AAN Classification of evidence for the rating of a therapeutic study

**Class I:** A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:
- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*
  1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
  2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
  3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
  4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

**Class II:** A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

**Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

**Class IV:** Studies not meeting Class I, II or III criteria including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).
### Table 1. Positive Evidence Classifications

<table>
<thead>
<tr>
<th></th>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Classification of Migraine Preventative Therapies</strong></td>
<td><strong>Pharmacotherapy and NSAID/CAM Update</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td><strong>Level B</strong></td>
<td><strong>Level C</strong></td>
<td><strong>Level U</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Established Efficacy</strong></td>
<td><strong>Should be offered</strong></td>
<td><strong>Probable Efficacy</strong></td>
<td><strong>Possibly effective</strong></td>
<td><strong>Inadequate or Conflicting</strong></td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td><strong>Should be considered</strong></td>
<td></td>
<td></td>
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</tr>
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</table>

#### Antiepileptics

- Divalproex sodium
- Sodium valproate
- Topiramate

#### Beta Blockers

- Metoprolol
- Propranolol
- Timolol
- Atenolol
- Nadolol
- Nebivolol
- Bisoprolol
- Pindolol

#### Antidepressants

- Amitriptyline
- Venlafaxine
- Fluvoxamine
- Fluoxetine
- Protriptyline

#### Triptans for short-term prophylaxis of menstrually associated migraine (MAM)

- Frovatriptan
- Naratriptan
- Zolmitriptan

#### NSAIDS

- Fenoprofen
- Ibuprofen
- Ketoprofen
- Naproxen
- Naproxen sodium
- Flurbiprofen
- Mefenamic acid
- Indomethacin
- Aspirin

#### Calcium Channel Blockers, ACE-Inhibitors, ARBs, Alpha-2 Agonist

- Lisinopril
- Candesartan
- Nicardipine
- Nifedipine
- Nimodipine
- Verapamil
- Clonidine
- Clonidine

#### Herbal preparations, vitamins, minerals, and other

- Butterbur
- Feverfew
- Riboflavin
- Subcutaneous histamine
- Co-Q10
- Estrogen
- Cyproheptadine
- Omega-3
- Hyperbaric

#### Miscellaneous

- Guanfacine
- Cyproheptadine
- Acetazolamide
- Warfarin
- Picotamide
Table 2. Negative Evidence Classifications

<table>
<thead>
<tr>
<th>Level A Drug</th>
<th>Level B Dosing Regimen</th>
<th>Coexisting Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex sodium Valproate</td>
<td>Depakote tablet, Stavzor: 250 mg twice daily; adjust dose based on patient response, up to 1000 mg/day</td>
<td>Use: Prolonged or atypical aura, anorexia, epilepsy, bipolar disorder</td>
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<tr>
<td>(Depakote, Depakote ER, Stavzor)</td>
<td>Depakote ER: 500 mg once daily for 7 days, then increase to 1000 mg once daily; adjust dose based on patient response; usual dosage range 500-1000 mg/day</td>
<td>Avoid: Liver disease, history of pancreatitis, thrombocytopenia, pregnancy (Pregnancy Category X: All Trimesters), obesity</td>
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<td>Topiramate</td>
<td>Initial: 25 mg once daily, increase weekly by 25 mg daily up to the recommended dose of 100 mg daily given in 2 divided doses. Doses &gt;100 mg daily have shown no additional benefit.</td>
<td>Use: Obesity, epilepsy</td>
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<td>(Topamax)</td>
<td>Dose and titration should be guided by clinical outcome. It is not necessary to monitor plasma concentrations.</td>
<td>Avoid: Anorexia, renal stones, cognitive impairment, pregnancy; especially first trimester pregnancy (Category D), alcohol use</td>
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<td>Beta Blockers</td>
<td>Metoprolol: 100 to 200 mg daily (succinate) or divided BID (tartrate)</td>
<td>Use: Anxiety, essential tremor, hypertension, myocardial infarction</td>
</tr>
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<td>Propranolol (Inderal): 20 to 40 mg twice daily, increased by 20 mg BID every one to two weeks; target maintenance: 80 to 160 mg daily, divided BID, or use LA product once daily.</td>
<td>Avoid: Asthma, bradycardia, 2nd or 3rd degree heart block, hypotension, elderly, peripheral vascular disease, Raynaud disease, Diabetes with frequent hypoglycemia, Heart failure</td>
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<td>Limit rizatriptan (Maxalt) to 5mg/dose in patients taking propranolol</td>
<td>May exacerbate depression</td>
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<td>Doses should be gradually increased based on individual response and tolerability. To avoid potential withdrawal symptoms (tachycardia, tremulousness) or increased headache, beta-blockers should be tapered over 2 weeks.</td>
<td>NOTE: If one beta-blocker is not well-tolerated or is ineffective, another can</td>
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Table 3. Level A Preventative Medications; dosing and coexisting considerations

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### Timolol (Blocadren): Initial

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<thead>
<tr>
<th>Initial: 10 mg BID or 20 mg once daily</th>
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<tbody>
<tr>
<td>Maintenance: 20 mg daily, to a maximum of 30 mg daily, divided</td>
</tr>
</tbody>
</table>

Therapeutic failure of one does not predict another will be ineffective.

### Butterbur (Petasites hybridus)

<table>
<thead>
<tr>
<th>75 mg BID; Petadolex formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taper off after 4 to 6 months, safety beyond 16 weeks is unknown</td>
</tr>
</tbody>
</table>

Avoid: Patients with liver disease or dysfunction should avoid raw butterbur extract with pyrrolizidine alkaloids due to potential for hepatotoxicity.

*Please note: This is a summary chart, not an all-inclusive representation.*
### Table e-1: US Headache Consortium Consensus on when to initiate preventive pharmacologic treatment

| 1. Medication use | - Initiate therapy with medications that have the highest level of evidence-based efficacy  
|                  | - Initiate therapy with a low dose of the drug and titrate upward slowly until clinical benefits are achieved in the absence of, or until limited by, adverse events  
|                  | - Give each drug an adequate trial. It may take as long as two to three months to achieve clinical benefit, and six months to achieve maximal benefit, after achieving a dose of established clinical efficacy  
|                  | - Avoid medications that increase headache frequency or severity (e.g., overuse of acute headache medications)  
| 2. Evaluation    | - Monitor the patient’s headache and headache medication consumption through a headache diary  
|                  | - Monitor the disability/impact associated with headache (e.g., HIT-6, MIDAS)  
|                  | - Re-evaluate therapy. After 6-12 months of excellent control of headache frequency and severity, discussion with the patient regarding tapering or discontinuing treatment is reasonable  
| 3. Patient education | - Maximize compliance. Discuss with the patient the rationale for a particular treatment, when and how to use it, and the potential adverse events  
|                  | - Address patient expectations. Discuss with the patient the expected benefits of therapy and how long it will take to achieve them  
|                  | - Create a formal management plan  
| 4. Coexisting conditions | - Take coexisting conditions into account. Some (comorbid) conditions are more common in persons with migraine (e.g., stroke, myocardial infarction, Raynaud’s phenomenon, epilepsy, affective and anxiety disorders). These conditions present both treatment opportunities and limitations  
|                  | - Select the best drug to treat each disorder. (therapeutic independence may be required; avoid picking a less-effective drug in order to treat both disorders with a single medication)  
|                  | - Establish that the treatments being used for migraine are not contraindicated for the coexistent disease  
|                  | - Establish that the treatments being used for coexistent conditions do not exacerbate migraine  
|                  | - Beware of all drug interactions  
|                  | - Direct special attention to women who are pregnant or want to become pregnant. Preventive medications may have teratogenic effects. If treatment is necessary, select a treatment with the lowest risk of adverse effects to the fetus  
| Nonpharmacologic treatments | - Many migraine patients try nonpharmacological treatment to manage their headaches before they begin drug therapy or concurrently with drug therapy  

Table 5. Clinical Considerations

<table>
<thead>
<tr>
<th>Coexisting factors</th>
<th>Clinical application comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Caution should be taken in using topiramate in thin or anorexic patients as it may exacerbate weight loss. In contrast, these patients may benefit from valproic acid, divalproex sodium, or cyproheptadine.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Propranolol and other beta-blockers may have adverse effects on patients with asthma.</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>A person with bipolar disease might benefit from valproic acid, assuming that they do not have underlying liver disease, thrombocytopenia, or pancreatitis and are aware of the risk of potential alopecia and weight gain.</td>
</tr>
<tr>
<td>Cardiac arrhythmias, heart block, bradycardia</td>
<td>Caution should be taken in using tricyclics in patients with cardiac arrhythmia, or verapamil in patients with a heart block. Propranolol and other beta-blockers may be avoided in patients with bradycardia.</td>
</tr>
<tr>
<td>Depression</td>
<td>Use of propranolol or other beta-blockers may exacerbate depression. Caution should be exercised in use of SSRI/NSRI agents as well as some AED, especially in teenagers, as they may exacerbate depression or be associated with suicidality.</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Topiramate may be avoided in subjects with cognitive concerns.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Topiramate, valproic acid, and gabapentin may be preferred options in migraineurs with coexisting epilepsy.</td>
</tr>
<tr>
<td>Hypotension and hypertension</td>
<td>Use of beta-blockers, ACEI/ARBs, and calcium channel blockers are a concern in patients with hypotension, which is not at all uncommon in young women with migraine. Angiotensin receptor blockers, beta-blockers, and calcium channel blockers are particularly attractive with coexistent hypertension. ACEI and ARBs may be especially beneficial in those with diabetes mellitus and renal disease.</td>
</tr>
<tr>
<td>Obesity</td>
<td>Caution should be taken in using valproic acid, tricyclic antidepressants, cyproheptadine, and gabapentin, as they may contribute to additional weight gain.</td>
</tr>
<tr>
<td>Other—glaucoma, renal stones</td>
<td>Some patients, with or without glaucoma, have developed acute angle-closure glaucoma as a result of an idiosyncratic allergic reaction of the ciliary body. Topiramate may be avoided in migraineurs oxalate salt or phosphate salt stones.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Valproic acid and angiotensin receptor blockers should not be used if there is a potential for pregnancy. This is of particular concern in light of the majority of migraineurs tending to be younger women of childbearing potential. In general, all drugs used for prevention should be avoided in those for whom pregnancy is planned or anticipated.</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Addition of SSRIs, such as fluoxetine, or an SSNRI, such as venlafaxine, in very rare occasions may exacerbate triptan effects. There is no contraindication to the combined use of SSRIs or SSNRI and triptans or ergotamine derivatives.</td>
</tr>
<tr>
<td>Stroke</td>
<td>Angiotensin receptor blockers, and ARBs, might offer benefits in terms of secondary stroke prevention for patients with migraine.</td>
</tr>
</tbody>
</table>

References


17. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodicmigraine in adults (Review). The Cochrane Library. 2013; Issue 6


