The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies

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The study aims to provide an updated assessment of the evidence for individual pharmacological therapies for acute migraine treatment. Pharmacological therapy is frequently required for acutely treating migraine attacks. The American Academy of Neurology Guidelines published in 2000 summarized the available evidence relating to the efficacy of acute migraine medications. This review, conducted by the members of the Guidelines Section of the American Headache Society, is an updated assessment of evidence for the migraine acute medications. A standardized literature search was performed to identify articles related to acute migraine treatment that were published between 1998 and 2013. The American Academy of Neurology Guidelines Development procedures were followed. Two authors reviewed each abstract resulting from the search and determined whether the full manuscript qualified for review. Two reviewers studied each qualifying full manuscript for its level of evidence. Level A evidence requires at least 2 Class I studies, and Level B evidence requires 1 Class I or 2 Class II studies. The specific medications – triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) and dihydroergotamine (nasal spray, inhaler) are effective (Level A). Ergotamine and other forms of dihydroergotamine are probably effective (Level B). Effective nonspecific medications include acetaminophen, nonsteroidal anti-inflammatory drugs (aspirin, diclofenac, ibuprofen, and naproxen), opioids (butorphanol nasal spray), sumatriptan/naproxen, and the combination of acetaminophen/aspirin/caffeine (Level A). Ketoprofen, intravenous and intramuscular ketorolac, flurbiprofen, intravenous magnesium (in migraine with aura), and the combination of isomethioprene compounds, codeine/acetaminophen and tramadol/acetaminophen are probably effective (Level B). The antiemetics prochlorperazine, droperidol, chlorpromazine, and metoclopramide are probably effective (Level B). There is inadequate evidence for butalbital and butalbital combinations, codeine/acetaminophen and tramadol/caffeine, butorphanol or meperidine injections, intranasal lidocaine, and corticosteroids, including dexamethasone (Level C). Ocreotide is probably not effective (Level B). There is inadequate evidence to refute the efficacy of ketorolac nasal spray, intravenous acetaminophen, chlorpromazine injection, and intravenous granisetron (Level C). There are many acute migraine treatments for which evidence supports efficacy. Clinicians must consider medication efficacy, potential side effects, and potential medication-related adverse events when prescribing acute medications for migraine. Although opioids, such as butorphanol, codeine/acetaminophen, and tramadol/acetaminophen, are probably effective, they are not recommended for regular use.

Key words: migraine, acute treatment, pharmacology, episodic migraine, clinical trial

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abort a migraine attack. In association with the American Headache Society, the American Academy of Neurology (AAN) has recently published guidelines for preventive treatment. The last AAN Guidelines for acute treatment were published in 2000.

Herein we report the results of an updated systematic review of the published literature addressing the efficacy of medications used for acute treatment of migraine. These studies of acute migraine medications use 1 or more of multiple possible end-points of efficacy, including headache relief (ie, reduction from severe or moderate intensity to mild or none), headache freedom, decreased disability, the absence of nausea or vomiting, and the absence of photophobia or phonophobia. Outcomes have been measured at varying intervals following medication administration. However, the International Headache Society Clinical Trial Guidelines published in 2012 suggests that the percentage of study participants headache-free at 2 hours should usually be used as the primary outcome in acute therapy trials. Sustained pain freedom with the absence of other migraine symptoms at 24 or 48 hours is also an important patient-centered outcome and is considered the “ideal” migraine treatment response. Since the last AAN Guidelines for acute treatment in 2000, multiple large, randomized acute pharmacological migraine treatment clinical trials have been conducted. This updated assessment of the evidence seeks to answer the following question: Which pharmacological therapies are effective in treating acute migraine?

DESCRIPTION OF THE ANALYTIC PROCESS

The American Headache Society Guidelines Committee performed this project using the AAN protocol for systematic development of clinical guidelines (Figure). The author panel comprised headache experts. The members of the guidelines group disclosed any conflict of interest prior to involvement. Persons with a substantial conflict of interest, based on a portion of their incomes pertinent to the study, were excluded. Although this project began before the publication of the new Institute of Medicine (IOM) Clinical Practice Guidelines, our methods were largely consistent with the IOM methods, for we attempted to follow these principles of guideline development, rating of evidence, rating strength, and external review.

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“acute” or “immediate” and “drug therapy” or “pharmacotherapy.” We excluded animal studies, non-English-language articles, and comments, letters, or editorials, and we removed duplicate articles. We did not consider unpublished data, gray literature, or conference abstracts for the purpose of this review. The search strategy may be found in Appendix 1. Two study team members reviewed each of the abstracts that resulted from the search, and then independently determined if the study should be excluded from further review or if the full manuscript should be reviewed. Two reviewers then independently evaluated each of the studies selected for full-text review and determined whether the study met criteria for inclusion. In the event of disagreement between the 2 reviewers, a third study team member reviewed the abstract and/or full manuscript to determine inclusion or exclusion. We rated each study based on the quality of study design, considering the study size and length of treatment, treatment technique and doses, methods of data collection (prospective or retrospective), presence or absence of placebo, primary and secondary outcomes, and adverse events. Although we did not exclude open-label or observational studies, Class I and II studies required a placebo control arm. We considered dropout rates to be less relevant in these studies since many investigated a single migraine attack. Both reviewers completed a standardized data extraction form for each study (Appendix 2). The rating of each study followed recommendations according to the AAN therapeutic classification of evidence scheme, ranging from Class I to Class IV. Class I studies, well-designed double-blind, randomized, placebo-controlled trials, were considered best, while Class IV studies were often retrospective studies or case reports with unclear outcomes data. For a detailed description of the evidence scheme, see Appendix 3.

When we found no new studies for a particular drug, ratings were based on previous AAN Guidelines. In the event of conflicting evidence, meaning at least 1 negative and 1 positive study for a particular medication, we considered the Class I studies to be more important in assigning a level of evidence.

Based on the quality of studies, a level of evidence was assigned for each drug, as follows:

- **Level A:** Established as effective (or ineffective) for acute migraine (supported by at least 2 Class I studies)
- **Level B:** Probably effective (or ineffective) for acute migraine (supported by 1 Class I study or 2 Class II studies)
- **Level C:** Possibly effective (or ineffective) for acute migraine (supported by 1 Class II study or 2 Class III studies)
- **Level U:** Evidence is conflicting or inadequate to support or refute the use of the medication(s) for acute migraine

The AAN review published in 2000 did not use the current AAN therapeutic classification. Group 1 consisted of medications with at least 2 double-blind, placebo-controlled studies supporting their use, while group 2 only required 1 study. The concept of Class I or Class II studies was not considered. Because a single Class II study only supports a Level C recommendation in the new AAN classification, many of the previous group 2 medications are Level C in this review.

**ANALYSIS OF EVIDENCE**

The original search produced 805 articles, of which 132 were selected for review. Studies were excluded from this report if they met any of the following criteria:

- Did not include adult subjects
- Did not evaluate medication (ie, were medical devices or procedures)
- Assessed treatment of migraine aura or preventive treatment (ie, prevention of menstrual migraine)
- Evaluated medications that are neither currently commercially available in the United States nor pending approval
- Used nonstandardized primary outcome measures, such as patient satisfaction or disability
- Focused on comparisons between 2 or more medications, rather than placebo

**RESULTS**

We found no new Class I or II studies published since the most recent guidelines for butorphanol (intra-
muscular or nasal spray), combinations of butalbital/aspirin or butalbital/aspirin/codeine, acetaminophen/codeine, dihydroergotamine (DHE) (nasal spray, intramuscular, or intravenous), flurbiprofen, hydrocortisone, isomethobucene, intranasal lidocaine, and meperidine. Thus, no new review of previous studies was done, and we assigned levels of evidence for these agents based on the 2000 AAN Guidelines. Currently, no Class I or II studies exist for the use of intravenous diphenhydramine, intravenous valproate, intravenous verapamil, oral tofenamic acid, or celecoxib. Rofecoxib 25 mg and the combination of ergotamine/caffeine/pentobarbital/Bellafloline were included in the previous version of the guidelines but deleted from this review as they are no longer available.

**Almotriptan.**—In a Class I study, subjects taking almotriptan 2 mg, 6.25 mg, 12.5 mg, and 25 mg had 2-hour headache relief of 30%, 56.3%, 58.5%, and 66.5%, respectively, compared with 32.5% with placebo \(P < .05\) for 6.25 mg, 12.5 mg, and 25 mg.\(^a\) Adverse events were reported by 17.1%, 16.2%, 18.3%, and 25.5% of the patients in the almotriptan 2 mg, 6.25 mg, 12.5 mg, and 25 mg groups compared with 15.0% in the placebo group. Another Class I study examined the treatment of 3 migraine attacks.\(^9\) Subjects reported headache relief at 2 hours for at least 2 of 3 attacks in 63.8% and 74.5% of subjects taking 6.25 mg and 12.5 mg, respectively; in 3 separate migraine attacks, compared with 35.7% of those using placebo \(P < .001\).

In another 4-arm, randomized, controlled Class I trial, rates of headache freedom at 2 hours when treating early (within 1 hour) with 12.5-mg almotriptan were 53% at 2 hours, and 38% when treating moderate to severe headache, compared with 25% treating early and 17% treating late with placebo \(P = .0004\) for early treatment; \(P = .0002\) for late treatment).\(^9\) Adverse events were low (<5%), with no difference between active drug and placebo. In a separate Class I trial, subjects received almotriptan 12.5 mg or placebo within 1 hour of headache onset.\(^15\) At 2 hours after headache onset, almotriptan-treated patients were more likely to be headache-free (37.0% vs 23.9% placebo; \(P = .010\)) and experience headache relief (72.3% vs 48.4% placebo; \(P < .001\)). In a Class I study specifically looking at sumatriptan nonresponders, subjects receiving almotriptan 12.5 mg, compared with placebo, were more likely to be headache-free at 2 hours (47.5% vs 23.2% placebo; \(P < .05\)) and experience headache relief at 2 hours (33% vs 14%; \(P < .05\)).\(^12\)

**Eleetiptan.**—Two parallel-group, Class I placebo-controlled trials of 1 migraine attack treated with eleetiptan demonstrated superiority against placebo for 20 mg, 40 mg, and 80 mg doses. Subjects in the first study who received 20 mg, 40 mg, and 80 mg had 2-hour headache relief of 64%, 67%, and 76%, respectively.\(^13\) All studied doses were superior to the placebo response of 51% \(P < .05\). The second study revealed 2-hour headache relief rates of 47%, 62%, and 59% for the 20 mg, 40 mg, and 80 mg doses, respectively, compared with 22% for placebo \(P < .01\).\(^14\) Headache freedom rates at 2 hours were 14%, 27%, and 27% for the 20 mg, 40 mg, and 80 mg doses, which were superior to the 4% rate of headache freedom among subjects receiving placebo \(P < .01\). In a Class I, 3-attack study comparing 40-mg and 80-mg eleetiptan against placebo, both eleetiptan doses were superior to placebo for headache relief at 2 hours and headache freedom at 2 hours (40 mg: 62% headache relief, 32% headache freedom; 80 mg: 65% headache relief, 34% headache freedom; placebo: 19% headache relief, 3% headache freedom; \(P < .001\)).\(^15\)

A Class I study of early treatment with eleetiptan 20 mg, eleetiptan 40 mg, or placebo for 1 migraine attack found headache-free rates at 2 hours of 22% for placebo, 35% for 20 mg \(P < .01\) compared with placebo), and 47% for 40 mg \(P < .001\) compared with placebo).\(^16\) Although subjects were encouraged to treat migraine early, early treatment was not required. In those who were treated when headache was mild, the 40-mg 2-hour headache-free rate was 68%, compared with 25% for placebo \(P < .001\).

Another double-blind, parallel-group, placebo-controlled Class I study specifically studied eleetiptan in subjects with poor response or tolerability to sumatriptan.\(^17\) Subjects with up to 3 attacks were treated with either eleetiptan 40 mg, eleetiptan 80 mg, or placebo. Both eleetiptan 40 mg and eleetiptan 80 mg demonstrated consistency of response that was
superior to placebo; headache relief rates at 2 hours on at least 2 of 3 attacks in subjects taking eletriptan 40 mg (66%), 80 mg (72%), or placebo (15%; \( P < .001 \)).

A Class I study that asked subjects to treat migraine with 80-mg eletriptan during the aura phase before headache onset failed to demonstrate superiority against placebo. Sixty-one percent of subjects who treated with eletriptan developed moderate-to-severe headache within 6 hours, vs 46% subjects who treated with placebo (\( P = \text{ns} \)).

Frovatriptan.—Two Class I combined parallel dose-titration studies reported that frovatriptan 2.5 mg was more effective than placebo at 2 hours for headache relief (40% vs 23%; \( P < .001 \)).

Doses higher than 2.5 mg were no more effective at 4 hours (\( P = \text{ns} \)).

A Class I dose-titration study comparing frovatriptan 0.5 mg, 1 mg, 2.5 mg, and 5 mg vs placebo found that 2.5 mg was more effective than placebo at 2 hours for headache relief (38% vs 25%; \( P < .05 \)), while the other doses of frovatriptan were not superior to placebo. All doses of frovatriptan were superior to placebo at 4 hours for headache relief (48% for 0.5 mg, 68% for 2.5 mg vs 33% for placebo; \( P < .02 \)).

In a Class II crossover study of 2 migraine attacks, 1 with frovatriptan 2.5 mg, followed by placebo in 2 hours if headache increased to moderate or severe, and the other with placebo, followed by frovatriptan 2.5 mg in 2 hours for moderate or severe headache, sustained headache freedom at 24 hours was more common in subjects taking frovatriptan early (40%) compared with those taking it late (31%; \( P < .05 \)).

Naratriptan.—The 2000 AAN Guidelines concluded that naratriptan was effective for acute migraine. Since that guideline, a Class I study evaluated naratriptan 2.5 mg vs placebo for the treatment of menstrually related migraine. Subjects taking naratriptan were more likely to be headache-free at 4 hours (58% vs 30%; \( P = .004 \)).

Rizatriptan.—Rizatriptan was established as effective for the treatment of acute migraine in the 2000 AAN Guidelines. Since that guideline, a Class I trial compared rizatriptan oral dissolvable tablets, 5 mg and 10 mg, vs placebo for the treatment of 1 attack. Headache relief at 2 hours was 74%, 59%, and 28% in the 10 mg, 5 mg, and placebo groups, respectively (\( P < .01 \)). The 10 mg dose was more effective than 5 mg (\( P < .05 \)). Headache-free rates at 2 hours were 42%, 35%, and 10% (\( P < .01 \)).

Two other Class I studies evaluated rizatriptan 10 mg vs placebo for the treatment of migraine of mild intensity treated within 1 hour of onset. Subjects using rizatriptan were more likely to achieve headache freedom at 2 hours (57.3% and 58.9% vs 31.1% and 31.1%; \( P < .001 \)) and had 24-hour sustained headache freedom (42.6% and 48.0% vs 23.2% and 24.6%; \( P < .001 \)).

Two Class I studies compared rizatriptan 10 mg and placebo (randomized 2:1) for the treatment of 1 menstrually related migraine attack. Rizatriptan was significantly more effective in terms of both 2-hour headache relief (70% and 73% vs 53% and 50% for placebo; \( P < .001 \)) and 24-hour sustained headache freedom (46% and 46% vs 33% and 33%; \( P = .016 \) study 1; \( P = .024 \) study 2).

A Class I study compared rizatriptan oral dissolvable tablets 10 mg with placebo in patients taking topiramate for migraine prophylaxis. Subjects with 3 attacks were treated in this randomized, placebo-controlled, double-blind, multiple-attack study; 2 with rizatriptan and 1 with placebo. Rizatriptan was superior to placebo in terms of 2-hour headache relief (55.0% vs 17.4%; \( P < .001 \)), sustained headache relief from 2 to 24 hours (32.6% vs 11.1%; \( P < .001 \)), and 2-hour headache freedom (36.0% vs 6.5%; \( P < .001 \)).

In a Class II study of sumatriptan nonresponders, rizatriptan 10 mg orally disintegrating tablet was compared with placebo for the treatment of a single migraine attack. To be included in the study, subjects had to fail treatment with open-label generic sumatriptan 100 mg in the baseline phase. Subjects with 3 attacks were treated: 2 with rizatriptan and 1 with placebo in random order. In this population, rizatriptan was superior for 2-hour headache freedom (22% vs 12%; \( P = .013 \)), 2-hour headache relief (51% vs 20%; \( P < .001 \)), and sustained headache freedom from 2 to 24 hours (20% vs 11%; \( P = .036 \)).

Sumatriptan.—The 2000 AAN Guidelines established sumatriptan tablets 25 mg, 50 mg, and 100 mg, sumatriptan nasal spray, and sumatriptan injection 4 mg and 6 mg as effective.
In a Class I study of sumatriptan 50 mg and 100 mg for 1 migraine attack compared with placebo, 51.1% and 66.2% of subjects were headache-free at 2 hours in the 50 mg and 100 mg groups, compared with 19.6% of subjects treating with placebo \((P < .001)\). Two large Class I pooled studies that comprised 2696 patients found sumatriptan was superior to placebo as early as 20 minutes with the 100 mg dose for headache relief \((6\% \text{ vs } 4\% \text{ placebo}; P < .05)\) and at 30 minutes with the 50 mg dose \((19\% \text{ vs } 14\% \text{ placebo}; P < .05)\). Two-hour headache-free rates, considered a secondary outcome measure in this study, were 40% with 50 mg, 47% with 100 mg, and 15% with placebo \((P < .01)\). Similar results were observed for the individual studies. In study 1, sumatriptan tablets were significantly more effective than placebo at 25 minutes with the 100 mg dose and at 50 minutes with the 50 mg dose. In study 2, sumatriptan tablets were significantly more effective than placebo at 17 minutes for the 100 mg dose and at 30 minutes for the 50 mg dose \((P < .05)\). In the pooled data, the cumulative percentages of patients with pain relief by 2 hours after dosing were 72% for the 100 mg dose and 67% for the 50 mg dose, compared with 42% for placebo \((P < .001; \text{ both sumatriptan doses vs placebo})\). The cumulative percentages of patients with a pain-free response by 2 hours were 47% for the 100 mg dose, 40% for the 50 mg dose, and 15% for placebo \((P < .001; \text{ both sumatriptan doses vs placebo})\). In the individual studies, significantly more patients receiving either sumatriptan dose were migraine-free 2 hours after dosing, and had sustained pain relief and a sustained pain-free response over 24 hours, compared with placebo \((P < .001; \text{ both sumatriptan doses vs placebo})\). The only drug-related adverse events reported in less than 2% of patients in any treatment group in either study were nausea (both studies: 3% sumatriptan 100 mg, 2% sumatriptan 50 mg, 1% placebo) and paresthesia (study 1: <1% sumatriptan 100 mg, <1% sumatriptan 50 mg, 0% placebo; study 2: 3% sumatriptan 100 mg, 1% sumatriptan 50 mg, <1% placebo).

A Class I study of sumatriptan injection 4 mg reported 2-hour headache relief in 70% of sumatriptan-treated subjects and 22% of those receiving placebo \((P < .001)\). Sumatriptan injections first showed superiority over placebo at 10 minutes for headache relief \((11\% \text{ vs } 6\%; P = .039)\). A Class I study compared a new iontophoretic patch formulation of sumatriptan \((6.5 \text{ mg transdermal with delivery over 4 hours})\) with placebo for acute migraine treatment. Sumatriptan patch was superior to placebo patch for the primary end-point of headache freedom at 2 hours \((18\% \text{ vs } 9\%; P = .0092)\). For secondary measures, active drug was superior at 2 hours for freedom from photophobia \((51\% \text{ vs } 36\%; P = .0028)\), freedom from phonophobia \((55\% \text{ vs } 39\%; P = .0021)\), freedom from nausea \((84\% \text{ vs } 63\%; P = .0001)\), and headache relief \((53\% \text{ vs } 29\%; P = .0001)\).

A Class I randomized, double-blind, parallel-group, placebo-controlled study compared the effectiveness of intranasal sumatriptan 10 mg, intranasal sumatriptan 20 mg with placebo for a single migraine attack. Patients were instructed to use a new bidirectional powder delivery device for a moderate to severe attack. Intranasal sumatriptan 10 mg \((54\% \text{ vs } 25\%; P < .05)\) and 20 mg \((57\% \text{ vs } 25\%; P < .05)\) were both superior to placebo for headache freedom and headache relief at 2 hours \((10 \text{ mg } 84\% \text{ vs } 44\%, P < .001; 20 \text{ mg } 80\% \text{ vs } 44\%, P < .01)\).

**Sumatriptan/Naproxen Sodium.**—Two large studies compared a fixed combination of sumatriptan 85 mg and naproxen sodium 500 mg against sumatriptan 85 mg alone, naproxen sodium 500 mg alone, and against placebo. In study 1, 2-hour headache-free rates were 34% for the sumatriptan 85 mg/naproxen sodium 500 mg combination, compared with 25% for sumatriptan 100 mg, 15% for naproxen 500 mg, and 9% for placebo. The sumatriptan/naproxen sodium combination was superior to sumatriptan alone \((P = .009)\), naproxen, and placebo \((P < .001)\). The incidence of headache relief 2 hours after dosing was 65%, 55%, 44%, and 28% with sumatriptan/naproxen sodium, sumatriptan monotherapy, naproxen sodium monotherapy, and placebo, respectively, in study 1 \((P < .001 \text{ for sumatriptan/naproxen sodium, sumatriptan, and naproxen sodium vs placebo})\). In study 2, 2-hour headache-free rates were 30% for the sumatriptan 85 mg/naproxen sodium 500 mg combination, compared with 23% for sumatriptan 100 mg, 16% for naproxen sodium 500 mg, and 10% for placebo. The
The sumatriptan/naproxen sodium combination was superior to sumatriptan alone (P = .02), naproxen, and placebo (P < .001). The headache relief percentages in study 2 were 57%, 50%, 43%, and 29% (P < .001 for sumatriptan/naproxen sodium, sumatriptan, and naproxen sodium vs placebo; P = .03 for sumatriptan/naproxen sodium vs sumatriptan).

In a Class I 2-attack, crossover study of sumatriptan 85 mg/naproxen sodium 500 mg against placebo in persons with poor response to short-acting triptans (almotriptan, eletriptan, rizatriptan, sumatriptan, or zolmitriptan), sumatriptan/naproxen sodium treatment was superior to placebo for 2- to 24-hour sustained headache-free response (study 1: 26% vs 8%; study 2: 31% vs 8%; P < .001 for both comparisons). Headache-free rates at 2 hours were also superior in the sumatriptan/naproxen sodium group (study 1: 40% vs 17%; study 2: 44% vs 14%; P < .001).

Zolmitriptan.—Oral zolmitriptan was rated as effective for acute migraine treatment in the 2000 AAN Guidelines.

In a Class I study of zolmitriptan 2.5 mg oral dissolvable tablets against placebo for 2 migraine attacks, 2-hour headache-free rates were higher in those taking zolmitriptan (40% vs 20%; P < .001). Headache-free rates were also higher at 1 hour (13% vs 8%, P = .004) and 1.5 hours (25% vs 15%; P < .001).

Zolmitriptan 5 mg oral dissolvable tablets were compared against placebo in a Class I study for the treatment of 1 migraine attack. For the primary endpoint, headache relief at 30 minutes, zolmitriptan was superior to placebo (16.5% vs 12.5%; P = .048). Sustained headache freedom for 24 hours with zolmitriptan 5 mg was also superior to placebo (42.5% vs 16.4%; P < .0001).

Two Class I studies compared zolmitriptan nasal spray 5 mg against placebo. In the first study, subjects with 1 or 2 attacks were treated with either zolmitriptan nasal spray or placebo. Headache relief at 2 hours was greater in the zolmitriptan nasal spray group compared with placebo (66.2% vs 35.0%; P < .001), with rates of headache relief from zolmitriptan being superior to placebo as early as 15 minutes. Actual headache relief rates for zolmitriptan nasal spray and placebo groups, respectively, were 18.3% and 11.4% at 15 minutes, 39.2% and 24.1% at 30 minutes, and 56.9% and 34.2% at 1 hour (P < .001).

The second study compared zolmitriptan nasal spray 5 mg with placebo for the treatment of 1 attack and used a primary outcome of total symptom freedom (freedom from headache, nausea, photophobia, and phonophobia) at 1 hour. Zolmitriptan nasal spray was superior to placebo for total symptom freedom (14.5% vs 5.1%; P < .0001) at 1 hour. Secondary outcomes showed zolmitriptan to be superior to placebo for headache relief as early as 10 minutes (15.1% vs 9.1%; P = .0079) and for headache freedom as early as 30 minutes (7.7% vs 3.2%; P = .0039). The headache relief rate at 2 hours post-dose was 66.2% for the zolmitriptan group, compared with 35.0% for the placebo group (P < .001). Zolmitriptan nasal spray also produced significantly higher headache relief rates than placebo at all earlier time points assessed, starting as early as 15 minutes post-dose (P < .001). Similar results were obtained for the analysis of the first attack. Significantly higher pain-free rates were obtained with zolmitriptan nasal spray, compared with placebo, from 15 minutes post-dose onward (P < .005).

DHE.—A Class I double-blind, placebo-controlled, proof-of-concept efficacy trial analyzed DHE administration with a breath-synchronized inhaler for the treatment of acute migraine.

Treatment was randomized to 0.5 mg, 1.0 mg, and placebo in a 2:2:1 ratio. Rates of headache relief at 2 hours were higher in those subjects receiving 0.5 mg (72%) compared with placebo (33%; P = .019), but not in those subjects receiving 1.0 mg (65%; P = .071). Subjects receiving 0.5 mg (44%) and 1.0 mg (35%) were more likely to be headache-free at 2 hours compared with placebo (7%; P = .015 and .050, respectively).

A larger Class I phase 3, double-blind, placebo-controlled, parallel-group, single-attack study compared inhaled DHE 1.0 mg with placebo for the treatment of acute migraine, with the primary endpoints of headache relief, and absence of photophobia, phonophobia, and nausea at 2 hours. Patients were treated with DHE at the time of moderate or severe headache. Subjects treating with DHE were more likely to experience headache relief at 2 hours...
(59% vs 35%; \(P < .0001\), and freedom from phono-
phobia (53% vs 34%; \(P < .0001\), photophobia (47% vs
27%; \(P < .0001\), and nausea or vomiting (67% vs
59%; \(P = .0210\). DHE was also significantly more
effective for headache freedom at 2 hours (28% vs
10%; \(P < .001\) and for 2- to 24-hour sustained head-
ache freedom (23% vs 7%; \(P < .001\).

Acetaminophen.—Based on the 2000 AAN Guide-
lines, oral acetaminophen was considered probably
effective for acute migraine based on available evi-
dence (Level B).41-42 Since that guideline, a Class I
study comparing oral acetaminophen 1000 mg with
placebo for non-incapacitating migraine, ie, vomiting
less than 20% attacks and no need for bed rest, found
2-hour headache relief in 57.8% of those taking aceto-
mninophen vs 38.7% taking placebo (\(P = .002\)).43
Acetaminophen was superior in terms of 2-hour
headache relief in those with severe headache (50.9% vs
27% placebo; \(P = .008\)). There was not a signifi-
cantly better response to acetaminophen in the sub-
group of subjects with moderate headache (62% vs
48.1% placebo; \(P = .07\)). Two-hour headache-free
rates were higher in subjects taking acetaminophen
(22.4%) than in those treating with placebo (11.3%;
\(P = .01\).

A Class II study of intravenous acetaminophen
1000 mg for the treatment of 1 acute migraine attack,
with 30 clinic patients in each group, failed to demon-
strate significant differences between acetaminophen
and placebo in terms of headache freedom at 2 hours
(10% vs placebo 13%; \(P = ns\)), headache relief at 2
hours (50% vs 20% placebo; \(P = ns\)), and headache
freedom after 24 hours (31% vs 33% placebo;
\(P = ns\)).44

Chlorpromazine.—A Class I study compared intra-
venous chlorpromazine 0.1 mg/kilogram vs placebo in
the acute treatment of migraine with or without aura
in the emergency department.45 Compared with
placebo, chlorpromazine-treated subjects had higher
rates of headache relief at 30 minutes (46% vs 7%;
\(P < .05\)) and at 60 minutes (82% vs 15%; \(P < .05\)). Rates
of headache freedom at 1 hour were greater
among chlorpromazine-treated subjects (65% vs 8%;
\(P < .05\)). Benefits were similar in subjects who had
migraine with aura and in those who had migraine
without aura.

Droperidol.—In a Class I study, droperidol pro-
vided superior rates of 2-hour headache relief com-
pared with placebo.46 Subjects in this study were
randomized to receive injections of 0.1 mg, 2.75 mg,
5.5 mg, and 8.25 mg or matching placebo for treat-
ment of moderate to severe migraine. Two-hour head-
ache relief rates were superior for subjects receiving
2.75 mg (87%), 5.5 mg (81%), and 8.25 mg (85%)
compared with placebo (57%; \(P < .002\)). Headache
relief from droperidol was superior to placebo as
early as 1 hour for the 2.75 mg dose (\(P < .01\)), 90
minutes for the 5.5 mg dose (\(P < .001\), and 30
minutes for the 8.25 mg dose (\(P < .001\).

Phenazone.—A Class II study of oral phenazone
1000 mg vs placebo for 1 migraine attack treated
within 4 hours of migraine onset determined that sub-
jects receiving phenazone were more likely to have
2-hour headache relief compared with placebo
(48.6% vs 27.2% placebo; \(P = .002\).47 Phenazone was
superior to placebo for those subjects with moderate
intensity headache (53.6% vs 32.4% placebo;
\(P = .016\)) and for those subjects with severe headache
(38.9% vs 17.1% placebo; \(P = .042\)). Two-hour head-
ache-free rates were also higher in the phena-
zone group vs placebo (27.6% vs 13.6%; \(P = .016\).

Aspirin.—The 2000 AAN Guidelines established
oral aspirin as effective for the acute treatment of
migraine. In a Class I crossover study of 2 migraine
attacks, using aspirin mouth-dispersible formulation
900 mg vs placebo, 2-hour headache relief was
achieved in 48% of the aspirin group compared with
19% of the placebo group (\(P < .0005\)).48 Aspirin
began to show superiority over placebo at 30 minutes
in terms of headache intensity and at 3 hours for
headache freedom.

In a separate double-blind, placebo-controlled
Class I study of 1 migraine attack, aspirin 1000 mg
was compared with placebo.49 Aspirin was superior in
terms of headache relief at 2 hours (52% vs 34%;
\(P < .001\), and 20% of patients receiving aspirin were
headache-free from 1 to 6 hours after treatment, com-
pared with 6% of those receiving placebo (\(P < .05\).

Diclofenac.—In the 2000 AAN Guidelines,
diclofenac was considered probably effective for the
acute treatment of migraine.49-50 Since that guideline,
a Class I study compared treatment with diclofenac
Headache

100 mg, diclofenac 50 mg, sumatriptan 100 mg, and placebo. Subjects were asked to treat 4 separate migraine attacks, and they received a different treatment for each attack (1 of each). One hundred forty-four patients received at least 1 treatment, and 115 patients (80%) completed the study. The primary outcome was 2-hour headache intensity using a visual analog scale where 100 mm was maximal headache. Both diclofenac 50 mg and 100 mg were superior to placebo (22 mm average with 100 mg, 26 mm with 50 mg, and 46 mm with placebo; \( P < .001 \)).

In another Class I trial, subjects treated 4 migraine attacks, 2 with diclofenac 65 mg and 2 with placebo, in random order. Subjects with migraine with aura were excluded. Subjects treating migraine with diclofenac were more likely to be headache-free at 2 hours (45.8% vs 25.1%; \( P < .001 \)).

Another Class I study evaluated the use of 50-mg diclofenac potassium sachets and diclofenac 50 mg tablets in comparison to placebo in a crossover trial. Patients using sachets were more likely to be headache-free at 2 hours than those using placebo (24.7% vs 11.7%; \( P < .0001 \)) and those using 50 mg tablets (24.7% vs 18.5%; \( P = .0035 \)). Subjects using tablets were more often headache-free at 2 hours than those using placebo (18.5% vs 11.7%; \( P = .0040 \)). For 2-hour headache relief, both sachets (46.0% vs 24.1%; \( P < .0001 \)) and tablets (41.6% vs 24.1%; \( P < .0001 \)) outperformed placebo.

Another Class I study compared 50-mg diclofenac potassium oral solution with placebo in a double-blind, randomized, placebo-controlled, single-attack trial. Diclofenac was superior for 2-hour headache freedom (25% vs 10%; \( P < .001 \)), freedom from nausea (65% vs 53%; \( P = .002 \)), freedom from photophobia (41% vs 27%; \( P < .001 \)), and phonophobia (44% vs 27%; \( P < .001 \)) compared with placebo.

Ibuprofen.—The 2000 AAN Guidelines established ibuprofen as effective for acute migraine treatment. Since that guideline, a Class II study compared ibuprofen 200 mg and ibuprofen 400 mg with placebo. Subjects were excluded if they experienced either incapacitating migraines requiring bed rest more than 50% of the time or vomiting more than 20% of the time. For mild to moderate intensity headaches, 2-hour headache relief occurred in 41.7% of those taking ibuprofen 200 mg, in 40.8% of those taking ibuprofen 400 mg, and in 28.1% of the placebo group (\( P = .004 \) for 200 mg; \( P = .006 \) for 400 mg). In those with severe migraine, 400 mg was superior to placebo (36.9% vs 21.6% placebo; \( P = .048 \)), but there was no significant difference for the 200 mg group.

Ketorolac.—A Class II study evaluated an intranasal formulation of ketorolac tromethamine, containing 6% lidocaine for the acute treatment of migraine with and without aura, treated within the first 4 hours of a migraine attack. There was no significant difference for headache freedom at 2 hours in the ketorolac group compared with placebo (18% vs 10%; \( P = .17 \)). Ketorolac was superior to placebo for several secondary outcome measures, including lack of disability at 2 hours (24% vs 10%; \( P = .009 \)) and 2-hour headache relief (51.5% vs 31.9%; \( P = .02 \)).

Tramadol/Acetaminophen.—A Class I study compared tramadol 75 mg/acetaminophen 650 mg (given as 2 tablets) with 2 placebo tablets for the treatment of a single migraine attack. Headache relief at 2 hours was superior for subjects taking tramadol/acetaminophen (55.8 vs 33.8% placebo; \( P < .001 \)).

Headache freedom at 2 hours was also superior in those taking tramadol/acetaminophen (22.1% vs 9.3% placebo; \( P < .001 \)). Tramadol/acetaminophen was superior to placebo for photophobia at 2 hours (34.6% vs 52.2%; \( P = .003 \)) and phonophobia (34.3% vs 44.9%; \( P = .008 \)), but not for migraine-related nausea (38.5% vs 29.4% placebo; \( P = .681 \)).

Tramadol.—Intravenous tramadol 100 mg was compared with placebo for acute emergency treatment of a single attack in a single-blind Class II study. Tramadol was superior for the primary endpoint of 50% headache relief at 1 hour (76% vs 35.6%; \( P = .04 \)), but not for the secondary end-point of headache freedom (29% vs 11% placebo; \( P = ns \)).

Octreotide.—In a Class I placebo-controlled crossover study, patients treated acute migraine with at least moderate intensity with either 100-µg subcutaneous octreotide or placebo. Octreotide was not superior for headache relief at 2 hours (14% vs 20% placebo; \( P = ns \)) or for pain freedom at 2 hours (2% vs 7% placebo; \( P = ns \)).

Magnesium.—In a Class II placebo-controlled trial of intravenous magnesium sulfate (1 g for the...
treatment of 1 migraine attack), magnesium provided benefit superior to placebo at 60 minutes for the treatment of migraine with aura attacks in regard to headache relief (50% vs 13%; \( P < .05 \)) and headache freedom (37% vs 7%; \( P < .05 \)). In subjects without aura, there was no significant difference between magnesium and placebo (headache relief: 33% vs 17%; headache freedom: 23% vs 10%; \( P = \text{ns} \) for both comparisons).

Another Class II study of intravenous magnesium compared treatment with 2-g magnesium sulfate with 10-mg metoclopramide and placebo in a 1:1:1 ratio for the treatment of 1 migraine attack in the emergency department. The primary end-point was headache intensity on a visual analog scale at 30 minutes. Average headache intensity at 30 minutes was 3.9 mm in those receiving magnesium, 3.7 mm after metoclopramide, and 4.8 after placebo. There were no significant differences between treatment arms, but there was a benefit from magnesium compared with placebo in the subgroup experiencing migraine with aura compared with placebo (\( P = .04 \)) and metoclopramide (\( P = .03 \)).

**Intravenous Valproate.**—In a Class IV open-label study, patients with various primary headache disorders received 1 treatment of intravenous valproate for headache of moderate or severe intensity using doses ranging from 300 mg to 1200 mg. The majority of patients (63.1%) reported improvement, although those with episodic headache were more likely to do so. Another Class IV study reported the use of intravenous valproate 500 mg via slow intravenous bolus injection for acute migraine. In this observational study, 32 of 36 patients, including those with or without ongoing valproate prophylaxis, reported improvement after treatment (Table).

**DISCUSSION**

This systematic assessment of the literature is a comprehensive evaluation of the evidence for efficacy of individual migraine acute medications. The strength of the evidence for each medication has been graded. Thus, this American Headache Society evidence assessment can be used as a guide for knowing which medications have been shown to be superior to placebo for the acute therapy of migraine and for knowing the strength of the evidence supporting that superiority. According to this evidence assessment, specific medications within the following classes are deemed effective for migraine acute therapy: triptans, ergotamine derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and combination medications. Several other medications are “probably effective” or “possibly effective” as listed above.

This systematic assessment of the literature does not provide guidance regarding which medications should be used for the acute therapy of migraine for a specific patient. Although a clinician would want to prescribe an acute migraine medication that has strong evidence in support of its efficacy, potential side-effects, potential adverse events, patient-specific contraindications to certain medications, and drug–drug interactions all need to be considered when choosing a migraine acute medication. In clinical practice, acute treatment can be associated with serious adverse events, such as tolerance and dependence with barbiturates or opioids, peptic ulcer or renal disease with NSAIDs, or worsening migraine from medication-overuse headache. Thus, categorization of a medication as having Level A evidence of benefit does not necessarily mean that the medication should be considered a first-line drug for the acute treatment of migraine. For example, although butorphanol nasal spray has strong evidence for its superiority over placebo, this medication is commonly avoided due to concerns about dependence, addiction, and development of medication-overuse headache.

This review also does not address acute migraine treatment in children or the elderly. There is limited evidence for the treatment of acute migraine in children, and both high placebo responses and the shorter attack length in pediatric migraine influence clinical trial design. Clinical trials usually exclude patients aged 65 and over, meaning there is little evidence for the acute treatment of migraine in elderly patients.

This systematic assessment of the literature cannot be used to compare the efficacy of individual migraine acute therapies. This assessment reports the strength of evidence supporting superiority of
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<th>Strength of the Evidence</th>
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<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
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<td>(for non-incapacitating attacks)</td>
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<td>*Nasal spray 10, 20 mg</td>
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<td>Patch 6.5 mg</td>
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<td><strong>Others</strong></td>
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<td>*Codeine 30 mg PO</td>
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<td>*Meperidine IM 75 mg</td>
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<td>*Butorphanol/acetaminophen/codeine 50/325/400 mg</td>
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</table>

*Based on 2000 American Academy of Neurology evidence review.
Level A: Medications are established as effective for acute migraine treatment based on available evidence.
Level B: Medications are probably effective for acute migraine treatment based on available evidence.
Level C: Medications are possibly effective for acute migraine.
Level U: Evidence is conflicting or inadequate to support or refute the efficacy of the following medications for acute migraine.
Level B negative: Medication is probably ineffective for acute migraine.
Level C negative: Medication is possibly ineffective for acute migraine.
individual drugs relative to placebo, but it does not compare the relative efficacy of migraine acute medications to one another. Such comparisons are best made through well-conducted, head-to-head studies or carefully conducted network meta-analyses. Furthermore, there is substantial variability in the design of the studies included in this assessment with regard to subject inclusion and exclusion criteria (eg, migraine phenotype, frequency, and severity; exclusion of patients with specific medical conditions; allowance for use of migraine prophylactic therapy; inclusion of patients who had failed prior migraine acute therapies), number of attacks treated, timing for administering the acute therapy (eg, treat when mild vs treat when moderate to severe; early after onset of migraine vs later after onset of migraine), and outcome measures. Primary outcome measures varied, but the most common were 2-hour headache relief, followed by 2-hour headache freedom. Other primary outcomes included change in headache intensity before and after treatment based on visual analog scales; time to headache freedom, 24-hour sustained relief; and 4-hour headache relief. Secondary measures also differed, but usually included relief of nausea, photophobia, phonophobia, and disability, as well as measures of headache relief. Headache freedom and sustained headache relief are harder to achieve than 2-hour headache relief, so studies that use headache relief instead of headache freedom as a primary outcome are more likely to have a higher percentage of responders.

The studies included in this assessment of the literature evaluated the efficacy of migraine acute medications in adults with episodic migraine with or without aura. However, they did not evaluate the efficacy of these medications for the treatment of status migraine, in patients with chronic migraine, or for the treatment of menstrual migraine. Furthermore, in some studies, subjects with especially severe migraine were excluded. Thus, the specific characteristics of an individual patient and the migraine attack that is to be treated must be considered before applying the findings of this evidence assessment. Some of the evidence assessments in this analysis rely on work done for the original 2000 AAN Guidelines. It is possible that errors or misclassifications that occurred during that process might not have been identified. This project was undertaken before the US Institute of Medicine published its recommendations for guidelines processes. Thus, these guidelines do not conform entirely to those recommendations. For example, we did not formally incorporate assessments of side effects and harms into our assessment process.

CONCLUSIONS

According to this systematic review of the literature and structured grading of the evidence strength, specific medications within the following classes are considered “effective” for the acute therapy of migraine: triptans, ergotamine derivatives, NSAIDs, opioids, and combination medications. Several other medications are considered “probably effective” or “possibly effective.” This evidence base for medication efficacy should be considered along with potential medication side effects, potential adverse events, patient-specific contraindications to use of a particular medication, and drug-to-drug interactions when deciding which medication to prescribe for acute therapy of a migraine attack.

Acknowledgments: Dr. Christina Szperka (Division of Neurology, Children’s Hospital of Philadelphia), Dr. Eric Hastriter (Department of Neurology, Mayo Clinic Scottsdale), Dr. Laura McGowan (Buffalo Medical Group), and Dr. Shatabdi Patel (Department of Neurology, Thomas Jefferson University) all reviewed articles for this study. The authors wish to thank the American Headache Society and Linda McGillicuddy for their assistance in organizing this study.

REFERENCES


# APPENDIX 1: ADVANCED SEARCH STRATEGY FOR RELEVANT ARTICLES

## Searches

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<td>4 cephalalg*.mp.</td>
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## Results

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<td>20 6 and 9 and 19</td>
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<td>21 limit 20 to (comment or editorial or letter)</td>
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<td>23 exp animals/ not (exp animals/ and exp humans/)</td>
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# APPENDIX 2: DATA EXTRACTION FORM

Sample Data Extraction Form  
(for therapeutics)

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**Author:**  
**Year:**  
**Journal:**  
**Title:**

**Article Funding Source:**

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<td>Meta-analysis</td>
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</tbody>
</table>

1. **Purpose of the study:**

2. **Sample Size:**

3. **Loss to follow-up:**

4. **Type(s) of patients studied:**

5. **Were standardized diagnostic criteria applied?** YES / NO  
   a. If YES, what standardized criteria were used?

6. **Type(s) of controls**

7. **Intervention**

8. **Outcome**
   a. Positive (describe)
   b. Negative (describe, including significant AE’s)
   c. If a review, model, or meta-analysis, what is the main utility for the guideline?

9. **Comments** (special reasons to include, noteworthy findings, etc.)
APPENDIX 3: STUDY CLASSIFICATION FOR THERAPEUTIC INTERVENTIONS FROM THE AMERICAN ACADEMY OF NEUROLOGY

Class I
- Randomized, controlled clinical trial in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
- Also required:
  a. Concealed allocation
  b. Primary outcome(s) clearly defined
  c. Exclusion/inclusion criteria clearly defined
  d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
  e. For non-inferiority or equivalence trials claiming to prove efficacy for 1 or both drugs, the following are also required*:
     1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
     2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (eg, for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
     3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
- The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers.

Class II
- Cohort study meeting criteria a–e (see Class I) or a randomized, controlled clinical trial that lacks 1 or 2 criteria b–e (see Class I)
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III
- Controlled studies (including well-defined natural history controls or patients serving as their own controls)
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV
- Did not include patients with the disease
- Did not include patients receiving different interventions
- Undefined or unaccepted interventions or outcome measures
- No measures of effectiveness or statistical precision presented or calculable