

# **Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine**

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**American Academy of Neurology**

**American Headache Society**

**American College of Emergency Physicians\***

**American College of Physicians-American Society of Internal Medicine**

**American Osteopathic Association**

**National Headache Foundation**

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\*Endorsement by ACEP means that ACEP agrees with the general concepts in the guidelines and believes that the developers have begun to define a process of care that considers the best interests of patients with migraine headache

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# Pharmacological Management for Prevention of Migraine

## A. Introduction

Headache, one of the most common patient complaints in neurologists' offices and the most common pain complaint seen in family practice, accounts for 10 million office visits a year.<sup>1</sup> Most headaches are of the primary type (e.g., migraine and tension-type headache). An estimated 6% of men and 15% to 17% of women in the United States have migraine, but only 3% to 5% of them receive preventive therapy.<sup>2</sup> Furthermore, migraine is often undiagnosed.<sup>3</sup> About half of migraine patients stop seeking care for their headaches, partly because they are dissatisfied with therapy. Indeed, public surveys indicate that headache sufferers are among the most dissatisfied patients.<sup>4</sup> In addition to being dissatisfied with their care, many migraineurs report significant disability and an impaired quality of life.

Migraine is heterogeneous (among sufferers and between attacks) in frequency, duration, and disability. Some migraineurs have fewer than one attack a month while others have one or more attacks a week.<sup>5</sup> Some are quite disabled by their headaches, while others are not. Therefore, it is appropriate to stratify the care of the migraine population by headache frequency, severity, and level of disability, and to consider prevention for those patients whose migraine has a substantial impact on their lives.<sup>6</sup>

With this background, the objective of the US Headache Consortium is to develop scientifically sound, clinically relevant practice guidelines for headache in the primary care setting. These headache Guidelines review the evidence published in the literature and propose diagnostic and therapeutic recommendations to improve the care and satisfaction of migraine patients. This specific document focuses on the prevention of migraine attacks. Additional recommendations for

migraine attack treatment, behavioral and cognitive therapies, and diagnostic approaches to migraine are found elsewhere in the Guidelines.<sup>7-9</sup>

Previously accepted recommendations for migraine prevention focus on patients who have two or more attacks per month.<sup>10</sup> These recommendations are arbitrary and do not account for individual patient needs or other migraine characteristics. Preventive therapy may be more appropriately guided by one or more of the following:

- recurring migraines that, in the patients' opinion, significantly interfere with their daily routines, despite acute treatment,
- frequent headaches,<sup>11</sup>
- contraindication to, failure of, or overuse of acute therapies,
- adverse events with acute therapies,
- the cost of both acute and preventive therapies,
- patient preference, and
- the presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction (to prevent neurologic damage—as based on expert consensus).

### **Goals of Treatment for Prevention of Migraine**

The goals of migraine preventive therapy are to: (1) reduce attack frequency, severity, and duration; (2) improve responsiveness to treatment of acute attacks; and (3) improve function and reduce disability.

### **Aims of the Guideline**

This Guideline seeks to present scientific evidence of the efficacy, tolerability, and safety of preventive therapies.<sup>§§</sup> The Guideline includes an evidence review table (Table 1) that highlights the level of scientific evidence and clinical experience. Where scientific evidence is lacking, recommended treatment strategies are based on the consensus of the US Headache Consortium members who prepared the Guideline. Consensus in this context means unanimous agreement unless explicitly stated otherwise.

## **B. Summary of the Evidence**

The *AHCPR Technical Review*<sup>12</sup> reviewed 283 controlled trials of pharmacological agents used to prevent migraine. The main findings of the *AHCPR Technical Review* are summarized below. The various classes of pharmacological agents are reviewed in alphabetical order. The *AHCPR Technical Review* included controlled trials indexed in MEDLINE January 1966 through December 1996. Several additional randomized controlled trials for migraine prevention were published after this date and are individually reviewed. Newly published materials not included in the evidence analysis are incorporated into treatment recommendations as appropriate, and these recommendations are based on consensus.

The process used to develop this Guideline was described in the *Evidenced-based Guidelines for Migraine Headache: Overview of the Program Description and Methodology*.<sup>13</sup> Analysis of preventive migraine therapies poses some methodological issues that differ from those

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<sup>§§</sup>This statement is provided as an educational service of the US Headache Consortium member organizations. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. These

previously described. For example, while most modern clinical trials of acute migraine treatment rely on uniform endpoints with minor variations, endpoints in migraine prevention trials are more diverse. Limitations from such studies include the following:

(1) Many preventive studies, especially early ones, used loose criteria to define migraine. (This shortcoming was eliminated in later studies that adhered to the International Headache Society [IHS] system of headache classification.<sup>14</sup>)

(2) Long-term studies are often associated with higher dropout rates, independent of treatment.

(3) Studies completed before 1991 (when the *IHS Guidelines for Conducting Clinical Trials*<sup>15</sup> were published) used a “headache index” (derived from mathematical formulae that included headache frequency and some combination of intensity and/or duration). The *AHCPR Technical Review* relied on a headache index for effect-size analysis despite the fact that this is confounded by acute and rescue therapies. Other endpoints included headache frequency and headache intensity. Clinical trials completed after 1991 often used a reduction in the total number of headache attacks in a 28-day period or the proportion of patients with a greater than 50% reduction in headache frequency as endpoints. When they were used, effect-size analysis was based on these endpoints.

(4) Most comparative trials of two or more active treatments did not include a placebo arm. The scientific rigor of these trials is weak, particularly in light of a potential placebo response (at least 20%) and since improvement over baseline could be a reflection of the natural history of the illness during treatment.<sup>16-18</sup>

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organizations recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

(5) Many preventive studies were poorly performed, did not provide adequate details of statistical methods, or were reported only as abstracts, making proper analysis of the evidence difficult.

### Alpha-2 agonists

The *AHCPR Technical Review* included 17 controlled trials of alpha-2 agonists for the prevention of migraine: 16 of clonidine,<sup>19-34</sup> and one of guanfacine.<sup>30</sup> The evidence from these trials suggests that alpha-2 agonists are minimally, and not conclusively, efficacious. Three of 11 placebo-controlled trials of clonidine found a significant difference in favor of the active agent, but the magnitude of the effect was small.<sup>23,27,28</sup> One study found that guanfacine was significantly better than placebo at reducing headache frequency, but no data on the magnitude of the effect were reported.<sup>30</sup>

Two comparative trials comparing clonidine with the beta-blockers metoprolol<sup>31</sup> and propranolol yielded mixed results.<sup>32</sup> Two additional comparative trials showed no significant differences among clonidine, practolol\*<sup>23</sup> and pindolol.<sup>33</sup> (The latter two agents are beta-blockers with intrinsic sympathomimetic activity.) One trial each found no significant differences between clonidine and pizotifen\*,<sup>34</sup> or between clonidine and carbamazepine.<sup>33</sup>

Clonidine's most commonly reported adverse events were drowsiness and tiredness. These and other symptoms were reported by a high proportion of patients, but were usually neither serious nor cause for withdrawal from the trials. In studies comparing clonidine with beta-

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\* Currently not available in the US.

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blockers, adverse events occurred at similar rates for both interventions. No information was available on adverse events associated with guanfacine.

### Anticonvulsants

Nine controlled trials of five different anticonvulsants were included in the *AHCPR Technical Review*.<sup>33, 35-42</sup> Five studies provided strong and consistent support for the efficacy of divalproex sodium<sup>34-36</sup> and the related compound, sodium valproate.<sup>38,39</sup> Two placebo-controlled trials of each of these agents showed them to be significantly better than placebo at reducing headache frequency.<sup>36-39</sup> (A single study, reported in abstract form only, compared divalproex sodium with propranolol and found differences favoring divalproex sodium; however, the statistical significance of these results could not be determined [open-label study with high drop-out rates].<sup>35</sup>) A more recent study (published after December 1996 and therefore not included in the *AHCPR Technical Review*) found divalproex sodium more effective compared with placebo, but not significantly different compared with propranolol, for prevention of migraine in patients with migraine without aura.<sup>40</sup>

Evidence for efficacy of the other anticonvulsants was weaker. The only placebo-controlled trial of carbamazepine suggested a significant benefit, but this trial was inadequately described in several important respects.<sup>41</sup> Another trial, comparing carbamazepine with clonidine and pindolol, suggested that carbamazepine had a weaker effect on headache frequency than either comparator treatment, though differences from clonidine were not statistically significant.<sup>33</sup> The anticonvulsant clonazepam (vs. placebo) was not an effective migraine preventive treatment.<sup>42</sup> Gabapentin (vs. placebo) was not found to be effective in one study,<sup>43</sup> but a more recent trial (not included in the *AHCPR Technical Review* and reported in abstract form with

limited information on adverse events) reported clinical efficacy for gabapentin for prevention of migraine.<sup>44</sup> This randomized controlled trial showed that gabapentin 1800-2400 mg was superior to placebo in reducing the frequency of migraine attacks. Also, the percentage of patients with >50% reduction in headache frequency compared with baseline was higher among the gabapentin patients than among controls.

In one placebo-controlled, double-blind study not included in the *AHCPR Technical Review*, lamotrigine (a new anticonvulsant) failed to show a clinical benefit for migraine prevention.<sup>45</sup> In a single placebo-controlled crossover trial not included in the *AHCPR Technical Review*, vigabatrin\* was found to significantly reduce headache frequency. No serious laboratory or clinical adverse effects were reported, but four patients (17%) dropped out of the trial and 3 patients (13%) were withdrawn due to poor compliance.<sup>46</sup> Vigabatrin\* has caused visual field constriction.<sup>47,48</sup>

In three of four placebo-controlled trials, the overall percentage of patients reporting adverse events with divalproex sodium or sodium valproate was not higher than with placebo. The fourth trial found significantly higher rates of nausea, asthenia, somnolence, vomiting, tremor, and alopecia when patients used divalproex sodium. (Additional adverse events are detailed in Table 1.) A significantly higher percentage of patients reported adverse events with carbamazepine than with placebo or pindolol; there was no significant difference in this respect between carbamazepine and clonidine. Limited data were reported on adverse events associated with clonazepam and gabapentin. The most common adverse events reported in association with these treatments were dizziness or giddiness, and drowsiness. Relatively high patient withdrawal rates due to adverse events were reported in some trials.<sup>12</sup>

## Antidepressants

A total of 16 controlled trials investigated the efficacy of the tricyclic antidepressants amitriptyline, clomipramine, and opipramol\*; the selective serotonin re-uptake inhibitors femoxetine\*, fluoxetine, and fluvoxamine; and the tetracyclic antidepressant mianserin\*.<sup>49-65</sup> Amitriptyline has been more frequently studied than the other agents, and is the only antidepressant with fairly consistent support for efficacy in migraine prevention. Three placebo-controlled trials found amitriptyline significantly better than placebo at reducing headache index or frequency.<sup>49-52</sup> One of these trials, conducted in patients whose headaches were frequently severe or disabling in intensity, found no significant difference between amitriptyline and propranolol.<sup>52</sup> Another trial reported that amitriptyline was significantly more efficacious than propranolol for patients with mixed migraine and tension-type headache, while propranolol was significantly better for patients with migraine alone.<sup>62</sup> Similarly, a trial conducted in a group of patients with mixed migraine and tension-type headache found that amitriptyline was significantly better than timed-released dihydroergotamine\* (TR-DHE\*) at reducing headache index.<sup>65</sup> However, an analysis of the data on headache duration, stratified by severity, showed that amitriptyline was significantly better than TR-DHE\* at reducing the number of hours of moderate and mild tension-type headache-like pain. In contrast, TR-DHE\* was significantly better than amitriptyline at reducing the number of hours of extremely severe and severe migraine-like pain.

The evidence was insufficient to support the efficacy of clomipramine,<sup>53,54</sup> opipramol\*,<sup>60</sup> femoxetine\*,<sup>55,56</sup> fluvoxamine,<sup>61</sup> and mianserin\*<sup>59</sup> for migraine prevention. Fluoxetine (racemic) was significantly better than placebo in one trial of migraine prevention,<sup>57</sup> but the results were not

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\* Currently not available in the US.

duplicated in a second study. In contrast, a recent randomized controlled trial not included in the *AHCPR Technical Review* showed that S-fluoxetine\* had a possible clinical benefit in migraine prevention, as measured by a reduction in migraine frequency, as early as one month after initiation of therapy.<sup>66</sup>

Anticholinergic symptoms were frequently reported with the tricyclic antidepressants studied, including amitriptyline. Adverse events were less common with selective serotonin reuptake inhibitors, with nausea and sexual dysfunction being the most frequently observed symptoms.<sup>12</sup>

### Beta-blockers

The *AHCPR Technical Review* analyzed 74 controlled trials of beta-blockers for migraine prevention, including 46 trials of propranolol, 14 trials of metoprolol, and trials of acebutolol, alprenolol\*, atenolol, bisoprolol, nadolol, oxprenolol\*, pindolol, practolol\*, and timolol. (For a complete list of studies see the *AHCPR Technical Review*.<sup>12</sup>)

Evidence consistently showed the efficacy of propranolol in a daily dose of 120 mg to 240 mg for the prevention of migraine. Twelve of 21 placebo-controlled trials of propranolol allowed estimation of effect sizes for headache frequency or headache index.<sup>67-78</sup> The 12 effect-size estimates were statistically homogeneous and, when combined, indicated a high degree of certainty that propranolol provides a moderate reduction in headache frequency or index. (For this analysis, the 95% confidence intervals around the effect-size estimate excluded a very small or

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\* Currently not available in the US.

very large effect. Three studies comparing daily propranolol doses of 80 mg and 160 mg reported mixed results.<sup>79-81)</sup>

Direct comparisons demonstrated few significant differences in efficacy between propranolol and flunarizine\*,<sup>82-85</sup> amitriptyline,<sup>52,62</sup> naproxen sodium,<sup>75</sup> mefenamic acid,<sup>71</sup> tolfenamic acid\*,<sup>72,86</sup> divalproex sodium,<sup>40</sup> and methysergide.<sup>87,88</sup> All these treatments were effective for migraine prevention. As noted above, one trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was superior for patients with mixed migraine and tension-type headache.<sup>62</sup>

Results from four trials comparing metoprolol with placebo reported mixed results.<sup>53, 89-91</sup> Direct comparisons of metoprolol with propranolol,<sup>88,92-94</sup> flunarizine\*,<sup>95,96</sup> and pizotifen\*<sup>97</sup> demonstrated few significant differences, suggesting that metoprolol is efficacious for the prevention of migraine. Timolol,<sup>77,98,99</sup> atenolol,<sup>100-102</sup> and nadolol<sup>103-108</sup> are also likely to be beneficial based on comparisons with placebo or with propranolol. Comparisons of nonpharmacological therapies to beta-blockers are reviewed in *Evidenced-Based Guidelines for Migraine Headache: Behavioral and Physical Treatments*<sup>8</sup> and in the *AHCPR Technical Review*.<sup>109</sup>

Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol\*, oxprenolol\*, pindolol) appear to be ineffective for the prevention of migraine.<sup>110-114</sup>

A few trials used long-acting or extended-release preparations of propranolol or metoprolol, but evidence was insufficient to determine whether these preparations were more efficacious and/or better tolerated than regular formulations of these agents.<sup>73,78,88,89,115,116</sup>

Adverse events most commonly reported with beta-blockers were fatigue, depression, nausea, dizziness, and insomnia. These symptoms appear to be fairly well tolerated and were seldom the cause of premature withdrawal from trials.<sup>12</sup>

### Calcium channel antagonists

The literature reviewed identified 45 controlled trials of calcium antagonists, including flunarizine\* (25 trials), nimodipine (11 trials), nifedipine (5 trials), verapamil (3 trials), cyclandelate\* (three trials), and nicardipine (one trial). (See *AHCPR Technical Review* for a complete list of studies.<sup>12</sup>) Flunarizine\* was compared with placebo in eight migraine prevention trials.<sup>117-124</sup> Effect sizes could be calculated for seven of the eight studies.<sup>117-123</sup> A meta-analysis of these seven trials indicated that they were heterogeneous. The summary effect size obtained was statistically significant in favor of flunarizine\*. Five comparisons of flunarizine\* with propranolol,<sup>82-85</sup> and two with metoprolol,<sup>96,125</sup> showed no significant differences between flunarizine\* and these beta-blocking agents. The trials reviewed also demonstrated no significant differences between flunarizine\* and pizotifen\*,<sup>126-128</sup> or between flunarizine\* and methysergide.<sup>129</sup> One trial comparing flunarizine\* and dihydroergokryptine\*<sup>130</sup> (DEK) reported mixed results, but suggested that differences in the effects of the two treatments were small.

Nimodipine has been less thoroughly studied than flunarizine and had mixed results in placebo-controlled trials. Three of five comparisons with placebo suggested no significant differences,<sup>131-133</sup> while the remaining two reported relatively large and statistically significant

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\* Currently not available in the US.

differences in favor of nimodipine.<sup>134,135</sup> Comparisons with flunarizine\*,<sup>136</sup> pizotifen\*,<sup>126-128</sup> and propranolol<sup>137</sup> showed few significant differences between these agents and nimodipine.

The evidence for nifedipine was difficult to interpret. Two comparisons with placebo yielded similar effect sizes that were statistically insignificant, but the 95% confidence intervals associated with these estimates were large and did not exclude either a clinically important benefit or harm associated with nifedipine.<sup>138,139</sup> Similarly ambiguous results were reported in one comparison with flunarizine\*<sup>140</sup> and in two comparisons with propranolol.<sup>92,141</sup> One trial found that metoprolol was significantly better than nifedipine at reducing headache frequency.<sup>92</sup>

Two of three placebo-controlled trials of verapamil found significant differences favoring the active agent, but both positive trials had high dropout rates, rendering the findings uncertain.<sup>116,142,143</sup> The single negative placebo-controlled trial also included a propranolol treatment arm, and investigators in this trial reported no significant difference between verapamil and propranolol for headache frequency.<sup>116</sup>

The efficacy of nifedipine is supported by a single comparison with placebo.<sup>144</sup>

Cyclandelate\* has not been tested in placebo-controlled trials for migraine prevention, but it has been compared with other migraine preventive medications. One trial each showed cyclandelate\* to be less effective than flunarizine\*,<sup>145</sup> more effective than pizotifen\*,<sup>146</sup> and not significantly different from propranolol.<sup>147</sup> In a recent randomized, controlled trial not included in the *AHCPR Technical Review*, cyclandelate was not significantly different than placebo or propranolol. Both active treatments were well-tolerated.<sup>148</sup>

The trials reviewed in the *AHCPR Technical Review* provided little useful information on the risk of adverse events with these agents. The proportion of patients reporting adverse events varied considerably from trial to trial, even among trials reporting on the same pharmacological

agent at the same dose. The adverse events most commonly associated with flunarizine\* were sedation, weight gain, and abdominal pain. Symptoms reported with other calcium channel antagonists included dizziness, edema, flushing, and constipation. Two trials of verapamil and one of nifedipine reported high dropout rates due to adverse events.<sup>12</sup>

## NSAIDs

The *AHCPR Technical Review* reviewed 23 controlled trials of 10 different Nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>71,72,95,102,149-165</sup> A meta-analysis of five of seven placebo-controlled trials of naproxen or naproxen sodium suggested a modest, but statistically significant, effect on headache index or frequency.<sup>75,149-154</sup> Similar trends were observed in placebo-controlled trials of flurbiprofen,<sup>161</sup> indobufen\*,<sup>162</sup> ketoprofen,<sup>102</sup> lornoxicam\*,<sup>164</sup> mefenamic acid,<sup>71</sup> and tolfenamic acid\*,<sup>72,160</sup> but fewer studies supported efficacy for each of these agents. Placebo-controlled trials of aspirin,<sup>155,156</sup> aspirin plus dipyridamole,<sup>156,157</sup> fenoprofen,<sup>158,159</sup> and indomethacin<sup>163</sup> were inconclusive. In a placebo-controlled, randomized, double-blind trial, nabumetone, an NSAID, was not found to be significantly different from placebo in reducing migraine frequency.<sup>166</sup>

Comparisons of NSAIDs with the beta-blockers propranolol<sup>165,167</sup> and metoprolol<sup>94</sup> demonstrated no important differences. In general, the NSAIDs tested (aspirin, mefenamic acid, naproxen sodium, and tolfenamic acid\*) had effects which, while not significantly different, appeared to be slightly smaller in magnitude than those associated with beta-blockers.<sup>12</sup>

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\* Currently not available in the US.

One trial compared naproxen sodium and pizotifen\* and found no significant difference between them for headache index.<sup>149</sup>

The proportion of patients reporting adverse events with naproxen or naproxen sodium ranged from 13% to 26%, and 2% to 10% of patients withdrew prematurely due to adverse events. Similar rates were reported in trials of other NSAIDs. These rates were not significantly higher than those seen with placebo, except in trials of flurbiprofen and lornoxicam\*.<sup>12</sup>

The most commonly reported adverse events with all NSAIDs were gastrointestinal symptoms; these included nausea, vomiting, gastritis, and blood in the stool. In the trials reviewed, such symptoms were reported by 3% to 45% of study participants.<sup>12</sup>

### Serotonergic agents

**Ergot derivatives** – Thirteen controlled trials examined the efficacy of ergot derivative compounds for the prevention of migraine.<sup>65,130,168-178</sup> TR-DHE\*, in a daily dose of 10 mg, had the strongest support, with consistently positive findings in four placebo-controlled trials.<sup>169-172</sup>

Another trial found no significant difference for headache index between a 10-mg dose once daily of TR-DHE\* and a 5-mg dose twice daily.<sup>175</sup> As described above, one trial of TR-DHE\* vs. amitriptyline was conducted in a group of patients with mixed migraine and tension-type headache.<sup>65</sup> Amitriptyline was significantly better than TR-DHE\* at reducing headache index, and at reducing the number of hours of moderate and mild tension-type headache-like pain. In contrast, TR-DHE\* was significantly better than amitriptyline at reducing the number of hours of extremely severe and severe migraine-like pain.

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\* Currently not available in the US.

The efficacy of DEK\* is less well established than that of TR-DHE\*, but is supported by one positive placebo-controlled trial conducted among women with menstrual migraine,<sup>174</sup> and by one comparison each with methysergide<sup>178</sup> and flunarizine\*.<sup>130</sup> One direct comparison of TR-DHE\* and DEK\* showed similar reductions in headache index and frequency with either treatment.<sup>177</sup>

Evidence is insufficient for the efficacy of ergotamine<sup>176</sup> or ergotamine plus caffeine plus butalbital plus belladonna alkaloids (Cafergot compound®)<sup>168</sup> for migraine prevention.

Limited information was reported on adverse events associated with these agents. The most commonly reported events for all the ergot alkaloids were gastrointestinal symptoms, including dyspepsia, epigastric pain, nausea, and vomiting.<sup>12</sup>

**Methysergide** – Methysergide is a semi-synthetic ergot alkaloid that is structurally related to methylergonovine. It was one of the first pharmacological agents to be used and studied for the prevention of migraine, but its usefulness is now limited by reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted, administration. Seventeen controlled trials of methysergide for migraine prevention were identified.<sup>87,88,129,176,178-187</sup> Four placebo-controlled trials suggested that methysergide was significantly better than placebo at reducing headache frequency.<sup>179-182</sup>

Four trials comparing methysergide and pizotifen\*<sup>181,183-185</sup> showed no statistically significant differences between the two treatments for headache index or frequency. The combined effect size from two of these trials suggested that methysergide was not better than pizotifen\* to any clinically important degree. Similarly, two trials directly comparing methysergide and propranolol failed to demonstrate any statistically significant differences between these

treatments.<sup>87,88</sup> However, the reported differences in response to the two pharmacological agents suggested that methysergide is not better than propranolol to any clinically significant degree. The only trial comparing methysergide with metoprolol reported an unusually low response to metoprolol (6%) and thus probably exaggerated the relative efficacy of methysergide.<sup>88</sup>

Methysergide was compared with flumetorexone\*,<sup>186</sup> oxitriptan\*,<sup>187,188</sup> lisuride\*,<sup>189</sup> DEK\*,<sup>178</sup> ergotamine,<sup>176</sup> and flunarizine\*.<sup>129</sup> These trials were too small to demonstrate equivalence and failed to show any statistically significant differences.

Methysergide was associated with a higher incidence of adverse events than was placebo. Gastrointestinal complaints were most common and included nausea, vomiting, abdominal pain, and diarrhea. Also frequently reported were leg symptoms (restlessness or pain), dizziness, giddiness, drowsiness, lassitude, and paresthesia. Adverse events were no more common with methysergide than with pizotifen\*. The duration of the trials reviewed here was too short to detect the fibrotic complications sometimes observed with long-term use of methysergide. The manufacturer's labeling suggests that methysergide be discontinued for 3 to 4 weeks after each 6-month course of treatment.<sup>12</sup>

**Miscellaneous serotonergic agents** – Other serotonergic agents that have been evaluated for the prevention of migraine include pizotifen\* (26 trials), lisuride\* (six trials), oxitriptan\* (four trials), iprazochrome\* (two trials), and tropisetron\* (two trials) (See *AHCPR Technical Review* for complete listing of trials.<sup>12</sup>) Evidence was inconsistent for the efficacy of pizotifen\*<sup>149,181,190-198</sup> from 11 placebo-controlled trials and 19 comparisons with other agents.<sup>34,97,126-128,146,149,181,183-</sup>

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\* Currently not available in the US.

<sup>185,196,199-205</sup> Analysis of the placebo-controlled trials suggested a large clinical effect that was statistically significant. In direct comparisons with other agents known to be efficacious for migraine prevention, no significant differences were demonstrated between pizotifen\* and flunarizine\*,<sup>126-128</sup> methysergide,<sup>181,183-185</sup> naproxen sodium,<sup>149</sup> or metoprolol.<sup>97</sup> However, in the 26 trials reviewed, pizotifen\* was generally poorly tolerated.<sup>12</sup> Substantial weight gain, tiredness, and/or drowsiness were frequently reported. Pizotifen\* was associated with a high rate of withdrawals due to adverse events.

Lisuride\* has consistent support from four placebo-controlled trials suggesting a significant benefit.<sup>206-209</sup> Direct comparisons with pizotifen\*<sup>201</sup> and with methysergide<sup>189</sup> demonstrated no significant differences between lisuride\* and these comparator treatments. Lisuride\* was associated with fewer adverse events than pizotifen\* and had a lower rate of patient withdrawals due to adverse events.<sup>12</sup>

None of the other serotonergic agents tested (ipرازochrome\*,<sup>196</sup> tropisetron\*,<sup>210</sup> or oxitriptan\*<sup>211-213</sup>) was shown to be more effective than placebo.

### Other treatments

**Hormone Therapy** – Six controlled trials examined the efficacy of estrogens and/or progestogens for migraine prevention. The trials were all relatively small, and they varied markedly in patient population, dosages used and clinical results. Two placebo-controlled trials of estradiol used perimenstrually in a gel or patch form suggested that a relatively high dose of this hormone (1.5 mg per day [gel]) may be efficacious in women whose migraine headaches are closely associated with the menstrual cycle.<sup>214,215</sup> One additional study (not included in the

*AHCPR Technical Review*) is consistent with these previous reports in reporting that estradiol (1.5 mg per day-[gel]) is significantly more effective than placebo in preventing migraine attacks associated with the menstrual cycle. A lower dose (50 mcg per day [patch]) was no more efficacious than placebo.<sup>216</sup> Furthermore, the attacks that did occur were shorter in duration.<sup>215</sup> This also was supported by a study not reviewed in the *AHCPR Technical Review* that found that an estradiol patch of 50 mcg per day (a relatively low dose) was not significantly more effective than placebo, as measured by headache duration or headache intensity.<sup>217</sup> Two placebo-controlled trials of flumedroxone\*, a modified oral progestogen, suggested that this agent may be efficacious, again especially among women whose migraine attacks are associated with the menstrual cycle.<sup>218,219</sup> An additional trial comparing flumedroxone\* and methysergide, in a poorly-described patient cohort, reported lower mean headache frequency with methysergide, but could not be analyzed statistically.<sup>186</sup> The evidence does not support the efficacy of estradiol or flumedroxone\* in women whose migraines are not associated with their menstrual cycle or in men who have migraine.

A single trial, comparing a combination oral contraceptive (Ovral® [norgestrel 0.5 mg plus ethinyl estradiol 50 mcg]) with no treatment, found no benefit from the active treatment.<sup>220</sup>

Adverse events associated with estradiol were minimal and caused very few withdrawals. Adverse events were much more common with flumedroxone\* than with placebo or methysergide. The most frequently reported symptoms among women taking flumedroxone\* were nausea, mastitis, polymenorrhea, and other menstrual disturbances; men commonly reported drowsiness, dyspepsia, and decreased libido.<sup>12</sup>

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\* Currently not available in the US.

**Feverfew** – Two trials, distinctly different in design, compared the herbal remedy, feverfew, with placebo or no treatment. One trial was conducted in a self-selected group of feverfew users and showed that withdrawal of feverfew led to a statistically significant increase in headache frequency.<sup>221</sup> The other, more conventional, trial was conducted in a larger group of migraineurs, most of whom (71%) had never used feverfew.<sup>222</sup> This trial reported a smaller difference between feverfew and the control treatment than did the first trial, but still found the difference to be statistically significant in favor of feverfew. A recent double-blind, randomized, crossover trial (not included in the *AHCPR Technical Review*) tested the efficacy of feverfew compared with placebo and reported that treatment with feverfew was associated with a significant reduction in pain intensity and nonheadache symptoms (nausea, vomiting, photophobia, and phonophobia).<sup>223</sup> One trial reported no significant differences between feverfew, given as an alcoholic extract, and placebo for reducing migraine frequency (not included in the *AHCPR Technical Review*).<sup>224</sup>

Limited information indicates that adverse events were no more common with feverfew than with the control treatment.<sup>12</sup>

### **Review of Studies of Vitamins and Minerals Not Included in the *AHCPR Technical Review***

**Magnesium** –Magnesium replacement has been studied in two trials of migraine prevention<sup>225,226</sup> and in one trial of migraine associated with premenstrual syndrome.<sup>227</sup> Two of the three studies favored the use of magnesium over placebo, but the third study failed to show any added benefit. These three studies measured different endpoints.

**Riboflavin** – One trial compared a high dose of vitamin B<sub>2</sub> (400 mg) against placebo. A significant benefit was observed three and four months following initiation of treatment.<sup>228</sup>

### **C. Transition from Evidence to Guidelines**

Recommendations for migraine prevention and Guidelines cannot be based solely on the *AHCPR Technical Review* because the report summarizes only the results of randomized, controlled trials of pharmacological treatments for the prevention of migraine. It does not address the general principles of care for migraine prevention, and it does not discuss which medication should be considered first. This fine-tuning process requires a consensus that incorporates levels of quality of the evidence, magnitude of the benefit of a particular medication, clinical impressions from prior experience, tolerability, and safety profile.

### **D. General Principles of Management**

The following consensus-based (not evidence-based) principles of care will enhance the success of preventive treatment. Additional success could be achieved when considering patient preference (formulations, cost, dosing schedules, and tolerability). Consideration of nonpharmacological therapies are reviewed in the *Evidenced-Based Guidelines for Migraine Headache: Behavioral and Physical Treatments*.<sup>8</sup>

1. Medication use:

- A. Initiate therapy with the lowest effective dose. Begin with a low dose of the chosen pharmacological agent and increase the dose slowly until clinical benefits are achieved in the absence of adverse events or until limited by adverse events.
  - B. Give each treatment an adequate trial. A clinical benefit may take as long as two to three months to manifest itself.
  - C. Avoid interfering medications (e.g., overuse of certain acute medications such as ergotamine).
  - D. Use of a long-acting formulation may improve compliance.
2. Patient education:
- A. Maximize compliance. Discuss with the patient the rationale for a particular treatment, when and how to use it, and what adverse events are likely.
  - B. Address patient expectations. Discuss with the patient the expected benefits of therapy and how long it will take to achieve them.
  - C. Create a formal management plan
3. Evaluation:
- A. Monitor the patients' headaches by having them keep headache diaries. Diaries help to track headache and related symptoms from one clinic visit to another. By consensus, they are considered the "gold standard" in headache attack evaluation. Diaries should be user-friendly and should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.

- B. Re-evaluate therapy. After a period of stability, consider tapering or discontinuing treatment.
4. Coexisting (comorbid) conditions: Some conditions are more common in persons with migraine. Take into account the presence of coexisting diseases. These include stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders. Coexisting diseases present both treatment opportunities and limitations. For example:
- A. Once the coexisting condition has been identified, select a pharmacological agent that will treat both disorders.
  - B. Establish that the coexisting condition is not a contraindication for the selected migraine therapies (e.g., beta-blockers are contraindicated in patients with asthma).
  - C. Establish that the treatments being used for coexisting conditions do not exacerbate migraine.
  - D. Beware of interactions between pharmacological agents used for migraine and those used for other conditions.
  - E. Direct special attention to women who are pregnant or want to become pregnant. Preventive medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus.

## **E. Specific Treatment Recommendations**

Individual medications have been put into treatment groups based on their established clinical efficacy, significant adverse events, safety profile, and clinical experience of the US Headache Consortium participants:

- Group 1. Medications with proven high efficacy and mild-to-moderate adverse events.
- Group 2. Medications with lower efficacy (i.e., limited number of studies, studies reporting conflicting results, efficacy suggesting only "modest" improvement) and mild-to-moderate adverse events.
- Group 3. Medication use based on opinion, not randomized controlled trials.
  - a) mild-to-moderate adverse events,
  - b) frequent or severe adverse events (or safety concerns), complex management issues (special diets, high potential for severe adverse drug interactions, or drug holidays).
- Group 4. Medication with proven efficacy but with frequent or severe adverse events (or safety concerns), or complex management issues (special diets, high potential for severe adverse drug interactions, or drug holidays).
- Group 5. Medication proven to have limited or no efficacy.

Table 1 provides a comprehensive review of the level and quality of scientific evidence found in the literature and based on clinical experience. Treatments were included in a specific

group based on these findings. The combined list of treatments and group assignments appears in Table 2.

## **F. Future Research**

Although many preventive drugs reviewed are rated as Class C for quality of the evidence, extensive clinical experience suggests their utility. Future directions in migraine prevention should include validating these clinical observations in scientifically sound, randomized, and controlled trials. Other shortcomings of the existing evidence became apparent during this review and analysis, and several areas worthy of future investigation include:

- acceptability, long-term use, safety, and effectiveness of specific preventive therapies and preventive therapies in general
- use of combination therapies:
  - drug therapy combined with behavioral treatment
  - combinations of two or more drugs
- placebo-controlled studies of older pharmacological agents, such as methylergonovine, phenelzine, and nortriptyline
- best duration of preventive treatment
- predictors of remission with or response to preventive treatment
- issues regarding comorbidities and use of:
  - combinations of treatments for migraine and comorbid conditions

- single agents for both migraine and comorbid conditions
- development of stepped care and other treatment strategies for particular types of migraine headache or particular subgroups of migraine patients
- compliance with preventive therapies

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## H. Tables and Figures

**Table 1: Preventive Therapies for Migraine**

(Dose ranges are presented for reference purposes only; no recommendations can be made regarding dosing regimens. Refer to the original *AHCPR Technical Review* and published literature for specific dosing information. No dosing information is provided for treatments lacking relevant, randomized controlled trials [Grade C].)

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b><u>Alpha-2 agonists</u></b>						
<b>Clonidine</b> (doses tested: 0.05 to 0.225 mg/day) (clinical efficacy: 0.075 to 0.15 mg/day)	B	0	0	Occasional to frequent	CNS adverse events common. Overwhelming evidence demonstrates no clinical benefit for prevention of migraine.	5
<b>Guanfacine</b> (doses tested: 0.5 to 1 mg/day) (clinical efficacy: 1.0 mg/day)	B	+	?	Infrequent (low dose)	Limited evidence indicating superiority of 1-mg dose over the 0.5-mg dose. Limited value in patients with coexistent hypertension.	2
<b><u>Antiepileptics</u></b>						
<b>Carbamazepine</b> (dose tested: 600 mg/day) (clinical efficacy dose: not established in placebo-controlled trials)	B	++	0	Occasional to frequent	Most common adverse events include vertigo, giddiness, and drowsiness. Not recommended based on limited evidence of efficacy, high incidence of adverse events, and methodological concerns.	5

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<p><b>Divalproex sodium</b> (doses tested: 500 to 1500 mg/day; serum level 70 to 120 mg/L) (efficacious doses in clinical trials: 500-1500 mg/day)</p> <p><b>Sodium valproate</b> (doses tested: 800 to 1500 mg/day; serum level 50 mg/L) (clinical efficacy: 800-1500 mg/day)</p>	A	+++	+++	Occasional to frequent	Some adverse events are more than occasionally seen (including nausea, asthenia, somnolence) when higher doses are used. Other side effects include weight gain, hair loss, tremor, neural tube defects and teratogenic potential. Recommended for patients with prolonged or atypical migraine aura. Not recommended in patients with liver disease. Safety and tolerability profiles for these agents specifically in migraineurs appears similar to those with other disorders. <sup>230</sup>	1
<p><b>Gabapentin</b> (doses tested: 900 to 2400 mg/day) (efficacious doses in clinical trials: 900-2400 mg/day)</p>	B	++	++	Occasional to frequent	Limited available data (two trials reported as abstracts) indicating benefit at doses ranging from 900 mg to 2400 mg.	2
<p><b>Vigabatrin*</b> (doses tested: 1000 to 2000 mg/day) (efficacious doses: not established in placebo-controlled trials)</p>	B	++	?	Occasional	Based on lack of clinical experience and published data, further studies are needed. Safety concerns with visual field constriction.	5
<b>Others Antiepileptics</b>						
<p><b>Tiagabine, Topiramate</b> (efficacious doses: not established in placebo-controlled trials)</p>	C	?	++	Occasional	Occasional CNS adverse events with both agents. Kidney stones and weight loss with topiramate. Sedation could occur at doses of topiramate required to achieve efficacy.	3a
<b>Antidepressants</b>						

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<i>Tricyclic antidepressants (TCAs):</i>						
<b>Amitriptyline</b> (doses tested: 25 to 150 mg/day) (efficacious doses in clinical trials:30-150 mg/day)	A	+++	+++	Frequent	Drowsiness, weight gain, and anticholinergic adverse events are common; long-term weight gain can be troublesome. Particularly useful in patients with migraine and tension-type headache and in patients with coexistent depression. Risk of drug interaction between cisapride and amitriptyline. May lower seizure threshold in patients with frequent seizures.	1
<b>Nortriptyline</b> (efficacious doses: not established in placebo-controlled trials)	C	?	+++	Frequent	Better tolerated than amitriptyline.	3a
<b>Protriptyline</b> (efficacious doses: not established in placebo-controlled trials)	C	?	++	Frequent	Nonsedating and not as frequently associated with weight gain as other TCAs.	3a
<i>Other TCAs</i>						
<b>Doxepin, Imipramine</b> (efficacious doses: not established in placebo-controlled trials)	C	?	+	Frequent	See prescribing information for adverse events.	3a

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<i>Selective serotonin reuptake inhibitors (SSRIs)</i>						
<b>Fluoxetine</b> (doses tested: 20 mg every other day to 40 mg/day) (efficacious doses in clinical trials: 20 mg every other day to 40 mg/day)	B	+	+	Occasional	Insomnia, fatigue, tremor, and stomach pain are the more common adverse events. Consider use in patients with coexistent depression. SSRIs rarely interact with 5-HT agonists.	2
<i>Other SSRIs</i>						
<b>Fluvoxamine, Paroxetine, Sertraline</b> (efficacious doses: not established in placebo-controlled trials)	C	?	+	Occasional	See prescribing information and text above.	3a
<i>Monoamine oxidase inhibitors (MAOIs)</i>						
<b>Phenelzine</b> (efficacious doses: not established in placebo-controlled trials)	C	?	+++	Frequent	Requires complex management with special dietary restrictions. High potential for drug-drug interactions. May be helpful in patients with coexistent depression or when antidepressants from other classes fail.	3b
<i>Other antidepressants</i>						
<b>Bupropion, Mirtazepine, Trazodone, Venlafaxine</b> (efficacious doses: not established in placebo-controlled trials)	C	?	+	Occasional	May be used in patients with coexistent depression or anxiety.	3a

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>Beta-blockers</b>						
<b>Atenolol</b> (dose tested:100 mg/day) (efficacious doses in clinical trials: 100mg/day)	B	++	++	Infrequent	Adverse events include tiredness, fatigue, and dizziness. May not be accepted by active patients (e.g., athletes). Particularly helpful in patients with coexistent anxiety/panic attacks and essential tremors (propranolol). When propranolol is used in conjunction with rizatriptan, a lower dose of rizatriptan should be given. Should not be used in patients with coexistent asthma, cardiac insufficiency, or Raynaud's disease. May exacerbate depression.	2
<b>Metoprolol</b> (doses tested:50 to 300 mg/day) (efficacious doses in clinical trials: 200 mg/day)	B	++	+++	Infrequent		2
<b>Nadolol</b> (doses tested: 80 to 240 mg/day) (efficacious doses in clinical trials: 80 to 240 mg/day)	B	+	+++	Infrequent		2
<b>Propranolol</b> (doses tested: 40 to 240 mg/day) (efficacious doses in clinical trials: 80 to 240 mg/day)	A	++	+++	Infrequent		1

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>Timolol</b> (doses tested: 20 to 30 mg/day) (efficacious doses in clinical trials: 20-30 mg/day)	A	+++	++	Infrequent		1
<b>Calcium Channel Blockers</b>						
<b>Cyclandelate*</b> (doses tested: 1200-1600 mg/day) (efficacious doses: not established in placebo-controlled trials)	B	+	?	Infrequent	The uncertainty regarding the efficacy of cyclandelate* is still considerable given the paucity of placebo-controlled trials. Limited information is available regarding adverse events.	2
<b>Diltiazem</b> (efficacious doses: not established in placebo-controlled trials)	C	?	0	Occasional	Tolerability similar to others in class.	3a
<b>Flunarizine*</b> (doses tested: 3 to 15 mg/day) (efficacious doses in clinical trials: 10 mg/day)	B	+++	?	Occasional to frequent	Most common adverse events are sedation, weight gain, and abdominal pain. Depression and extrapyramidal symptoms can be observed, usually in elderly people. Commonly used where available.	4
<b>Nimodipine</b> (dose tested: 60 to 120 mg/day) (efficacious doses in clinical trials: 120 mg/day)	B	+	+	Occasional	Abdominal discomfort common. Cost may be prohibitive.	2
<b>Verapamil</b> (dose tested: 240 mg/day) (efficacious doses in clinical trials : 240 mg/day)	B	+	+	Occasional	Constipation common. Do not use if conduction block is present. Alternative to beta-blockers in athletes. Recommended in patients with coexistent stroke, or for prolonged or atypical migraine aura.	2

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>NSAIDs</b>						
<p><b>Aspirin</b> (doses tested: 325 mg every other day; 1300 mg/day) (efficacious doses in clinical trials: 1300 mg/day)</p> <p><b>Fenoprofen</b> (dose tested: 600 to 1800 mg/day), (efficacious doses in clinical trials: 1800 mg/day)</p> <p><b>Flurbiprofen</b> (dose tested: 200 mg/day) (efficacious doses in clinical trials: 200 mg/day)</p> <p><b>Mefenamic acid</b> (dose tested: 1500 mg/day) (efficacious doses in clinical trials 1500 mg/day)</p>	B	+	+	Infrequent	Common adverse events include abdominal discomfort, gastritis, occult GI bleed. May be useful for patients with arthritis. Consider aspirin in patients with coexistent stroke.	2

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<p><b>Aspirin + dipyridamole</b> (dose tested: 975 to 1300 + 75 mg/day) (efficacious doses in clinical trials: 975 + 75 mg/day)</p> <p><b>Indobufen*</b> (dose tested: 400 mg/day) (efficacious doses in clinical trials: 400 mg/day)</p> <p><b>Tolfenamic acid*</b> (dose tested: 300 mg/day) (efficacious doses in clinical trials: 300 mg/day)</p>	B	+	?	Infrequent		2
<p><b>Ibuprofen</b> (efficacious dose: not established in placebo-controlled trials)</p>	C	?	+	Infrequent		3a
<p><b>Ketoprofen</b> (dose tested: 150 mg/day) (efficacious doses in clinical trials: 150 mg/day)</p>	B	++	+	Infrequent		2

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>Lornoxicam*</b> (dose tested:12 mg/day) (efficacious doses in clinical trials: 12 mg/day)	B	++	?	Infrequent		2
<b>Naproxen</b> (dose tested: 500 mg/day) (efficacious dose: not established in placebo-controlled trials)	B	++	++	Infrequent		2
<b>Naproxen sodium</b> (dose tested: 1100 mg/day) (efficacious doses in clinical trials:1100 mg/day)						
<b>Serotonin Antagonists</b>						
<b>Cyproheptadine</b> (efficacious dose: not established in placebo-controlled trials)	C	?	+	Frequent	Used in pediatric migraine. Weight gain and fatigue are common adverse events.	3a
<b>DEK*</b> (dose tested: 20 mg/day) (efficacious dose: not established in placebo-controlled trials)	B	+	?	?	Limited published data on adverse events.	5
<b>TR-DHE*</b> (oral) (dose tested: 10 mg/day) (efficacious doses in clinical trials: 10 mg/day)	A	+++	?	?	Limited published data on adverse events.	4

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>Ergotamine + caffeine + butalbital + belladonna alkaloids</b> (dose tested: 2 caps/day for 3 days before, during, and 2 days after menses) (efficacious dose: not established in placebo-controlled trials)	B	++	++	Occasional	Cafergot comp® taken twice daily during the perimenstrual period was shown to reduce headache frequency for migraine associated with menses. Limited information available regarding adverse events associated with treatment for migraine associated with menses.	2
<b>Lisuride*</b> (doses tested: 0.075 to 0.225 mg/day) (efficacious doses in clinical trials: 0.075 to 0.15 mg/day)	A	++	?	Occasional	Limited published data on adverse events.	1
<b>Methylergonovine (methylergometrine)</b> (efficacious dose: not established in placebo-controlled trials)	C	?	+	Frequent	May be used in hormonally influenced migraine.	3b
<b>Methysergide</b> (doses tested: 2 to 10 mg/day; based on body weight) (efficacious doses in clinical trials: 6 mg/day)	A	+++	+++	Frequent	GI adverse events common. Serious adverse events include retroperitoneal or retropleural fibrosis which may be associated with uninterrupted use. Use triptans and ergotamines with caution.	4
<b>Pizotifen*</b> (dose tested: 0.5 to 6 mg/day) (efficacious doses in clinical trials: 1.5 to 6 mg/day)	A	+++	?	Frequent	Weight gain and drowsiness common.	4
<b>Others</b>						

	<b>Quality of Evidence†† (A, B, C)</b>	<b>Scientific Effect‡ (-, +/-, +, ++)</b>	<b>Clinical Impression of Effect** (-, +/-, +, ++)</b>	<b>Adverse Effects (Aes) infrequent, occasional, frequent</b>	<b>Comments (based on clinical reports and clinical experience)</b>	<b>Group (scale 1-5; see text for definitions)</b>
<b>Estradiol</b> (percutaneous gel) (dose tested:1.5 mg/day for 7 days) (efficacious doses in clinical trials: 15 mg/day for 7 days)	B	++	++	Infrequent	Short-term prevention of migraine associated with menses. Adequate dose required.	2
<b>Feverfew</b> (doses tested:50 to ~82 mg/day) (efficacious doses in clinical trials: 50 to ~82 mg/day)	B	++	+	Infrequent	Mild adverse events. Withdrawal of feverfew may be associated with increased frequency of headaches.	2
<b>Flumedroxone*</b> (dose tested:10 to 30 mg/day) (efficacious doses in clinical trials: 10 to 30 mg/day)	B	+	+	Occasional to frequent	Common adverse events in males include drowsiness, dyspepsia, and decreased libido. adverse events reported in females include menstrual disturbances.	5
<b>Magnesium</b> (doses tested: 400 to 600 mg/day) (efficacious doses in clinical trials: 400 to 600 mg/day)	B	+	+	Infrequent	Use of nonchelated formulation is associated with significant diarrhea at clinically effective doses. May be useful in patients with PMS.	2
<b>Vitamin B2</b> (dose tested: 400 mg/day) (efficacious doses in clinical trials: 400 mg/day)	B	+++	++	Infrequent	Rare adverse events; no known interaction with other drugs.	2

\* Currently not available in the US.

? = Not known.

CNS, central nervous system; GI , gastrointestinal; DEK, dihydroergokryptine; TR-DHE, timed-release dihydroergotamine; PMS, premenstrual syndrome.

**††Strength of evidence (quality of evidence)<sup>230</sup>**

- A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.
- B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, either  
5 few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group for the recommendation.
- C. The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.

10 **‡Scientific effect measures**

- 0 The medication is ineffective or harmful.
- + The effect of the medication is either not statistically or not clinically significant (i.e., less than the minimal clinically significant benefit).
- ++ The effect of the medication is statistically significant and exceeds the minimally clinically significant benefit.
- +++ The effect is statistically significant and far exceeds the minimally clinically significant benefit.

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**\*\*Clinical impression of effect**

- 0 Ineffective: most people get no improvement.
- + Somewhat effective: few people get clinically significant improvement.
- ++ Effective: some people get clinically significant improvement.
- 20 +++ Very effective: most people get clinically significant improvement.

**Table 2: Preventive Therapies for Migraine<sup>‡‡</sup>**

<b>Group 1:</b> <b>Medium to high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency (infrequent to frequent) of side effects</b>	<b>Group 2:</b> <b>Lower efficacy than those listed in first column, or limited strength of evidence, and mild to moderate side effects</b>	<b>Group 3:</b> <b>Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy</b>	<b>Group 4:</b> <b>Medium to high efficacy, good strength of evidence, but with side effect concerns</b>	<b>Group 5:</b> <b>Evidence indicating no efficacy over placebo</b>
Amitriptyline Divalproex sodium Lisuride* Propranolol Timolol	Aspirin <sup>‡‡</sup> Atenolol Cyclandelate* Fenoprofen Feverfew Flurbiprofen Fluoxetine (racemic) Gabapentin Guanfacine Indobufen* Ketoprofen Lornoxicam* Magnesium Mefenamic acid Metoprolol Nadolol Naproxen Naproxen sodium Nimodipine Tolfenamic acid* Verapamil Vitamin B2	<p><b><u>a. mild-to-moderate side effects</u></b></p> Cyproheptadine Bupropion Diltiazem Doxepin Fluvoxamine Ibuprofen Imipramine Mirtazepine Nortriptyline Paroxetine Protriptyline Sertraline Tiagabine Topiramate Trazodone Venlafaxine	Methysergide Flunarizine* Pizotifen* TR-DHE*	Acebutolol Alprenolol* Carbamazepine Clomipramine, Clonazepam Clonidine DEK* Femoxetine* Flumedroxone* Indomethacin Iprazochrome* Lamotrigine Mianserin* Nabumetone Nifedipine Oxprenolol* Oxitriptan* Pindolol Tropisetron* Vigabatrin*
		<p><b><u>b. (side effect concerns)</u></b></p> Methylergonovine (methylergometrine) Phenelzine		

<sup>‡‡</sup> Does not include combination products.

\* Currently not available in the US.