 days/week and often has to redose. What is the next best step?

A. Replace sumatriptan with naproxen
B. Switch to subcutaneous sumatriptan
C. Discuss preventive treatments with her
D. Arrange for 3 days of DHE in the infusion center
E. Watchful waiting
Attack Frequency at Baseline Predicts CDH at Follow-Up

*Top line predicted incidence of intermediate frequent headaches (105 to 179 days/year)
Bottom line shows predicted incidence of CDH (180+ days/year).

The patient is reluctant to take medication every day for a problem that isn’t daily, but after discussing the matter she agrees to try preventive medicine and to learn biofeedback.

What would you recommend?
# Common Preventive Medications

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Medication</th>
<th>Usual Daily Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Atenolol</td>
<td>50-100 mg</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Propranolol ✓</td>
<td>80-240 mg</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Metoprolol</td>
<td>50-150 mg</td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>Verapamil</td>
<td>180-480 mg</td>
<td>Downgraded, favorable AE profile</td>
</tr>
<tr>
<td>A</td>
<td>Divalproex sodium ✓</td>
<td>250-1500 mg</td>
<td>FDA pregnancy category X</td>
</tr>
<tr>
<td>U</td>
<td>Gabapentin</td>
<td>300-1800 mg</td>
<td>Downgraded, favorable AE profile</td>
</tr>
<tr>
<td>A</td>
<td>Topiramate ✓</td>
<td>25-150 mg</td>
<td>FDA pregnancy category D</td>
</tr>
<tr>
<td>B</td>
<td>Amitriptyline</td>
<td>10-150 mg</td>
<td>Downgraded but strong clinical impression of benefit</td>
</tr>
<tr>
<td>B</td>
<td>Venlafaxine</td>
<td>37.5-150 mg</td>
<td>Well tolerated, not sedating</td>
</tr>
<tr>
<td>C</td>
<td>Cyproheptadine</td>
<td>2-8 mg</td>
<td>Pediatric population, sedating</td>
</tr>
</tbody>
</table>

The patient calls back a month later to say that there is no change in her headaches. She is tolerating propranolol well, however.

What would you do?

A. Remind her that preventive drugs can take 2-3 months to show benefit
B. Increase the dose of propranolol
C. Add a small dose of topiramate to the propranolol
D. Switch from propranolol to another drug
What is an adequate trial of prevention?

- Duration? 2 - 3 months
- Dose At target dose
- Monitoring Tracked with diary or calendar
- Combinations? Maybe…
Is combination therapy better than single tx?

• Standard therapeutic trials to start with
• Then: Rational co-pharmacy or combination therapy
  – Standard of care for most other chronic medical conditions
  – Targets multiple pathophysiological mechanisms
  – Can address comorbidities

Evidence to support combination therapy

• Beta blocker + valproate
  – Effective in more than 50% of previously resistant cases, but 20% were unable to tolerate low doses

• Beta blocker + topiramate
  – 60% of those patients had 50% or greater reduction but 17% discontinued due to AEs
Propranolol added to topiramate

- Subjects with chronic migraine randomized to topiramate (50-100 mg/day); then either 240 mg propranolol LA or placebo were added.
- Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24) compared with baseline (weeks -4 to 0).
- Stopped early for futility.
- The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs topiramate a not significantly different:
  4.0 vs 4.5 days (28-day headache rate; p = 0.57) and
  6.2 vs 6.1 days (total 28-day headache rate; p = 0.91).

Mean change in number of migraine days per 30 days

Optimised acute treatment plus:
- Placebo
- β blocker
- Placebo + behavioural migraine management
- β blocker + behavioural migraine management

Change in migraine days/30 days

Month

Run-in

Behavioural migraine management and dose adjustment

Evaluation

©2010 by British Medical Journal Publishing Group

Holroyd K A et al. BMJ 2010;341:bmj.c4871
Several years later, despite aggressive attempts at preventive treatment with multiple medications, the patient has migraine 18-20 days/month. Which of the following is/are FDA approved for chronic migraine?

A. Topiramate
B. Onabotulinum toxin A
C. Amitriptyline
D. Topiramate and onabotulinum toxin A
Onabotulinum toxin type A: approved for chronic migraine only

- 155 Units administered intramuscularly (IM)
- 31 injections divided across 7 specific head/neck muscle areas.
- Repeated every 12 weeks.
- Few drug interactions
- Rare cases of systemic side effects
- Local irritation, neck pain (9%)

Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial *Cephalalgia* April 5, 2012 0:0333102412441721v1-333102412441721
Optimize Preventive Therapy With a Diary

• The basics:
  – Track headache frequency and severity
  – Record acute medications and response
  – Are we achieving our acute and preventive goals?

• Customize for individual patients:
  – Monitor nonpharmacological goals
    • e.g. exercise program, fluid intake, etc.
  – Track potential risk factors
  – Menstrual cycle
Patient headache calendar from the New England Center for Headache. Patients are asked to track the severity of each headache, medication intake, menstrual cycles, triggering events, and degree of relief from acute care medication on a calendar. The completed calendars are discussed with the patient at each revisit and form the basis for treatment decisions (1999 The New England Center for Headache)

• Patient recall of headache frequency vs diary: frequency recall accurate over a 4 week period but patients recalled a higher intensity of headaches than diaries showed.

• It seems unlikely that patient recall of headaches that occurred in the distant past is particularly accurate, however.

Behavioral treatments

• “Relaxation training, thermal biofeedback combined with relaxation training, electromyographic (EMG) biofeedback, and cognitive-behavioral therapy are all modestly effective in treating migraine when compared to a wait-list control.”

Behavioral treatments

Fig 2.—Meta-analyses of behavioral and pharmacological treatments for migraine: percentage improvement scores by treatment condition. RLX: relaxation training; BF: biofeedback; EMG: electromyographic; CBT: cognitive-behavioral treatment; Ceph. Vaso. BF: cephalic vasomotor biofeedback.

Physical treatments

• 6 small trials of acupuncture: “mixed results”
• A few, small trials for:
  • transcutaneous electrical nerve stimulation (2 trials)
  • cervical mobilization and manipulation (1 trial)
  • occlusal adjustment (1 trial)
  • hyperbaric oxygen (1 trial)
• “There are insufficient data about any of the physical treatments to draw conclusions about their efficacy.”

Figure 1 The stimulation electrode placed on the forehead covers the supratrochlear and supraorbital nerves. Reproduced with permission from STX-Med.

Figure 3 Study outcomes (A) Decrease in number of migraine days over the trial duration compared to run-in in verum and sham groups.

“As medical journal editors we are convinced that the requirement for prospective trial registration is the single most valuable tool we have to ensure unbiased reporting. It allows us to make sure that the published paper accurately reports the prespecified trial outcomes, samples sizes, and other planned analyses. It is the only way to identify outcome reporting bias and other deviations from the planned study to prevent such distortions from reaching publication.”

Weber, Merino, Loder. Trial registration 10 years on. BMJ 2015;351:h3572
Proportion of subjects achieving a 50% or greater reduction in frequency

Lisinopril
Candesartan
Topiramate
Riboflavin
Beta blocker
Valproate

When should treatment be adjusted, changed or discontinued?

American College of Physicians and American Academy of Family Physicians 2002

“After a period of stability...”

US Headache Consortium 2000

“After a period of stability, consider tapering or discontinuing treatment.”
When should treatment be adjusted, changed or discontinued?

| British Association for the Study of Headache | 2000 | “Prophylactic drugs that are effective should be continued for 4-6 months then withdrawn (stopped abruptly or tapered) to establish continued need. Uninterrupted use over a year or longer is rarely appropriate.” |
| Canadian Headache Society | 2012 | Review after 6 months, but longer treatment for patients with frequent or severe migraine...can be continued for a long time |
Figure 3  Change in the number of migraine days from open-label endpoint values during the double-blind phase. Bars indicate 95% CI for the comparison with baseline. Below the graph are numbers of patients assessed for each period. Numbers are higher for th...
Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial

Annals of Neurology
13 Nov 2015 DOI: 10.1002/ana.24534
Further study details as provided by Beth Israel Deaconess Medical Center:

Primary Outcome Measures:
  - Migraine frequency [Time Frame: Month 9] [Designated as safety issue: No]
    Frequency of migraine attacks

Secondary Outcome Measures:
  - Duration of Migraine [Time Frame: Month 9] [Designated as safety issue: No]
    Duration of each migraine attack

Estimated Enrollment: 80
Study Start Date: September 2010
Estimated Study Completion Date: December 2015
<table>
<thead>
<tr>
<th></th>
<th>Key</th>
<th>Peer</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>4 (14)</td>
<td>6 (21)</td>
<td>0.53</td>
</tr>
<tr>
<td>Asthma</td>
<td>4 (14)</td>
<td>2 (7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Raynaud's</td>
<td>1 (4)</td>
<td>3 (10)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Migraine characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recorded migraine days/past 3 m, median (IQR)</td>
<td>25.5 (14.5 to 34.0)</td>
<td>18.0 (14.0 to 23.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Migraine usually starts unilaterally, No. (%)</td>
<td>21 (75)</td>
<td>25 (86)</td>
<td>0.28</td>
</tr>
<tr>
<td>Throbbing migraine pain, No. (%)</td>
<td>22 (79)</td>
<td>24 (83)</td>
<td>0.69</td>
</tr>
<tr>
<td>Photophobia</td>
<td>27 (96)</td>
<td>28 (97)</td>
<td>0.98</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>23 (82)</td>
<td>26 (90)</td>
<td>0.41</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (82)</td>
<td>24 (83)</td>
<td>0.95</td>
</tr>
</tbody>
</table>
“It sounds crazy and I couldn’t quite believe it at first, but I read up on it afterwards and apparently this piercing really can help with headaches. Since I had the piercing done, I’ve had virtually no pain in my head, which was almost constant before.”

The Daily Mail
August 14, 2015
Thanks!
eloder@partners.org
Twitter: @eloder