

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

## **David B. Matchar, MD**

Professor of Medicine and Director, Center for Clinical Health Policy Research,  
Duke University Medical Center, Durham, NC

## **William B. Young, MD**

Assistant Professor of Neurology Thomas Jefferson University, Jefferson Headache Center,  
Philadelphia, PA

## **Jay H. Rosenberg, MD, FAAN**

Department of Neurology, Southern California Permanente Medical Group, and Clinical Professor of  
Neurology, Voluntary Faculty, UCSD School of Medicine,  
San Diego, CA

## **Michael P. Pietrzak, MD, FACEP**

Alexandria, VA

## **Stephen D. Silberstein, MD, FACP**

Professor of Neurology, Thomas Jefferson University, and Director of Jefferson Headache Center,  
Philadelphia, PA

## **Richard B. Lipton, MD**

Professor of Neurology, Epidemiology, and Social Medicine, Albert Einstein College of Medicine,  
Bronx, NY

## **Nabih M. Ramadan, MD**

Research Advisor, Eli Lilly & Co., Adjunct Professor, Department of Neurology,  
Indiana University Medical Center, Indianapolis, IN

## **US Headache Consortium:§**

**American Academy of Family Physicians**

**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**

§The US Headache Consortium participants: J. Keith Campbell, MD; Frederick G. Freitag, DO; Benjamin Frishberg, MD; Thomas T. Gilbert, MD, MPH; David B. Matchar, MD; Douglas C. McCrory, MD, MHSc; Donald B.

Penzien, PhD; Michael P. Pietrzak, MD, FACEP; Nabih M. Ramadan, MD; Jay H. Rosenberg, MD; Todd D. Rozen, MD; Stephen D. Silberstein, MD, FACP; Eric M. Wall, MD, MPH; William B. Young, MD

\*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 of Acute Attacks**

### **A. Introduction**

Effective long-term management of patients with migraine is challenging because of the complexity of the condition. Migraine is a chronic condition with recurrent episodic attacks, and its characteristics vary among patients, and often among attacks within a single patient. Headache is subdivided into two types, primary and secondary. In primary headaches, the disorder is the headache itself (as in migraine, tension-type headache, and cluster headache). In secondary headaches, the headache is a symptom of a secondary abnormality such as dental pain, subarachnoid hemorrhage, or brain tumor. As part of diagnosing migraine, the physician excludes any secondary causes of the patient's headache. In addition, the physician determines whether the patient has other coexisting primary headache (e.g., tension-type headache).

Once a diagnosis of primary headache is established, patients and their health care providers should together decide how to treat acute attacks and whether to use preventive medications. Various acute and preventive treatments are available. Individualized management is often required since patient responses to these therapies are not always predictable. Therefore, management is often individualized. The choice of treatment should consider, among other characteristics, the frequency and severity of attacks, the presence and degree of temporary disability, and the profile of associated symptoms such as nausea and vomiting. The patient's history of, response to, and tolerance for specific medications must also be considered. Coexisting conditions (such as heart disease, pregnancy, and uncontrolled hypertension) may limit treatment choices. Consequently, a thorough

evaluation of the patient's headache and medical history is needed before a treatment program can be developed. These programs, if collaboratively created by the physician and patient, have many advantages, including an improved likelihood of compliance. Such a formal plan of care empowers patients to manage their condition with the potential to reduce the number of office and emergency visits.

The US Headache Consortium identified the following goals of long-term migraine treatment:

- reduce attack frequency and severity,
- reduce disability,
- improve quality of life,
- prevent headache,
- avoid headache medication escalation, and
- educate and enable patients to manage their disease.

### **Aims of the Guideline**

The objective of the US Headache Consortium is to develop scientifically sound, clinically relevant practice guidelines on chronic headache for the primary care setting. This specific Guideline reviews the pharmacological treatment of acute migraine attacks.<sup>§§</sup> Evidence to support pharmacological treatment strategies indicates which medications can be effective, but it does not provide sufficient evidence to establish how to select one therapy over another. Therefore, Class I

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§§ 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 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.

evidence (one or more well-designed randomized, controlled clinical trials, including overviews [meta-analyses] of such trials) may indicate more than one therapeutic alternative.

### **Goals of Acute Migraine Treatment**

Establishing an effective acute migraine treatment plan requires that the physician and the patient identify specific short-term goals. Migraine varies widely in its frequency, severity, and impact on quality of life. The physician's task is to work with the patient to develop a treatment plan that meets the patient's expectations, needs, and goals. The US Headache Consortium identified the following goals for successful treatment of acute attacks of migraine:

1. treat attacks rapidly and consistently without recurrence,
2. restore the patient's ability to function,
3. minimize the use of back-up and rescue medications,
4. optimize self-care and reduce subsequent use of resources,
5. be cost-effective for overall management, and
6. have minimal or no adverse events.

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

The principal findings of the *AHCPR Technical Reviews* (for acute treatment of migraine), are summarized below and are supplemented by a review by Duke University Center for Clinical Health Policy Research (DUCCHPR) of studies published after the AHCPR review analysis.<sup>1,2</sup> This section discusses the classes of pharmacotherapies in alphabetical order, and individual agents within each class of drug are described, starting with those that have the most published trials and leading to

those with the least number of published trials. Table 1 provides an overview of the level of evidence and tolerability measures for each class of treatment.

## **Antiemetics**

Sixteen trials compared the efficacy for migraine headache relief for rectally and parenterally administered medications commonly recognized as antiemetics.<sup>3-18</sup> Prochlorperazine administered IV, IM, or PR (one trial each)<sup>4,5,10</sup> significantly relieved headache pain, compared with placebo. In two of three trials, metoclopramide IV was shown to be effective compared with placebo,<sup>3,6,7</sup> and one study suggested superiority of metoclopramide IV compared with oral ibuprofen.<sup>6</sup> Metoclopramide IM<sup>5</sup> or PR<sup>8</sup> showed a trend toward improvement, but significant differences compared with placebo were not reached. Chlorpromazine IM was not significantly different from placebo.<sup>9</sup> Granisetron<sup>10</sup> and zatsetron\*<sup>11</sup> did not demonstrate differences compared with placebo. Two studies examined the effect of administering domperidone\* during the migraine prodrome. One study conducted among patients with migraine with aura found that domperidone\*, taken at the onset of premonitory symptoms, was significantly more effective than placebo at aborting or preventing attacks.<sup>12</sup> A subsequent study found evidence of a dose-response relationship, with a 40-mg dose significantly more effective than a 20-mg dose.<sup>13</sup>

Direct comparison between antiemetics found that prochlorperazine IV and IM was significantly superior to metoclopramide in the corresponding forms.<sup>3,5</sup> One study showed no differences between IV treatments of chlorpromazine vs. metoclopramide.<sup>14</sup> Metoclopramide administered IM was not different from placebo in providing headache relief when administered as add-on therapy to acetaminophen plus diazepam.<sup>8</sup> Chlorpromazine IV was not significantly different

from dihydroergotamine (DHE) IV or ketorolac IM.<sup>15,16</sup> Chlorpromazine was found to be superior to meperidine IV<sup>17</sup> and lidocaine IV;<sup>15</sup> however, neither of these agents was shown to be effective for acute migraine. No significant differences were noted between methotrimeprazine\* IM and meperidine plus dimenhydrinate IM.<sup>18</sup>

Metoclopramide, prochlorperazine, and chlorpromazine all shared the common adverse event of drowsiness or sedation. Acute dystonic reactions and akathisia normally associated with phenothiazine derivatives were rarely reported. No adverse events were reported with domperidone\* administered during the prodrome. Specific information on adverse events is detailed in the *AHCPR Technical Reviews*.<sup>1,2</sup>

### **Barbiturate Hypnotics**

Throughout the literature, 10 separate controlled trials were identified that tested the efficacy of butalbital-containing agents for the treatment of headache. Only one of these trials was conducted among patients with migraine, and it did not include a placebo arm. This trial compared butalbital plus aspirin plus caffeine plus codeine (Fiorinal<sup>®</sup> with Codeine) to butorphanol, administered as a nasal spray (Stadol<sup>®</sup>).<sup>19</sup> Butorphanol was superior in efficacy to the butalbital combination with codeine at two hours, but differences between the two treatments were not significant at 4 hours.

The remaining 9 trials identified by the literature search examined the efficacy of butalbital-containing agents for the treatment of episodic tension-type headache. This Guideline project is intended to review migraine treatment; therefore, trials of butalbital-containing agents in episodic tension-type headache are not detailed.<sup>20</sup>

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\* Currently not available in the US.

Butalbital combination with codeine (Fiorinal<sup>®</sup> with Codeine) was associated with significantly fewer adverse events than was butorphanol nasal spray.<sup>19,20</sup>

## **Ergot Alkaloids and Derivatives**

Results from 23 controlled trials of ergotamine tartrate, ergotamine-containing compounds, and ergostine-containing compounds were inconsistent and difficult to interpret. This is in part because many of these trials are older and used different dosing strategies and outcome measures.<sup>1,2</sup> (More recent studies testing the efficacy of an ergot derivative, namely, DHE, used current headache outcome measures and reported improved efficacy results.)

Conclusions from five placebo-controlled trials of ergotamine ranged from finding no effect to finding large differences favoring ergotamine.<sup>21-25</sup> Three trials comparing ergotamine plus caffeine with placebo also reported mixed results.<sup>26-28</sup> One placebo-controlled trial supported the efficacy of ergostine plus caffeine.<sup>27</sup> A proprietary combination of ergotamine, caffeine, pentobarbital, and Belafolline<sup>®</sup>\* was shown in one trial each to be superior to placebo and ergotamine plus caffeine.<sup>26</sup> Otherwise, no significant differences were shown among ergotamine tartrate, ergotamine plus caffeine, ergotamine plus caffeine plus butalbital plus belladonna alkaloids (Cafergot Comp.<sup>®</sup>)<sup>29</sup>, and ergostine.<sup>27,29</sup>

Two of three studies comparing ergotamine with aspirin found ergotamine significantly more effective in achieving headache relief.<sup>22,30,31</sup> Ergotamine was not significantly different from ketoprofen PR\*,<sup>23</sup> naproxen sodium,<sup>32</sup> tolfenamic acid\*,<sup>22</sup> aspirin plus dextropropoxyphene chloride plus phenazone plus [2-diaminoethyl] phentiazin carboxyl chloride plus caffeine (Doleron<sup>®</sup>\*),<sup>30</sup> aspirin plus dextropropoxyphene napsylate plus phenazone (Doleron novum<sup>®</sup>\*),<sup>31</sup> metoclopramide,<sup>33</sup>

or an isometheptene combination (Midrid®).<sup>21</sup> Studies of ergotamine plus caffeine found this combination to be less effective than the combination of isometheptene, dichloralphenazone, and acetaminophen (Midrid®),<sup>34</sup> less effective than oral sumatriptan,<sup>35</sup> and not significantly different from DHE nasal spray<sup>36</sup> or naproxen sodium.<sup>28</sup>

Ergot alkaloids were consistently associated with higher rates of adverse events – especially nausea and vomiting compared with placebo, sumatriptan, Midrin®/Midrid®, NSAIDs, and dextropropoxyphene compounds. Most of the ergotamine combinations (ergotamine plus caffeine, Migwell®\*/Migril®, Cafergot Comp.®, ergotamine plus caffeine plus pentobarbital plus Belafolline®\*, and ergotamine plus metoclopramide) resulted in rates of nausea and vomiting lower than those associated with ergotamine alone.<sup>1,2</sup>

Nine placebo-controlled trials reported on the efficacy and safety of DHE nasal spray.<sup>37-45</sup> These trials were generally consistent in demonstrating the superiority of DHE nasal spray, though the magnitude of benefit observed was small-to-moderate. Three comparisons of different doses of DHE nasal spray were inconclusive.<sup>39,40,42</sup> Two placebo-controlled trials did not clearly establish whether DHE IV (with an added antiemetic) is effective or ineffective for the treatment of acute migraine.<sup>46,47</sup>

Two trials compared DHE nasal spray with other treatments for acute migraine. One found no significant difference between DHE and ergotamine plus caffeine for headache relief (defined as a 50% or greater reduction in headache severity).<sup>36</sup> The other trial found that subcutaneous sumatriptan was significantly better than DHE nasal spray for both headache relief and complete relief (including pain-free response).<sup>48</sup> One trial tested the efficacy of subcutaneous DHE and found to it be less

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\* Currently not available in the US.

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effective than subcutaneous sumatriptan for headache relief at 1 and 2 hours, but this difference was not seen at 3, 4, and 24 hours following treatment.<sup>49</sup> Subcutaneous DHE treatment was associated with significantly lower incidence of headache recurrence compared with subcutaneous sumatriptan. Two trials compared DHE IV plus metoclopramide IV with meperidine IM plus hydroxyzine IM, and found that DHE with these other agents was significantly better at relieving headache pain at 30 and 60 minutes.<sup>50,51</sup> Using a 50% lower dose of DHE than described previously, a single trial compared DHE (0.5 mg) plus metoclopramide (1 mg) IV vs. meperidine (75 mg) plus promethazine (25 mg) IM and found no differences between treatments.<sup>52</sup> Similarly, a more recent trial (not included in the *AHCPR Technical Review*<sup>2</sup>) demonstrated that DHE IM plus hydroxyzine was as effective as meperidine plus hydroxyzine IM.<sup>53</sup>

A single trial of DHE nasal spray during the migraine prodrome demonstrated statistically significant superiority over placebo in preventing the anticipated migraine attack.<sup>41</sup>

The most common adverse event associated with DHE was mild-to-moderate rhinitis, which was clearly related to the route of administration. Compared with ergotamine plus caffeine, DHE nasal spray had a similar incidence of adverse events. Compared with subcutaneous sumatriptan, it had a significantly lower rate of adverse events. Nausea and vomiting were the most common adverse events associated with parenteral DHE treatment.<sup>1,2</sup>

## **NSAIDs (Nonsteroidal Anti-inflammatory Drugs), Combination Analgesics, and Nonopiate Analgesics**

The analysis of NSAIDs and other nonopiate analgesics included 33 controlled trials. Comparisons with placebo consistently demonstrated the efficacy of this class of agents for pain relief

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of acute migraine headache. Three studies of aspirin,<sup>22,54,55</sup> and two each for ibuprofen,<sup>56,57</sup> tolfenamic acid\*,<sup>22,58</sup> and naproxen sodium<sup>28,59</sup> supported the superiority of these agents over placebo. In addition, there was one positive placebo-controlled study each for diclofenac-K,<sup>60</sup> flurbiprofen,<sup>61</sup> naproxen,<sup>62</sup> piroxicam SL,<sup>63</sup> piroprofen\*,<sup>29</sup> and proquazone\*.<sup>64</sup> Diclofenac sodium IM\* was superior to placebo<sup>65</sup> and low doses of acetaminophen IM\*.<sup>66</sup> Only one placebo-controlled study of acetaminophen (PO) for acute treatment of migraine was identified in the search, and it failed to demonstrate a significant effect over placebo.<sup>67</sup> Recently, three trials tested the efficacy of the combination of acetaminophen, aspirin, and caffeine (Excedrin®) in migraine patients (studies recently published and not included in the *AHCPR Technical Review*). Approximately 66% of the patients treated had migraine headache of moderate intensity. In all three studies, significantly greater headache relief was reported for patients taking the combination analgesic, compared with placebo.<sup>68</sup>

Three trials directly compared one agent in this class with another. One of the three found that tolfenamic acid\* was superior to acetaminophen,<sup>69</sup> otherwise, no significant differences were observed compared to aspirin<sup>22</sup> or ibuprofen.<sup>70</sup> A series of trials examining the effect of adding an antiemetic or caffeine to tolfenamic acid or aspirin suggested that these combinations offered no advantages over the analgesics alone for the measured pain outcomes.<sup>55,58,71</sup>

Comparisons with pharmacotherapies in other classes demonstrated few important differences. Two trials indicated that opiate-containing aspirin compounds (Doleron®\* and Doleron novum®\*) were more efficacious than aspirin alone.<sup>30,31</sup> Ergotamine was superior to aspirin in two trials.<sup>30,31</sup> No significant differences were observed between ergotamine (± caffeine) and ketoprofen PR\*,<sup>23</sup> naproxen sodium,<sup>28,32,72</sup> or tolfenamic acid\*.<sup>22</sup> One trial each comparing aspirin plus

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\* Currently not available in the US.

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metoclopramide and lysine acetylsalicylate plus metoclopramide with oral sumatriptan found no significant differences between the analgesic compounds and sumatriptan for headache relief.<sup>73</sup>

Evidence concerning the clinical efficacy of ketorolac IM in comparative trials was inconclusive due to small sample size and the lack of placebo control.<sup>16,74-76</sup>

Long-term side effects associated with aspirin and other NSAIDs (especially gastric symptoms) are well documented. However, in the short-term trials reviewed in the *AHCPR Technical Review*,<sup>1</sup> aspirin was generally well tolerated. Other NSAIDs were associated with higher rates of gastric irritation/discomfort, nausea, and vomiting. NSAIDs were consistently associated with lower overall adverse event rates when compared with ergotamine; in particular, lower rates of nausea and vomiting were noted. Studies indicated that adding an antiemetic did not reduce the adverse gastrointestinal events typically associated with NSAIDs.<sup>1,2</sup>

## **Opiate Analgesics**

Six placebo-controlled, randomized trials tested the efficacy of a variety of oral codeine-containing agents, including acetaminophen plus codeine and proprietary combinations of acetaminophen, codeine, and doxylamine (Mersyndol®<sup>\*</sup>) or buclizine (Migralve®<sup>\*</sup>). Though meta-analysis of the results was not possible (because these trials used varying doses of slightly different agents) the evidence suggests, on the whole, that these agents provide significant relief.<sup>54,77-81</sup>

In one trial, the addition of doxylamine to acetaminophen plus codeine failed to improve efficacy.<sup>72</sup> One trial found no significant differences between acetaminophen plus codeine and

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\* Currently not available in the US.

aspirin,<sup>54</sup> and another trial found no significant difference between Migraleve®\* and ergotamine plus cyclizine plus caffeine (Migril®).<sup>82</sup>

Two trials compared aspirin plus dextropropoxyphene plus phenazone combinations (Doleron®\*, Doleron novum®\*) with aspirin alone and found that these combination agents were significantly more effective than aspirin at providing complete relief at 30 minutes.<sup>30,31</sup> The same two trials found no significant difference between Doleron®\*/Doleron novum®\* and ergotamine; however, Doleron novum®\* was significantly better than ergotamine for controlling nausea and vomiting.<sup>31</sup>

One trial reported that methadone IM was significantly better than placebo at relieving head pain lasting more than two hours.<sup>83</sup> Two trials reported consistent results showing butorphanol nasal spray to be superior to placebo.<sup>83,84</sup> Butorphanol 2 or 3 mg IM was superior to butorphanol 1 mg IM.<sup>85</sup> One study demonstrated that butorphanol nasal spray (Stadol®) was superior to Fiorinal® with Codeine in patients with migraine.<sup>19</sup> No clear differences in analgesic efficacy were demonstrated when parenteral opiate analgesic treatments (butorphanol IM vs. meperidine IM plus hydroxyzine IM,<sup>50</sup> methadone IM vs. butorphanol IN) were compared.<sup>83</sup> Butorphanol IM failed to show superiority compared with DHE plus metoclopramide IV, as measured by pain outcomes 30 minutes following treatment.<sup>50</sup> Meperidine IV or IM plus dimenhydrinate IV or IM was not significantly different compared with chlorpromazine IV<sup>17</sup> or methotrimeprazine\* IM,<sup>18</sup> respectively. Studies comparing meperidine with ketorolac IM<sup>74</sup> or DHE IV<sup>50-52</sup> were inconclusive. The results from the studies with meperidine showed that it was not superior to other effective medications

(chlorpromazine IV, methotrimeprazine\* IM, ketorolac IM, DHE plus metoclopramide IV).

However, there have been no placebo-controlled trials with meperidine.

The oral opiate analgesics reviewed were associated with a higher rate of adverse events than was placebo, but were similar to aspirin and better than ergotamine in that respect. The most commonly reported adverse events included dizziness, fatigue, nausea, and drowsiness. Adverse events were much more frequently reported with nasal butorphanol than with placebo or with oral opiate analgesics.<sup>1,2</sup>

### **"Triptans" (Serotonin [5-HT<sub>1B/1D</sub>] Agonists)**

**Subcutaneous 5-HT<sub>1B/1D</sub> Agonists:** Fourteen placebo-controlled trials were consistent in showing subcutaneous (SC) sumatriptan, in a dose of 6 mg, to be superior to placebo for headache relief and complete relief at 1 and 2 hours.<sup>86-99</sup> Two of these studies suggested that a second dose of sumatriptan SC, administered 1 hour after the first, provided no added benefit.<sup>90,98</sup> A recent placebo-controlled, randomized trial with the newly developed 5-HT<sub>1B/1D</sub> agonist, almotriptan SC, also reported significant headache relief for acute treatment of migraine<sup>100</sup> (recently published as an abstract and not included in the *AHCPR Technical Review*).

Two trials directly compared subcutaneous and oral formulations of sumatriptan. Methodological differences between the trials complicated their comparison and interpretation, but both studies found subcutaneous sumatriptan to be significantly more effective than oral sumatriptan at 2 and 4 hours.<sup>101,102</sup>

One trial each compared subcutaneous sumatriptan with subcutaneous DHE<sup>49</sup> and DHE nasal spray.<sup>48</sup> In both trials, 1- and 2-hour data on headache relief and complete relief favored sumatriptan, while 2- to 24-hour recurrence rates favored DHE.

One placebo-controlled trial suggested that sumatriptan SC is effective for the treatment of recurrent headache after initially successful treatment with sumatriptan.<sup>103</sup> Another trial found that sumatriptan, administered during the migraine aura, before the onset of headache pain, was no more effective than placebo at preventing the development of a moderate-to-severe headache.<sup>87</sup>

A significantly higher proportion of patients reported adverse events in association with subcutaneous sumatriptan than with placebo. Adverse event rates with subcutaneous sumatriptan were higher than with DHE nasal spray, but lower than with subcutaneous DHE. The most commonly reported symptoms associated with sumatriptan SC were injection site reactions, flushing, dizziness/vertigo, and paresthesia/tingling. Small numbers of patients reported transient chest symptoms in many of the trials included in the analysis.<sup>1,2</sup>

**Oral 5-HT<sub>1B/1D</sub> Agonists:** The first 5-HT<sub>1B/1D</sub> agonist to be developed and tested for oral administration was sumatriptan, followed by zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan (the later three agents are in clinical development as of this writing). Eleven placebo-controlled trials provided consistent evidence that oral sumatriptan, in a dose of 100 mg (doses currently available in US: sumatriptan 25 mg and 50 mg) is significantly more effective than placebo for headache relief and complete relief at 2 and 4 hours.<sup>104-114</sup> Three of these trials also supported the efficacy of lower doses of the medication (25 mg and 50 mg).<sup>104,110,112</sup> In the only multi-dose study reporting 4-hour outcomes, headache relief and complete relief rates with the 50-mg dose were comparable to those reported with 100 mg, and superior to the 25 mg dose.<sup>110</sup> In general, the proportions of patients reporting relief with oral sumatriptan were lower than with subcutaneous sumatriptan. As noted above, two trials directly comparing subcutaneous and oral sumatriptan suggested that the subcutaneous formulation provides superior relief.<sup>101,102</sup>

Eleven randomized, placebo-controlled trials tested the efficacy of the newer oral 5-HT<sub>1B/1D</sub> agonists for the treatment of acute attacks of migraine. Four trials found that rizatriptan was significantly better than placebo for headache relief and complete relief at 2 hours; doses tested ranged from 5 mg to 40 mg, with higher rates of relief reported with the higher doses (doses currently available in US: rizatriptan 5 mg and 10 mg).<sup>114-117</sup> Zolmitriptan (2.5 mg or 5 mg) was shown in three trials to be significantly more effective than placebo for headache relief and complete relief at 2 and 4 hours.<sup>118-120</sup> The only trial that directly compared the 2.5- and 5-mg doses of zolmitriptan found no significant difference between them.<sup>118</sup> Two trials tested the efficacy of naratriptan and found a significant clinical benefit over placebo for the 1- and 2.5-mg doses at 4 hours post-treatment.<sup>121-122</sup> Rates of relief with naratriptan were lower than with the other oral 5-HT<sub>1B/1D</sub> agonists. Two trials of eletriptan provided less information, but suggested that this agent may also be effective in some doses (40 mg, 80 mg).<sup>105,123</sup> Recently, the first clinical reports for two newly developed 5-HT<sub>1B/1D</sub> agonists also have been reported in abstract form (not included in the *AHCPR Technical Review*). Specifically, placebo-controlled, randomized trials in migraine patients suggest a clinically significant migraine relief for oral almotriptan<sup>124</sup> and frovatriptan.<sup>125-127</sup>

To date, only one published study directly compared oral sumatriptan (100 mg) and rizatriptan (10, 20, 40 mg) and found that a high dose of rizatriptan (40 mg) produced significantly better results at 2 hours.<sup>115</sup> There were no significant differences between sumatriptan and the lower doses of rizatriptan (at 2 hours). Other comparative trials are either underway or have recently been completed. Although statistical differences may be achieved between different agents and/or doses, the clinical relevance of these differences is not clear. Some of the comparative trials have been presented only in abstract form, and therefore, firm conclusions on a differential efficacy among the different oral 5-HT<sub>1B/1D</sub> agonists cannot be established at this time.

One trial each compared sumatriptan 100 mg with aspirin plus metoclopramide,<sup>73</sup> lysine acetylsalicylate plus metoclopramide,<sup>113</sup> and a rapid-release formulation of tolfenamic acid\*.<sup>106</sup> These trials found no significant differences between the analgesic compounds tested and sumatriptan for headache relief at 2 hours, and only one of the three trials found sumatriptan to be significantly better for complete relief.<sup>73</sup> The single trial comparing sumatriptan with ergotamine plus caffeine found sumatriptan to be significantly more effective for both headache relief and complete relief at 2 hours.<sup>35</sup>

Two trials showed that the use of a second dose of oral sumatriptan, 2 hours to 4 hours after the first, did not provide any additional relief from the initial headache.<sup>128,129</sup> Similarly, three trials showed that a second dose of the medication did not prevent headache recurrence.<sup>128-130</sup> However, four trials of sumatriptan,<sup>111,128,129,131</sup> and one trial each of rizatriptan<sup>117</sup> and zolmitriptan<sup>118</sup> found that these agents were significantly better than placebo at relieving recurrent headache pain. One small study did not support the use of zolmitriptan during the aura phase for the short-term prevention of migraine.<sup>132</sup>

Adverse events—most commonly malaise/fatigue, dizziness/vertigo, asthenia, and nausea—were generally more frequent (and in some cases significantly more frequent) with the oral 5-HT<sub>1B/1D</sub> agonists than with placebo. The incidence of adverse events was dose-dependent with rizatriptan and zolmitriptan. Significantly more patients reported adverse events with sumatriptan than with aspirin/lysine acetylsalicylate plus metoclopramide. For all treatments in this drug class, small numbers of patients reported transient chest symptoms.<sup>1,2</sup>

**Nasal 5-HT<sub>1B/1D</sub> Agonists:** Six placebo-controlled trials supported the efficacy of sumatriptan nasal spray for headache relief at 1 and 2 hours.<sup>133-136</sup> A dose-response relationship was

demonstrated, with superiority to placebo at the 10-, 20-, and 40-mg doses. Results with the 5-mg dose were mixed, and the 1-mg dose was shown to be ineffective. Significantly more patients reported adverse events with sumatriptan nasal spray than with placebo, the most common symptom being "taste disturbance."

**Other Delivery Methods for 5-HT<sub>1B/1D</sub> Agonists:** One trial each tested the efficacy of sumatriptan IM\*<sup>137</sup> and sumatriptan PR\*.<sup>138</sup> Sumatriptan IM\* 6 mg was found to be as effective as chlorpromazine IV at 1 and 2 hours post-treatment. Sumatriptan PR\* (12.5 mg or 25 mg) was significantly more effective than placebo at 2 hours, with a stronger clinical benefit observed with the higher dose.

## Other Medications

**Isometheptene and Isometheptene Combination Agents:** In two placebo-controlled trials, isometheptene attained borderline significance in relieving headache pain.<sup>139-141</sup> Isometheptene mucate plus acetaminophen plus dichloralphenazone (Midrin®/Midrid®) was significantly more effective than placebo in two of three trials, although the magnitude of the effect was relatively modest.<sup>67,139,140</sup>

Two studies examined the clinical efficacy of Midrin® in comparison with one of its constituents (acetaminophen and isometheptene, respectively) and found no significant advantages to the combination product.<sup>67,140</sup> One trial showed Midrid® to be significantly more effective than ergotamine plus caffeine at reducing headache intensity,<sup>34</sup> Midrid® was also associated with significantly less nausea and vomiting.

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\* Currently not available in the US.

Adverse events associated with isometheptene and Midrin®/Midrid® were not significantly more frequent than with placebo or with the comparator medications described above.

**Lidocaine:** Lidocaine IV demonstrated limited benefit over placebo in one small study that failed to demonstrate clinically significant benefit or harm.<sup>142</sup> In a second trial, lidocaine was significantly less effective than chlorpromazine IV and not more effective than DHE IV.<sup>15</sup> One study suggested the intranasal lidocaine is effective in relieving headache pain quickly (within 15 minutes), but a high incidence of recurrence and pronounced local adverse events were also reported.<sup>143</sup> A more recently published abstract (not included in the *AHCPR Technical Review*) also indicated that intranasal lidocaine provided rapid relief; however, the previously reported high incidence of recurrence<sup>143</sup> was not confirmed in this later study.<sup>144</sup>

**Dexamethasone IV or Hydrocortisone IV:** Two small studies have been done, but they provide insufficient data from which to draw conclusions about the efficacy or safety of either dexamethasone IV or hydrocortisone IV for acute treatment of migraine.<sup>47,145</sup>

**Diazepam PO and Chlormezanone\* PO:** A single, moderately large trial suggested that neither diazepam nor chlormezanone\* significantly enhanced the antimigraine effects of a combination of metoclopramide IM and oral acetaminophen.<sup>146</sup>

### C. Transition from Evidence to Guidelines

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\* Currently not available in the US.

A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have been demonstrated to be effective in the management of acute migraine headache. It also provides a clear understanding of the adverse events associated with various agents. The challenge lies in incorporating this information effectively into clinical practice. A list of effective and well-tolerated antimigraine treatments does not provide direct guidance on how these medications should be used in a clinical setting.

Some medications that are commonly used to treat migraine (e.g., butalbital) have not been well studied in controlled trials in migraineurs. Other trials have only limited data reported (e.g., in abstract form), making it difficult to assign reliable quality scores. In addition, many of the trials have focused on patients recruited from specialty headache clinics. These patients may have more severe or disabling headaches than most patients with migraine. It is unclear how these clinical trials may apply to the general population of migraineurs.

As reviewed above, for many agents, statistically significant differences were noted compared with placebo, other active treatments, and baseline measures. Results reported as "statistically significant" do not necessarily reflect the clinical relevance of these improvements. This is seen clearly with statistically significant differences achieved between active treatments such as ergot alkaloids and derivatives, and with triptans, with statistically significant differences in therapeutic response of 4% to 8%. In these instances, doctors may not rely on clinical efficacy alone. Rather, other measures (such as patient preference, modes of delivery, frequency of adverse events, and/or onset of action) can help determine the agent of choice for the particular patient. Consequently, for many agents, statistical significance cannot be adopted without considering clinical relevance and other treatment factors.

Migraine patients clearly differ in treatment needs based on factors such as pain intensity, level of disability, coexisting conditions, response to specific medications, and associated nonheadache symptoms. Evidence to support a choice among agents in a general class of drugs (e.g., NSAIDs), or how to combine or alternate therapies has not been established in clinical trials.

For all these reasons, the translation of scientific evidence to Guidelines must rely not only on the collective assembly of proven clinical efficacy and safety data, but also on expert consensus. The following sections provide recommendations on general principles of migraine management and specific treatment recommendations. These recommendations complement the available evidence summarized in the *AHCPR Technical Review*<sup>1,2,20</sup> and help provide complete patient management for treatment of acute migraine attacks.

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

In addition to the general principle guiding the development of this document that acute migraine treatment selection should be based, to the extent possible, on scientific evidence, the US Headache Consortium identified two general principles of care. These general principles are not evidenced-based, but are the foundation of a practical approach to treating the patient with acute migraine. The general principles are:

- engage patients in their own management (e.g., discuss treatment/medication preferences)
- tailor treatment to the individual's needs (e.g., based on severity of illness, comorbidity/coexisting conditions, prior response to medications).

Based on these general principles, the US Headache consortium agreed unanimously on several recommendations, listed below.

**Educate migraine sufferers about their condition and its treatment, and encourage them to participate in their own management.** There are at least three reasons that migraine sufferers should be educated about their condition and its treatment and encouraged to participate in their own management. First, patient input can provide the best guide to treatment selection, as there is a strong belief that certain patients respond better to some agents than to others. Second, engaging the patient permits the physician to better understand and accommodate patient treatment goals. For example, it may not always be possible to fulfil the goal of “complete relief” and “maintenance of function;” patient preferences here are crucial. Third, developing an effective acute migraine management strategy can be complex and an engaged patient is more likely to negotiate this process successfully.

**Use migraine-specific agents (triptans, DHE, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine.** Despite the lack of evidence that headaches of different type and severity respond to specific agents, strong clinical impression suggests that this is true. Failure to use an effective treatment promptly may increase pain, disability, and the impact of the headache.

**Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.** In some patients, concomitant treatment with an antiemetic and an oral migraine medication may be appropriate. Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is

one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.

**Consider a self-administered rescue medication for patients with severe migraine that do not respond well to (or fail) other treatments.** A rescue medication is an agent that the patient can use at home when other treatments have failed. While rescue medications often do not completely eliminate pain and return patients to normal activities, they permit the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department. A cooperative arrangement between provider and patient may extend to the use of rescue medication in appropriate situations.

**Guard against medication-overuse headache. (“Rebound headache” or “drug-induced headache” are sometime used interchangeably with “medication over-use headache.”)** Medication-overuse headache results from frequent use of acute medications<sup>147</sup> and is a pattern of increasing headache frequency often resulting in daily headaches.<sup>148</sup> (Rebound headache is distinct from medication-overuse headache in that rebound headache is associated with withdrawal of analgesics or abortive migraine medication. Our understanding of this phenomenon is based on strong clinical impression and limited research.<sup>147, 148</sup> There is no uniform agreement about which agents can cause rebound headache, although ergotamine [not dihydroergotamine], opiates, triptans, NSAIDs, simple and mixed analgesics containing butalbital, caffeine, or isometheptene are generally thought to do so. There is less uniform opinion about other antimigraine agents.) To decrease the risk of medication-overuse headaches, many experts suggest limiting acute therapy for patients who have

more than two headache days per week on a regular basis. In patients with suspected medication overuse or patients at risk of medication overuse, consider preventive therapy.<sup>149</sup>

## **E. Specific Treatment Recommendations**

Evidence is insufficient to support a definitive algorithmic approach to the pharmacological therapy of acute migraine attacks. Further, the lack of head-to-head clinical trials comparing the relative efficacy and cost/benefit among agents precludes creating scientific standards that specify the use of one agent over the other. Consequently, the US Headache Consortium created a scientifically supported list of specific recommendations regarding individual medications that is based on a combination of scientific evidence and clinical opinion. Table 3 lists places specific medications into different groups based on the based on a combination of scientific evidence and clinical opinion. Individual treatment efficacy and safety summaries are detailed in Table 1 and are judged based on several measures:

1. quality of the evidence (Grade A, B, or C [ A = multiple well-designed randomized, clinical trials, directly relevant to the recommendation, and yielded a consistent pattern of findings. B = some evidence from randomized clinical trials, but the scientific support was not optimal— as further described below. C = the US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized, controlled trials.]),<sup>150</sup>
2. overall scientific effect (based on proven efficacy results from randomized, controlled, clinical trials),
3. clinical impression (based on the expert consensus of the US Headache Consortium), and

4. adverse effects.

**Antiemetics**

- Antiemetics— Oral

Findings: Studies of specific agents, such as domperidone\* and prochlorperazine, suggest some clinical benefit, but studies were limited. No studies were identified for other oral antiemetics as monotherapy to manage acute migraine attacks for headache relief.

Recommendations: Oral antiemetics may be used as an adjunct in the treatment of nausea associated with migraine (Grade C).

- Metoclopramide IM

Finding: Studies did not demonstrate efficacy of metoclopramide IM as monotherapy for treatment of acute migraine.

Recommendation: Metoclopramide IM may be considered as an adjunct to control nausea in the treatment of migraine (Grade C).

- Metoclopramide IV

Finding: Two out of three studies reported metoclopramide IV effective for acute treatment of migraine.

Recommendation: Metoclopramide IV may be an appropriate choice as adjunct therapy for the treatment of headache pain or nausea for migraine in the appropriate setting (Grade C). Metoclopramide IV may be considered as monotherapy for migraine pain relief (Grade B).

- Prochlorperazine (parenteral)

Findings: One study each evaluated the efficacy of prochlorperazine IM/IV/PR and found it to be relatively safe and effective for the treatment of migraine headache and associated nausea and vomiting.

Recommendations: Prochlorperazine IV, IM, and PR may be a therapeutic choice for migraine in the appropriate setting (Grade B). Prochlorperazine PR may be considered an adjunct in the treatment of acute migraine with nausea and vomiting (Grade C).

- Serotonin receptor (5-HT<sub>3</sub>) antagonists

Findings: Studies testing the efficacy of granisetron and zatosetron\* did not demonstrate a statistically significant clinical benefit for headache relief. Sufficient studies have not been done to demonstrate the clinical efficacy of this class of drug.

Recommendations: Evidence is insufficient at this time to establish, or refute, a role for 5-HT<sub>3</sub> antagonists as monotherapy in the management of acute attacks (Grade B). However, 5-HT<sub>3</sub> antagonists may be considered as adjunct therapy to control nausea in selected patients with migraine attacks (Grade C).

## **Barbiturate Hypnotics**

- Butalbital-containing agents

Findings: No randomized, placebo-controlled studies prove or refute efficacy for butalbital-containing agents in the treatment of acute migraine headaches.

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\* Currently not available in the US

Recommendations: Based on concerns of overuse, medication-overuse headache, and withdrawal, the use of butalbital-containing analgesics should be limited and carefully monitored (Grade B).

### **Ergot Alkaloids and Derivatives**

- Ergotamine PO/PR (and caffeine combination)

Findings: Evidence was inconsistent to support efficacy of ergotamine for the treatment of migraine. Studies documented a higher incidence of adverse events with ergots as compared with placebo, sumatriptan, isometheptene, NSAIDs, or dextropropoxyphene compounds.

Recommendations: In the treatment of selected patients with moderate-to-severe migraine, ergot derivatives may be considered (Grade B).

- DHE SC/IV/IM

Findings: No placebo-controlled trials in migraine patients have demonstrated the efficacy and safety of DHE SC, IM, or IV as monotherapy. Clinical opinion suggests that DHE SC is relatively safe and effective when compared with other migraine therapies, and DHE SC has less adverse events than when delivered IV.

Recommendations: Because of their inability to tolerate or take oral medication, patients with nausea and vomiting may be given DHE SC, IV, IM (Grade C). Initial treatment with DHE SC, IM is a reasonable choice when:

- the headache is moderate-to-severe, or

- an adequate trial of NSAIDs or other nonopiate analgesics (including combination analgesics such as acetaminophen plus aspirin plus caffeine) has failed to provide adequate relief in the past (Grade C).

The use of DHE IM, SC may be considered in patients with moderate-to-severe migraine (Grade B).

- DHE IV plus antiemetics IV

Findings: DHE IV plus antiemetics has been shown to be effective and moderately safe in the treatment of moderate-to-severe migraine, compared with parenteral opiates.

Recommendations: DHE IV plus antiemetics is an appropriate treatment choice for patients with severe migraine (Grade B).

- DHE nasal spray

Findings: DHE nasal spray is safe and effective for the treatment of acute migraine attacks.

Recommendations: The use of DHE nasal spray is an appropriate treatment choice and should be considered for use in patients with moderate-to-severe migraine (Grade A).

Because of their inability to tolerate or take oral medications, patients with nausea and vomiting may be given intranasal DHE (Grade C). Initial treatment with DHE nasal spray is a reasonable choice when:

- the headache is moderate-to-severe, or
- an adequate trial of NSAIDs or other non-opiate analgesics (including combination analgesics as acetaminophen plus aspirin plus caffeine) has failed to provide adequate relief in the past (Grade C).

## **NSAIDs, Combination Analgesics, and Non-opiate Analgesics**

- Acetaminophen

Findings: No evidence establishes the efficacy of acetaminophen in the acute treatment of migraine.

Recommendation: Acetaminophen is not a specific treatment option for migraine (Grade B).

- NSAIDs (oral) and combination analgesics

Findings: The most consistent evidence exists for aspirin, ibuprofen, naproxen sodium, tolfenamic acid\*, and the combination agent acetaminophen plus aspirin plus caffeine for the acute treatment of migraine. Limited (only one study) or inconsistent (some positive and some negative) evidence exists for other NSAIDs.

Recommendations: Their favorable tolerability make these agents a reasonable first-line treatment choice for mild-to-moderate migraine attacks or severe attacks that have been responsive in the past to similar NSAIDs or nonopiate analgesics (Grade A).

- Ketorolac IM

Findings: To date, no placebo-controlled trials testing the efficacy of ketorolac IM for treatment of acute migraine attack have been published. Small comparative trials suggest possible equivalence to some agents, and a single comparison trial with meperidine demonstrated inferiority.

Recommendation: Ketorolac IM is an option that may be used in a physician-supervised setting, although conclusions regarding clinical efficacy cannot be made at this time (Grade C).

## Opiate Analgesics

- Butorphanol nasal spray

Findings: The clinical efficacy of butorphanol specifically in migraine has been documented in two published reports.

Recommendation: Clinical experience and expert consensus concur that butorphanol represents a treatment option for some patients with migraine (Grade A). Specifically, butorphanol may be considered when other medications cannot be used or as a rescue medication when significant sedation would not jeopardize the patient (Grade C). Clinical concerns regarding the use of butorphanol lie in the fact that it is widely used despite the established risk of overuse and dependence. In special patients for whom use might be indicated, special attention should be given to these clinical concerns.

- Opiates— Oral combination

Findings: Studies demonstrated the effectiveness of oral opiate combination agents in terms of pain relief.

Recommendation: Oral opiate combinations may be considered for use in acute migraine when sedation side effects will not put the patient at risk and/or the risk for abuse has been addressed (Grade A).

- Opiates IM/IV

Findings: To date, only one placebo-controlled study has been published for methadone IM, and meperidine IM. This study demonstrated the effectiveness of opiates for pain relief.

Recommendation: Parenteral opiates may be considered for rescue therapy in a supervised setting for acute migraine when sedation side effects will not put the patient at risk and when the risk abuse has been addressed (Grade B).

### **Triptans (Serotonin<sub>1B/1D</sub> Receptor Agonists)**

- Naratriptan, rizatriptan, sumatriptan, zolmitriptan

Findings: Triptans are effective and relatively safe for the acute treatment of migraine headaches. To date, no evidence supports their use during the aura phase of a migraine attack. (Published case reports of cardiovascular ischemic events with this class of drug are found in the literature and are included in the product label.)

- Recommendations: The triptans are an appropriate treatment choice and may be considered for use in patients with moderate-to-severe migraine who have no contraindications for its use (Grade A).  
Because of their inability to take oral medications, patients with nausea and vomiting may be given intranasal or subcutaneous sumatriptan (Grade C). Use migraine-specific agents (triptans, DHE, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to NSAIDs or combination analgesics such as aspirin plus acetaminophen plus caffeine (Grade C).

### **Other Medications**

- Isometheptene and isometheptene-combination agents

Findings: Isometheptene-containing compounds were superior to placebo, with a small but statistically significant effect.

Recommendations: Based on clinical evidence and favorable tolerability, isometheptene-containing compounds may be a reasonable choice for patients with mild-to-moderate headache (Grade B).

- Dexamethasone or hydrocortisone

Findings: No good quality studies support or refute the effectiveness of steroids for acute migraine.

Recommendations: Corticosteroids may be considered as a treatment choice for rescue therapy for patients with status migrainosus (Grade C).

- Lidocaine— Intranasal

Findings: Limited studies reported lidocaine superior to placebo in relieving acute migraine headache at 15 minutes. The incidence of recurrence has been reported with mixed results.

Recommendations: Evidence is insufficient at this time to establish a defined role for intranasal lidocaine in the management of acute migraine headache (Grade B).

- Lidocaine IV

Findings: A few small studies suggested that lidocaine IV is not significantly better than placebo and is less effective than other parenteral therapies for treatment of acute migraine.

Recommendations: Evidence is insufficient to support the role for lidocaine IV in the management of acute migraine (Grade B).

## **F. Future Research**

Substantial progress has been made toward understanding which medications are effective for migraine headache. However, a host of unanswered questions remain. The *AHCPR Technical Reviews*,<sup>5,6,20</sup> as well as this Guideline, have reinforced the need for additional research. Several specific research topics are listed in Table 2. These research topics include general management issues as well as questions about the role and dosage of specific therapies.

In advancing this research agenda, it is important to recognize the complementary role of various forms of high quality evidence, including clinical trials, epidemiological studies, and cohort studies of practice patterns and resource use. As additional evidence becomes available, creating more comprehensive and authoritative recommendations for migraine therapy will be possible.

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## H. Tables and Figures

**Table 1: Evidence Summary for Treatment of Acute Attacks of Migraine**

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

5

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
<b>Antiemetics</b>						
Chlorpromazine IM (doses tested: 0.1 mg/kg for 1 to 3 doses to 1 mg/kg)	C	++	++	Mild to moderate	Extrapyramidal adverse events (e.g., dystonia), and sedation are associated with metoclopramide but rarely reported in the clinical trials reviewed. In some patients with migraine, sedation may be useful. Has role in pregnancy. Postural hypotension is an adverse event with chlorpromazine.	Adjunct therapy
IV (doses tested: 12.5 to 37.5 mg)	B	++	++			
Metoclopramide IM (dose tested: 10 mg) PR (dose tested: 20 mg) IV (doses tested: 0.1 mg/kg for 1-3 doses to 10 mg)	B B B	+ ++ ++	+ ? ++	Infrequent to occasional		Adjunct therapy
Prochlorperazine PR (dose tested: 25 mg) IM (doses tested: 10 mg) IV (doses tested: 10 mg)	B B B	+++ +++ +++	+ ++ +++	Occasional Occasional Frequent		Consider IM or IV as adjunct first-line therapy in emergency department or office; consider PR as adjunct.

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
Other antiemetics: Domperidone* (doses tested: 30 to 120 mg)	B	?	?	?	?	Possible use for pre-emptive treatment of migraine (i.e., given during prodrome).
<b>Barbiturate Hypnotics<sup>150</sup></b>						
Butalbital plus aspirin plus caffeine	C	?	+++	Occasional	Sedation common adverse event.	Occasional use for moderate and severe migraine. Limit use due to increased risk of headache rebound and medication-overuse.
Butalbital plus aspirin plus caffeine plus codeine (dose tested: 50 mg plus 325 mg plus 40 mg plus 30 mg)	B	++	+++			
<b>Ergot Alkaloids and Derivatives</b>						
DHE SC (dose tested: 1 mg) (dose approved: 1 mg)	B	+++	+++	Occasional	Most common adverse events with DHE include nausea, vomiting, dysphoria, flushing, restlessness, and anxiety. Should not be used in patients at risk for ischemic heart disease. Treatment associated with low	Use in patients with moderate-to-severe migraine.
IM (dose tested: 1 mg)	B	++	+++	Occasional		
IV (doses tested: 1 to 2 mg)	B	++	+++	Frequent		

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
DHE IV plus antiemetics (doses tested: 0.5 to 1 mg DHE)	B	+++	+++	Frequent	recurrence rates. DHE SC/IM has considerable less adverse events than IV. Adverse events associated with addition of antiemetic are described above.	Useful in patients with long-standing headache. May be used as therapy of choice in emergency department.
DHE nasal spray (doses tested: 0.5 to 4 mg) (dose approved: 2 mg)	A	++	+++	Occasional	Common adverse events include nasal congestion, nausea, and vomiting. Should not be used in patients with risk of ischemic heart disease. Associated with low incidence of recurrence.	Moderate-to-severe headache. Treatment option for patients with nausea and/or vomiting.

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
Ergotamine (doses tested: 1 to 5 mg) (dose approved: 2 mg)  Ergotamine plus caffeine (doses tested: 2 to 6 mg ergotamine; 200 to 600 mg caffeine) (dose approved: 2 mg ergotamine plus 200 mg caffeine)  Ergostine plus caffeine (doses tested: 2 mg plus 200 mg)	B	+	++	Frequent	Nausea and vomiting common adverse events. Treatment may be associated with ischemia, ergotism, and rebound.	Consider for selected patients with moderate-to-severe migraine.
<b>NSAIDs, Combination Analgesics, and Non-opiate Analgesics</b>						
Acetaminophen (doses tested: 650 to 4000 mg)	B	0	+	Infrequent	Well tolerated.	May be considered for use in either pediatric or pregnant migraine patients.
Diclofenac sodium IM* (doses tested: 75 mg)	B	+++	?	?	?	?
Ketoprofen PR* (doses tested: 100 mg)	B	+	?	?	?	
Ketorolac IM (doses tested: 30 to 60 mg)	B	+	++	Infrequent	Drowsiness and nausea common adverse events. Should not be used in	Consider for use in emergency department.

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
					Should not be used in patients with renal and GI diseases.	
NSAIDs— oral Aspirin (doses tested: 500 to 1000 mg)	A	++	++	Occasional	Gastric irritation/ discomfort, nausea, and vomiting common adverse events. NSAIDs should not be used in patients with ulcer or renal disease.	First-line for patients with migraine.
Diclofenac K (doses tested: 50 to 100 mg)	B	++	++			
Flurbiprofen (doses tested: doses tested: 100 to 300 mg)	B	+	++			
Ibuprofen (doses tested: 400 to 2400 mg)	A	++	++			
Naproxen (doses tested: 750 to 1250 mg)	B	+	++			
Naproxen sodium (doses tested: 750 to 1750 mg)	A	++	++			
Piroxicam SL (doses tested: 40 mg)	B	+	++			

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence<sup>††</sup></b>	<b>Scientific Effect<sup>‡‡</sup></b>	<b>Clinical Impression of Effect<sup>**</sup></b>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
Pirprofen* (doses tested: 400 mg)	B	+	++			
Tolfenamic acid* (doses tested: 200 to 400 mg)	A	++	++			
Combination Analgesics  Acetaminophen plus aspirin plus caffeine (dose tested: 500 mg plus 500 mg plus 130 mg[2 tablets]) (dose approved: 500 mg plus 500 mg plus 130 mg [2 tablets])	A	+++	++	Infrequent	Common adverse events described above and include insomnia.	First-line for patients with migraine.
<b>Opiate Analgesics</b>						
Butorphanol nasal spray (doses tested: 1 to 2 mg) (dose approved: 1 mg)	A	+++	+++	Frequent	Adverse events include dizziness, drowsiness, nausea and/or vomiting, vertigo, blurred vision, nervousness, and taste perversion.	For moderate-to-severe migraine; use as a rescue therapy. Limit use due to risk of rebound and medication-overuse.
Opiates—oral combinations  Acetaminophen plus codeine	A	++	++	Occasional	Common adverse events include dizziness, fatigue, nausea, and drowsiness.	Moderate-to-severe migraine. Limit use due to increased risk of headache rebound and dependency.

<b>Drug</b> (doses tested as reported in evidence reviewed) (initial dose approved for migraine [in the US])	<b>Quality of Evidence</b> <sup>††</sup>	<b>Scientific Effect</b> <sup>‡‡</sup>	<b>Clinical Impression of Effect</b> <sup>**</sup>	<b>Adverse Effects</b>	<b>Comments</b> (See full prescribing information for complete list of adverse events and contraindications.)	<b>Role (by consensus)</b>
<p>combinations (doses tested: 400 to 650 mg plus 16 to 25 mg)</p> <p>Migraleve®* (doses tested: 2 to 8 tablets)</p>						
<p>Opiates— parenteral</p> <p>Butorphanol IM (doses tested: 1 to 3 mg)</p> <p>Meperidine IM (doses tested: 75 to 100 mg)</p> <p>Meperidine IV (doses tested: 0.4 mg/kg up to 3 doses)</p> <p>Methadone (dose tested: 10 mg)</p>	B	++	++	Frequent	Sedation, nausea, and dizziness common adverse events. Although opiates provide significant pain relief, physicians must evaluate the risk-benefit ratio. Dependency may be a concern in some patients.	Reserved for emergency department use or as rescue medication. Limit use due to increased risk of headache rebound and dependency.

<b>Triptans (Serotonin<sub>1B/1D</sub> Receptor Agonists )</b>						
Sumatriptan nasal spray (doses tested: 1 to 40 mg) (dose approved: 5, 10, 20 mg)	A	+++	+++	Occasional	Adverse events with the nasal spray include unpleasant taste, and flushing. Chest symptoms are common but true ischemic events are rare. Contraindicated in patients with risk of heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension. Based on post-marketing information, rare incidences of myocardial infarction and stroke have been reported. Naratriptan is associated with a slower onset of action and lower recurrence rate. Sumatriptan SC is associated with a very rapid onset of action.	Moderate-to-severe migraine. Especially useful when nonoral route of administration is needed.
Oral triptans Naratriptan (doses tested: 1 to 2.5 mg) (doses approved: 1, 2.5 mg) Rizatriptan (doses tested: 5 to 40 mg) (doses approved: 5, 10 mg) Sumatriptan (doses tested: 25 to 100 m g) (doses approved: 25, 50 mg) Zolmitriptan (doses tested: 1 to 25 mg) (doses approved: 2.5, 5 mg)	A	++	++	Infrequent		Moderate-to-severe migraine.
	A	+++	+++	Occasional		
	A	+++	+++	Occasional		
Sumatriptan SC (doses tested: 1 to 8 mg) (dose approved: 6 mg)	A	+++	+++	Frequent		Moderate-to-severe migraine. Especially useful when nonoral route of administration is needed.
<b>Other Medications</b>						
Corticosteroids IV plus antiemetics  Dexamethasone (dose tested: 6 mg)	C	+	++	Infrequent	Consider limiting treatment to once per week.	Rescue therapy in status migrainosus.

Hydrocortisone (dose tested: 50 mg)						
Isometheptene (dose tested: 130 to 780 mg)  Midrid® (dose tested: 2 to 6 capsules)  Midrin® (dose tested: 2 to 5 capsules)	B	+	++	Infrequent	Drowsiness, dizziness, and nausea.	Consider for patients with mild-to-moderate headache.
Lidocaine IN (dose tested: 4% solution, 1 to 4 drops)	B	++	?	Frequent	Intranasal sensation/irritation common; short duration of action and possible headache recurrence.	Uncertain

\* Currently not available in the US

? = Not known.

†† **Quality of the evidence**<sup>150</sup>

- A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.
- 5 B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, either 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.

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†† **Scientific effect**

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

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

- 0 Most patients do not get relief.
- + Few people get complete relief; some get some relief.
- 20 ++ Some people get complete relief; most get some relief.
- +++ Most people get complete or nearly complete relief.

25 Medications with one negative trial and no positive trials vs. placebo: acetaminophen, acetaminophen + metoclopramide, acetaminophen + metoclopramide + diazepam, chlorpromazine IM, chlormezanone\* plus metoclopramide plus acetaminophen, diclofenac sodium PR\*, ergotamine plus caffeine plus butalbital plus belladonna alkaloids (Cafergot Comp.®), granisetron IV, lidocaine IV, zatosetron\* IV.

**Table 2: Acute Therapies for Migraine**

<p><b>Group 1: Proven pronounced statistical and clinical benefit</b> <i>(at least 2 double-blind, placebo-controlled studies + clinical impression of effect)</i></p>	<p><b>Group 2:</b> Moderate statistical and clinical benefit <i>(1 double-blind, placebo-controlled study + clinical impression of effect)</i></p>	<p><b>Group 3:</b> Statistically but not proven clinically OR clinically but not proven statistically effective <i>(conflicting or inconsistent evidence)</i></p>	<p><b>Group 4:</b> Proven to be statistically or clinically ineffective <i>(failed efficacy vs. placebo)</i></p>	<p><b>Group 5:</b> Clinical and statistical benefits unknown <i>(insufficient evidence available)</i></p>
<p>Acetaminophen plus aspirin plus caffeine PO Aspirin PO Butorphanol IN DHE SC, IM, IV DHE IV plus antiemetic DHE IN Ibuprofen PO Naproxen sodium PO Naratriptan PO Prochlorperazine IV Rizatriptan PO Sumatriptan SC, IN, PO Zolmitriptan PO</p>	<p>Acetaminophen plus codeine PO Butalbital plus aspirin plus caffeine, plus codeine PO Butorphanol IM Chlorpromazine IM, IV Diclofenac K, PO Ergotamine plus caffeine plus pentobarbital plus Belafolline® PO Flurbiprofen, PO Isometheptene compound, PO Ketorolac IM Lidocaine IN Meperidine IM, IV Methadone IM Metoclopramide IV Naproxen PO Prochlorperazine IM, PR</p>	<p>Butalbital, aspirin, plus caffeine PO Ergotamine PO Ergotamine plus caffeine PO Metoclopramide IM, PR</p>	<p>Acetaminophen PO Chlorpromazine IM Granisetron IV Lidocaine IV</p>	<p>Dexamethasone IV Hydrocortisone IV</p>

### Table 3. Future Research

#### General Migraine Management

- *Treatment selection based on headache severity and phase*– A basic unanswered question is whether targeting therapy to headache severity is effective. An additional important subject for study is whether less severe migraine or migraine prodrome may benefit significantly from early aggressive therapy.
- *Treating headache recurrence*– Headache recurrence is not well understood and clear treatment strategies to prevent its occurrence are more elusive. Studies need to be done to better understand the etiology of headache recurrence, how to avoid it, and once present, how to most effectively treat it.
- *Treating rebound headache*– Overuse of analgesics has been considered to cause rebound headache in some patients. Studies are lacking that investigate which patients are susceptible, what agents and what doses of these agents are associated with the highest incidence of rebound headache, and the efficacy of long-acting NSAIDs in patients suspected to have analgesic rebound headaches.
- *The roles of rescue medications*– Rescue medications are often used to allow the patient to avoid the unnecessary inconvenience and expense of a visit to the clinic or emergency department. It is not clear, however, for whom this strategy is likely to be effective.

#### Role and dosing of specific agents

• *Long-term use of opiate analgesics*– Longer-term studies need to examine the efficacy of headache management strategies incorporating opiate analgesics in terms of effect on headache frequency, severity, duration, and headache-related disability. Such studies could examine the problems of analgesic rebound headache, dependence, tolerance, and drug-related adverse events that may arise from long-term use of opiate analgesics.

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• *Use of domperidone\* to prevent onset of migraine headache*– Large, placebo-controlled trials should address the results of the two small trials suggesting that the antiemetic, domperidone\*, taken during the migraine prodrome, may be effective at aborting or preventing attacks of migraine with aura.

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• *Use of butalbital in migraine*– Despite its widespread use in migraine, butalbital-containing analgesics have not been studied in migraine. Specifically, no randomized, placebo-controlled trials have paid special attention to physical dependence upon these agents.

15 Word count: 12,833

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\* Currently not available in the US