Technical Review 2.3

Drug Treatments for the Prevention of Migraine Headache

Prepared for:
Agency for Health Care Policy and Research
Department of Health and Human Services
U.S. Public Health Service
Rockville, Maryland

Contract No. 290-94-2025

Prepared by:
Center for Clinical Health Policy Research
Duke University

February 1999

Project Directors:	Douglas C. McCrory, MD, MHSc
	David B. Matchar, MD
Project Manager:	Rebecca N. Gray, DPhil
Contributing Authors:	Rebecca N. Gray, DPhil
	Ruth E. Goslin, MAT
	Douglas C. McCrory, MD, MHSc
	Kristen Eberlein, BA
	James Tulsky, MD
	Vic Hasselblad, PhD
Research Assistants:	Patricia Weston, RN
	Susan Farese, RN
	Pramod Gumpeni, BA
Technical Advisors:	Joel Saper, MD
	George Sands, MD
	Barry Baumel, MD
	Harvey Blumenthal, MD
	James Couch, MD
	Jerome Goldstein, MD
	Herbert Markley, MD
	Alan Rapoport, MD
	Sherry Siegel, MD
	Jerry Swanson, MD
	Jerome Walker, MD
AHCPR Project Officer:	Ernestine Murray, RN, MAS

This document does not necessarily represent the views of the Department of Health and Human Services. It is available from the National Technical Information Service at 1-800-553-6847. Suggested citation:

Duke University, Center for Clinical Health Policy Research. Drug Treatments for the Prevention of Migraine Headache. Technical Review 2.3. February 1999. (Prepared for the Agency for Health Care Policy and Research under Contract No. 290-94-2025. Available from the National Technical Information Service; NTIS Accession No. PB99-127953.)

Structured Abstract

Objectives: To identify and summarize evidence from controlled trials on the efficacy and tolerability of drug treatments for the prevention of migraine.

Search strategy: A strategy combining the MeSH term "headache" (exploded) and a previously published strategy for identifying randomized controlled trials were used on the January 1966 to December 1996 MEDLINE database. Other computerized bibliographic databases, textbooks, and experts were also utilized.

Selection criteria: We selected English-language controlled trials involving patients with migraine headache in which at least one treatment offered was a drug given regularly during headache-free intervals with the aim of preventing the occurrence of migraine attacks.

Data collection and analysis: Measures of headache index and headache frequency reported as group means (and standard deviations) were used to calculate standardized mean differences (or effect sizes). The number of patients obtaining at least a 50% reduction in headache index, frequency, or severity was recorded and used to calculate odds ratios. Where similar trials provided data, meta-analysis of efficacy measures was performed. The identity and rates of adverse events were recorded and statistically compared.

Main results: Placebo-controlled trials support the efficacy of several drugs for the prevention of migraine. Drugs with multiple placebo-controlled trials suggesting at least moderate efficacy include: propranolol (effect size, 0.55; 95% confidence interval, 0.42 to 0.69), timolol (0.69; 0.18 to 1.2), sodium valproate and divalproex sodium (0.93; 0.39 to 1.5), naproxen sodium (0.29; 0.01 to 0.57), amitriptyline (0.62; 0.15 to 1.1), methysergide (no effect size estimate), flunarizine (0.52; 0.24 to 0.80), pizotifen (0.91; 0.50 to 1.3), and lisuride (no effect size estimate). Other beta-blockers demonstrated efficacy similar to that of propranolol, except for those with intrinsic sympathomimetic activity, which did not appear to be efficacious. Within other, more diverse drug categories -- such as antidepressants, calcium antagonists, and anticonvulsants -- there was more variability in the efficacy of different agents. Except for the comparison of propranolol with flunarizine, equivalence has not been demonstrated among the various agents found to be efficacious in placebo-controlled trials. Many efficacious preventive drugs were poorly tolerated in the reviewed trials and were associated with substantial rates of patient withdrawals.

Conclusions: Several specific agents have been shown to be efficacious for the prevention of migraine; however, there are few data to guide the choice among agents, and poor tolerability and lack of availability in the U.S. limit the usefulness of many of the drugs reviewed.

Contents

Page

Structured Abstract iii

Summary 1

Technical Review 13
- Introduction 14
- Methodology 16
- Alpha-2 Agonists 24
- Anticonvulsants 29
- Antidepressants 35
- Beta-blockers 45
- Calcium Antagonists 56
- Ergots 67
- Methysergide 72
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs) 78
- Other Serotoninergic Agents 84
- Other Treatments 93
- Future Research 99

References 102

Evidence Tables 124

Appendix A: Miscellaneous Trials Not Reviewed in This Report 416

Appendix B: MEDLINE Search Strategy 417

Appendix C: Data Collection Form 418

Summary

Overview

Background

Migraine is a common and disabling health problem among adult Americans. Surveys from the U.S. and elsewhere suggest that 6% of men and 15% to 17% of women experience migraine headaches. These headaches result in significant disability and work loss; estimated aggregate indirect costs to employers in the U.S. for reduced productivity due to migraine range from $6.5 billion to $17 billion annually.

Patterns of medical care for the treatment of migraine are highly variable. A substantial proportion of migraineurs never consult a physician about their headaches. Among those who do seek medical attention, many do not continue with the course of treatment prescribed by their physician, citing the availability of nonprescription medications and negative side effects associated with prescription medications among the reasons for self-treatment.

Preventive drug treatments are used by a small percentage of migraineurs -- 3% to 5% of patients in various studies. It is not known whether the patients in these studies who were not using preventive drug therapy had never been offered such treatment or had tried it and found it ineffective or intolerable.

A substantial body of high-quality evidence exists describing the effectiveness of various drugs for the prevention of migraine. Synthesis and dissemination of this information may help correct the underuse or misuse of preventive drug treatment strategies for migraine.

Scope of the Report

The objective of this evidence report is to provide a comprehensive review and analysis of published reports of randomized controlled trials (RCTs) and other prospective, comparative clinical trials of drug treatments for the prevention of migraine. The present report does not cover all drugs that may be used for the prevention of migraine, but only those that have been studied in controlled trials among a population of migraineurs. These include (in alphabetical order): *alpha-2 agonists* (clonidine, guanfacine); *anticonvulsants* (divalproex sodium, sodium valproate, carbamazepine, clonazepam, gabapentin); *antidepressants* (amitriptyline, clomipramine, femoxetine, fluoxetine, fluvoxamine, mianserin, opipramol); *beta-blockers* (propranolol, metoprolol, acebutolol, alprenolol, atenolol, bisoprolol, nadolol, oxprenolol, pindolol, practolol, timolol); *calcium antagonists* (cyclandelate, flunarizine, nicardipine, nifedipine, nimodipine, verapamil); *ergots* (dihydroergotamine [DHE], dihydroergokryptine [DEK], ergotamine, and the combination agent Cafergot comp.®); *methysergide*; *nonsteroidal anti-inflammatory drugs (NSAIDs)* (aspirin, fenoprofen, flurbiprofen, indobufen, indomethacin, ketoprofen, lornoxicam, mefenamic acid, naproxen, naproxen sodium, tolfenamic acid); *other*

serotoninergic drugs (pizotifen, lisuride, oxitriptan, iprazochrome, tropisetron); and *other treatments* (hormonal preparations [estradiol, mixed estradiol/progestogen oral contraceptives, flumedroxone] and the herbal remedy feverfew). Several drugs for which there is a large body of evidence are unavailable in the U.S., including flunarizine, pizotifen, and lisuride.

Methodology

The literature review addressed the question "What are the *effects on headache pain and/or headache frequency* when drug treatments aimed at preventing episodes of migraine are compared with placebo, alternative drug treatments, and non-drug therapies among patients with migraine headache?"

To be considered for this review, studies were required to be prospective, controlled trials of a drug treatment given regularly in headache-free intervals with the aim of preventing the occurrence of migraine attacks in patients with migraine headaches.

Although the use of a specific set of diagnostic criteria (e.g., those developed by the Ad Hoc Committee on the Classification of Headache and the Headache Classification Committee of the International Headache Society [IHS]) was not required, diagnoses were required to be based on at least some of the distinctive features of migraine, e.g., nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. As the IHS criteria allow, we considered patients described as having "mixed" migraine and tension-type headache or "combination" headache to have migraine.

Studies were included only if allocation to treatment groups was randomized or quasi-randomized (based on some nonrandom process unrelated to the treatment selection or expected response); concurrent cohort comparisons and other nonexperimental designs were excluded. Control groups could comprise no intervention, placebo or sham interventions, usual care, or a specified alternative drug or non-drug treatment.

Relevant controlled trials were identified by searching MEDLINE (January 1966 through December 1996) using the MeSH term "headache" (exploded) and a published strategy for identifying randomized controlled trials. Additional search strategies included computerized bibliographical searching of PsycINFO and CINAHL databases; retrospective and prospective hand-searching of the journals *Headache*, *Cephalalgia*, and *Headache Quarterly* from the inception of each (1961, 1981, and 1990, respectively); searching the reference lists of review articles and included studies; searching books related to headache; and consulting experts in the field. We also searched a database of randomized trials in pain relief which is now part of the Cochrane Controlled Trials Register.

Studies identified by the literature search were screened for further review based on criteria focusing on patient population, intervention, study design, and type of outcome data reported.

Studies passing the initial screen were reviewed for methodological quality based on the following considerations: the use of random allocation; description of an adequate method of concealment of allocation; the use of double-blinding; description of an adequate method of blinding; and a description of dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial. Each trial could score 1 point for each

criterion (for a total of from 0 to 5 points), with higher scores indicating higher quality in the conduct or reporting of the trial.

Efficacy data were abstracted from the original reports onto specially designed forms. We collected trial data on symptomatic outcomes related to head pain (frequency, severity/intensity, and duration) and other symptoms of migraine (nausea, vomiting, photophobia, phonophobia). Secondary outcomes recorded included medication use, functional status (disability), and quality of life. We did not consider physiological or other measures not directly relevant to the patients' symptomatic experience.

We preferred that outcome data be based on daily recording of headache symptoms by patients, rather than on global or retrospective assessments performed by patients or investigators. Outcomes were recorded post-treatment and at followup, if available.

We preferred combined measures of headache symptoms such as headache indexes (variously defined combinations of frequency, intensity, and duration). In the absence of a headache index, we recorded headache frequency alone. If neither headache index values nor frequency data were reported, we analyzed data on headache intensity.

For dichotomous outcomes (e.g., success/failure), we required that the threshold for distinguishing between success and failure be clinically significant; for example, we interpreted a 50% or more decrease in headache frequency or headache index (two of the most common definitions) as meeting this criterion. Dichotomous outcomes meeting our definition of a clinically significant threshold were reported as proportions (or response rates for each treatment) which may be directly compared (difference in proportions). We also used these proportions to calculate odds ratios.

In the few instances in which outcome data were reported on an ordinal scale (e.g., for reduction in headache frequency: none, some, moderate, significant, very significant), we selected a threshold based on the definition of clinically significant improvement (discussed above) and converted these data into a dichotomous outcome.

Most of the trials reported outcomes on a continuous scale (e.g., mean headache index or mean headache frequency). In these cases, whenever variance estimates were also available, we rescaled and standardized the continuous outcome data for each treatment condition in each study using a published method. We used the standardized outcome measures to calculate individual effect sizes for pair-wise comparisons of drug and control treatments. When multiple trials provided effect size estimates of the same drug-placebo or drug-drug comparisons, the effect sizes were tested for homogeneity, and used to calculate summary effect sizes for each type of treatment, using a random-effects model.

Throughout the report, wherever we have used the word "significant" to describe results, we mean "statistically significant at an alpha level of 0.05 for the two-sided alternative hypothesis." Wherever we have reported on results that are clinically, rather than statistically, significant, we have explicitly used the word "clinically."

The incidence of adverse events was recorded and the proportion of patients experiencing adverse events calculated for each treatment group, whenever possible. The difference between rates of adverse events was calculated, along with a 95% confidence interval (CI) for the difference. A 95% CI that excludes zero suggests that the rates are significantly different

between groups. The identity and rates of specific adverse events reported were summarized for each study.

Findings

The evidence supporting different agents or classes of agents reviewed in this report varies considerably in quantity and quality. This section summarizes the results of our analysis; the next section describes the most urgent priorities for future research.

Alpha-2 Agonists

Our analysis included 16 controlled trials of clonidine and one of guanfacine. The principal findings were:

- There is not sufficient evidence to conclude that *clonidine* is effective for the prevention of migraine. The existing trials suggest that this agent is, at most, mildly effective, but this has not been demonstrated conclusively. Placebo-controlled trials reported both positive and negative results. In comparisons with beta-blockers with intrinsic sympathomimetic activity (practolol and prindolol), for which evidence for efficacy is lacking, clonidine has consistently been shown to be no more effective.

- Adverse events (most commonly drowsiness or tiredness) were observed in a high proportion of patients in trials of clonidine, but the reported symptoms were usually neither serious nor the cause of patient withdrawals from trials.

Anticonvulsants

Our analysis included nine controlled trials involving the following agents: divalproex sodium, sodium valproate, carbamazepine, clonazepam, and gabapentin. The principal findings of the analysis were as follows:

- Strong and consistent evidence supports the efficacy of *divalproex sodium* and the related compound *sodium valproate* for the prevention of migraine.

- The evidence for the efficacy of other anticonvulsant agents is weaker. *Carbamazepine* has mixed support from one placebo-controlled trial (suggesting efficacy) and one comparison with prindolol and clonidine (suggesting a smaller effect on headache frequency than either comparator). Neither *clonazepam* nor *gabapentin* appears to be an effective migraine preventive drug.

- Adverse events -- most commonly dizziness and drowsiness -- were frequently observed with anticonvulsants and were a frequent cause of patient withdrawals from trials.

Antidepressants

Our analysis included 16 controlled trials involving the following agents: amitriptyline, clomipramine, femoxetine, fluoxetine, fluvoxamine, mianserin, and opipramol. Opipramol, fluoxetine, and mianserin are not available in the U.S. The principal findings of the analysis are described below:

- Of all the antidepressants, the tricyclic *amitriptyline* has been most frequently studied for the prevention of migraine and is the only agent with reasonably consistent support for efficacy. Although this has not been demonstrated conclusively, amitriptyline may be more efficacious for patients with mixed migraine and tension-type headache than for patients with migraine alone.

- None of the other agents reviewed -- *clomipramine, femoxetine, fluoxetine, fluvoxamine, mianserin*, or *opipramol* -- has sufficient data to support its efficacy, though substantial uncertainty still exists for these agents.

- Tolerability was a problem with the tricyclic antidepressants studied (amitriptyline, clomipramine, and opipramol), with anticholinergic symptoms frequently reported. Adverse events were less frequently reported with the selective serotonin re-uptake inhibitors (femoxetine, fluoxetine, and fluvoxamine). However, the particular adverse events most commonly observed with these agents (nausea and sexual dysfunction) may be of greater concern to many migraineurs than the anticholinergic effects associated with tricyclic antidepressants.

Beta-blockers

Our analysis covered 74 controlled trials, including a large number of trials of propranolol (46 trials) and metoprolol (15 trials), and much smaller numbers of trials of acebutolol, alprenolol, atenolol, bisoprolol, nadolol, oxprenolol, pindolol, practolol, and timolol. The principal findings of the analysis were:

- *Propranolol*, in a daily dose of 120 mg to 240 mg, has strong and consistent support for efficacy in reducing headache frequency and headache index. *Timolol, metoprolol, atenolol,* and *nadolol* are also likely to be beneficial, based on trials comparing these agents to placebo or to propranolol.

- Beta-blockers with intrinsic sympathomimetic activity -- including *acebutolol, alprenolol, oxprenolol,* and *pindolol* -- appear to be ineffective for the prevention of migraine.

- There is insufficient evidence to conclude that extended-release preparations of propranolol and metoprolol are more or less effective, or more or less well tolerated, than regular formulations of these drugs.

- While some studies had high dropout rates, most patients appear to have tolerated the adverse events associated with beta-blockers (principally fatigue, depression, nausea, dizziness, and insomnia). Dropouts were rarely due to adverse events associated with the active treatments.

Calcium Antagonists

Our analysis included 45 controlled trials of the following agents: cyclandelate, flunarizine, nicardipine, nifedipine, nimodipine, and verapamil. Flunarizine, the agent in this class most frequently studied for migraine prevention, is not available in the US, nor is cyclandelate. The main findings of the analysis are described below:

- *Flunarizine* has strong and consistent evidence from eight placebo-controlled trials for efficacy in migraine prevention. This evidence is strengthened by comparisons with propranolol, another drug whose efficacy is well-established for migraine prevention, which demonstrates reasonable equivalence.

- Other calcium antagonists have been less thoroughly studied. *Nimodipine* had mixed results in six placebo-controlled studies.

- *Nifedipine* had consistently poor results in four trials, two placebo-controlled and two comparisons with propranolol.

- *Verapamil* is the calcium antagonist most commonly used for migraine prevention in the U.S. Two small placebo-controlled trials suggested that this agent is effective in migraine prevention. However, both trials were plagued by high dropout rates. Our best estimate of the efficacy of this agent therefore carries substantial uncertainty.

- *Nicardipine* has a single positive trial supporting its efficacy. The effect size from this trial was intermediate between those associated with the other dihydropyridine calcium antagonists, nifedipine and nimodipine.

- *Cyclandelate* has not been tested in placebo-controlled trials for migraine prevention, but it has been compared with several drugs of established efficacy, viz. flunarizine, propranolol, and pizotifen. Cyclandelate was found to be less effective than flunarizine, but more effective than pizotifen; the comparison with propranolol was uninformative. The uncertainty regarding the efficacy of this agent is still considerable, given the lack of placebo-controlled trials.

- The adverse event rates reported for calcium antagonists varied widely between studies, even between studies of the same dose of the same drug, and provided little in the way of reliable information on the risk of adverse events associated with these agents.

Ergots

Our analysis included 13 controlled trials of the following agents: dihydroergotamine (DHE), dihydroergokryptine (DEK), ergotamine, and the combination agent Cafergot comp.® (ergotamine + caffeine + butalbital + belladonna alkaloids). The principal findings of the analysis are described below:

- *Dihydroergotamine* appears to be efficacious for migraine prevention when used in a daily dose of 10 mg, based on four placebo-controlled trials with consistent findings. A single trial suggested that DHE may be less effective than amitriptyline for patients with mixed migraine + tension-type headache.

- The efficacy of *dihydroergokryptine* is less certain, but is supported by one placebo-controlled study in women with menstrual migraine and by one direct comparison each with flunarizine and methysergide.

- *Cafergot comp.*® and *ergotamine* do not have support for efficacy in migraine prevention.

- The limited data reported on adverse events reported suggest that unwanted gastrointestinal symptoms are common with all the drugs in this class.

Methysergide

Methysergide was one of the first drugs to be used for the prevention of migraine. Our analysis included 16 controlled trials of this agent. The main conclusions were as follows:

- Four placebo-controlled trials suggested that *methysergide* is moderately effective at reducing headache frequency. These trials were all conducted in the 1960s using earlier or no diagnostic criteria for migraine, and their generalizability to patients diagnosed under the more precise diagnostic criteria of the IHS is uncertain.

- In direct comparisons with other migraine preventive agents, methysergide appeared to be no more effective than pizotifen or propranolol.

- A handful of trials comparing methysergide to other drugs (oxitriptan, lisuride, DEK, ergotamine, flumedroxone [Demigran®], and flunarizine) were too small to demonstrate equivalence and failed to demonstrate any statistically significant differences.

- Short-term adverse events (principally gastrointestinal complaints) led to discontinuation of treatment in up to 20% of patients treated with methysergide in the reviewed trials. The risk of adverse events associated with the long-term use of methysergide (particularly fibrotic changes in the retroperitoneal, pleuropulmonary, cardiac, and other tissues) is, however, probably a greater deterrent to the use of this agent.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Our analysis included 23 controlled trials involving the following NSAIDs: aspirin, fenoprofen, flurbiprofen, indobufen, indomethacin, ketoprofen, lornoxicam, mefenamic acid, naproxen, naproxen sodium, and tolfenamic acid. The main findings of the analysis are described below:

- Multiple trials of *naproxen* or *naproxen sodium* consistently showed a moderate reduction in headache symptoms compared with placebo.

- Some of the other agents studied -- including *flurbiprofen, indobufen, ketoprofen, lornoxicam, mefenamic acid,* and *tolfenamic acid* -- appeared to have similar moderate effects, but fewer studies supported the efficacy of these agents.

- The effects of *aspirin, aspirin + dipyridamole, fenoprofen,* and *indomethacin* are less certain. The reviewed trials of these agents described unusually large or small effects that have not been replicated.

- Gastrointestinal (GI) adverse events were common with NSAIDs and often led to withdrawal from trials. The relatively short-term trials reviewed here were inadequate to assess adverse events that may be associated with the long-term use of NSAIDs.

Other Serotoninergic Agents

Our analysis included 40 controlled trials involving the following agents: pizotifen, lisuride, oxitriptan, iprazochrome, and tropisetron. None of these agents is currently available in the US. The principal findings of the analysis were as follows:

- There is strong and consistent evidence from 11 placebo-controlled trials and 19 comparisons with other agents suggesting that *pizotifen*, in doses of 1.5 mg to 4 mg/day, is effective for the prevention of migraine attacks. In direct comparisons with other drugs known to be efficacious (e.g., flunarizine and metoprolol), pizotifen has been found to be no less effective. However, in the trials reviewed here, pizotifen was generally poorly

tolerated, commonly causing substantial weight gain or drowsiness, and was associated with a high incidence of patient withdrawals due to adverse events.

- *Lisuride* has consistent support from four placebo-controlled trials showing significant benefit, and from direct comparisons with pizotifen and methysergide, in which lisuride was no less effective. Lisuride was associated with a lower incidence of adverse events than was pizotifen, and a lower rate of patient withdrawal due to adverse events.

- None of the other drugs considered (*iprazochrome, oxitriptan,* or *tropisetron*) has been shown to be effective compared to placebo. Iprazochrome and oxitriptan have been shown to be less effective than pizotifen.

Other Treatments

In addition to the treatments described above, we reviewed six trials of estrogens or progestogens for the prevention of migraine, and two trials of the herbal remedy, feverfew. The main findings of our analysis were as follows:

- Data on the use of estrogens and progestogens for migraine prevention are relatively poor, with only a few small trials and marked variation in subject population, dosages employed, and clinical results. Trials of *estradiol* used perimenstrually in a gel or patch form suggest that a relatively high dose of this hormone may be efficacious in women whose migraine attacks are associated with their menstrual cycles. The trials using lower doses of estradiol perimenstrually or *mixed estradiol/progestogen oral contraceptives* in a cyclic fashion do not support efficacy for migraine prevention.

- Three trials of the progestogen *flumedroxone* indicate that this agent can be efficacious, particularly among women whose migraine headaches are associated with their menstrual cycle. The use of this agent is, however, limited by the frequency of polymenorrhea and other adverse events.

- The data analyzed do not support the efficacy of estrogens or progestogens in women whose migraines are not associated with their menstrual cycle, or in male migraineurs.

- Two trials provide evidence that *feverfew* is efficacious for migraine prevention.

Future Research

Further research is required into the safety and efficacy of currently available drugs if their use for the long-term prevention of migraine attacks is to be optimized. The recommendations described below may be made.

Conduct and Reporting of Trials

(1) The generalizability of the results of trials conducted among patients in headache specialty centers to primary care populations is uncertain. More trials should be conducted among patients recruited from general practice settings.

(2) The diagnosis of migraine -- even when made according to specific criteria such as the IHS criteria for migraine with aura and migraine without aura -- encompasses a wide range of symptomatology. Researchers should be as precise as possible in describing any operational inclusion or exclusion criteria they employed in addition to headache diagnosis, such as headache frequency, severity, and chronicity.

(3) The use of medications for the treatment of acute migraine episodes during the trial of preventive therapy was handled in a variety of ways in different studies. Because effective treatment of acute migraine attacks can significantly affect headache severity and duration measures, the uncontrolled use of such medications can confound the results of a preventive trial. Future studies should measure and describe the use of medications for the treatment of acute migraine attacks.

(4) More head-to-head comparisons of preventive treatments should be performed in order to help clinicians and patients make informed choices among the many available therapies. Such comparative trials are particularly important for older drugs.

(5) Future trials should use common scales for measuring pain outcomes, if possible. The IHS recommends the use of headache frequency per 4-week observation period as the primary measure of efficacy. The consistent adoption of this recommendation in trials of migraine preventive drugs would greatly facilitate future meta-analyses.

(6) Because many preventive drugs are poorly tolerated, future trials should expand the scope of the clinically relevant outcomes measured. Overall or disease-specific quality-of-life measures, along with careful assessment and complete reporting of adverse events, would help in evaluating the overall efficacy of the treatment.

(7) Adverse events should be reported for all patients taking study medication, including those who withdraw prematurely. The number of patients experiencing adverse events with each intervention should be reported, and the specific adverse events reported should be described.

New Directions for Research

(8) Adverse events associated with long-term use of some migraine preventive agents have been identified (e.g., fibrotic complications associated with methysergide, weight gain with flunarizine, and gastrointestinal symptoms with many NSAIDs). The relatively

short-term clinical trials reviewed in this report do not effectively capture these adverse events. New approaches to ascertaining long-term or rare complications of treatment are needed.

(9) The real-life management of headache disorders often involves multiple simultaneous interventions, including an acute drug treatment plan (which might include an initial and rescue medication), a preventive drug treatment plan, behavioral therapy or other self-management education, or skills training. Such multidisciplinary interventions, usually delivered in specialty clinics, have been reported to show dramatic response rates in uncontrolled studies. Testing these bundled multiple interventions in a prospective, controlled trial may provide more understanding of how to care for patients with chronic headache disorders than do the short-term, single-intervention preventive drug studies reviewed here.

(10) Further research is needed regarding the delivery of migraine care, in general, and of preventive therapies, in particular. It is important to ascertain whether there are patterns of use of different migraine treatment approaches in different settings and among different types of providers (e.g., generalists versus specialists).

(11) Limited data suggest that most patients do not remain on migraine preventive drugs for long-term use; however, little is known about the reasons for discontinuing the drugs or about the effect of this discontinuation on patients' headaches. Preventive drug treatments for migraine are often undertaken with the expectation that after a period of successful treatment (e.g., 6 to 12 months), treatment can be discontinued without the patient's headaches either worsening or returning to the same intensity experienced prior to treatment. Further research on the effects of withdrawing migraine preventive treatments would help address the issue of whether to discontinue or taper treatment and the best time frame for doing so.

(12) Few studies have attempted to identify predictors of response or nonresponse to particular migraine preventive drugs, leaving physicians with little guidance for choosing among efficacious agents. Particularly informative would be tests of association between treatment response and patient-level factors, such as headache characteristics, demographic characteristics, or response (or nonresponse) to other drugs for the acute or preventive treatment of migraine. Furthermore, protocols describing particular selection criteria or order of drug trials in individual patients could be tested in a controlled fashion.

Technical Review

Introduction

Background

Migraine is a common and disabling health problem among adult Americans. Surveys from the US and elsewhere suggest that 6% of men and 15%-17% of women experience migraine headaches (Stewart, Shechter, and Rasmussen, 1994). These headaches result in significant disability and work loss; estimated aggregate indirect costs to employers in the US for reduced productivity due to migraine range from $6.5 billion to $17 billion annually (Osterhaus, Gutterman, and Plachetka, 1992).

Patterns of medical care for the treatment of migraine are highly variable. A substantial proportion of migraineurs never consult a physician about their headaches. Among those who do seek medical attention, many do not continue with the course of treatment prescribed by their physician (Edmeads, Findlay, Tugwell, et al., 1993), citing the availability of nonprescription medications and negative side effects associated with prescription medications among the reasons for self-treatment.

Preventive drug treatments are used by a small percentage of migraineurs – 3% to 5% of patients in various studies (Clarke, MacMillan, Sondhi, et al., 1996; Edmeads, Findlay, Tugwell, et al., 1993; Rasmussen, Jensen, and Olesen, 1992). It is not known whether patients in these studies had never been offered preventive therapy or had tried it and found it ineffective or intolerable.

The pathophysiology of migraine is poorly understood, but recent advances in neuroimaging, neurobiology, genetics, and pharmacology have resulted in a changing view of migraine pathogenesis, from one favoring vascular and muscle tone as primary causes to one involving a primary neuronal event producing secondary vascular changes. There continues to be controversy among headache researchers and clinicians over whether tension-type headache and migraine are part of a single spectrum of headache disorders or different conditions with distinct etiologies. The diagnostic distinction between the two types of headache is, however, generally assumed in clinical trials, most of which have focused on one or the other diagnosis.

A substantial body of high-quality evidence exists describing the effectiveness of various drugs for the prevention of episodes of migraine. Synthesis and dissemination of this information may help correct the underuse or misuse of preventive drug treatment strategies for migraine headache.

Objectives and Organization of the Report

The objective of this evidence report is to provide a comprehensive review and analysis of published reports of randomized controlled trials (RCTs) and other prospective, comparative clinical trials of self-administered drug treatments for the prevention of migraine headaches. The present report does not cover all drugs that may be used for the treatment of acute migraine, but only those that have been studied in controlled trials among a population of migraineurs. These

include (in alphabetical order): *alpha-2 agonists* (clonidine, guanfacine); *anticonvulsants* (divalproex sodium, sodium valproate, carbamazepine, clonazepam, gabapentin); *antidepressants* (amitriptyline, clomipramine, femoxetine, fluoxetine, fluvoxamine, mianserin, opipramol); *beta-blockers* (propranolol, metoprolol, acebutolol, alprenolol, atenolol, bisoprolol, nadolol, oxprenolol, pindolol, practolol, timolol); *calcium antagonists* (cyclandelate, flunarizine, nicardipine, nifedipine, nimodipine, verapamil); *ergots* (dihydroergotamine [DHE], dihydroergokryptine [DEK], ergotamine, and the combination agent Cafergot comp.®), *methysergide*; *nonsteroidal anti-inflammatory drugs (NSAIDs)* (aspirin, fenoprofen, flurbiprofen, indobufen, indomethacin, ketoprofen, lornoxicam, mefenamic acid, naproxen, naproxen sodium, tolfenamic acid); *other serotoninergic drugs* (pizotifen, lisuride, oxitriptan, iprazochrome, tropisetron); and *other treatments* (hormonal preparations [estradiol, mixed estradiol/progestogen oral contraceptives, flumedroxone] and the herbal remedy feverfew). We identified a small number of trials of other miscellaneous agents, but chose not to review these because the drugs involved have been studied in only a few trials (in most cases, only one), are not widely available, and/or have been shown to be ineffective. Appendix A provides a complete list of these trials. Several drugs for which there is a large body of evidence are unavailable in the US, including flunarizine, pizotifen, and lisuride.

The report is organized into chapters according to classes or categories of drugs: alpha-2 agonists, anticonvulsants, antidepressants, beta-blockers, calcium antagonists, ergots, methysergide, NSAIDs, other serotoninergic drugs, and other treatments.

The text of the report in each chapter briefly describes the studies identified by the literature review, summarizes the evidence for efficacy and the data on adverse events, and draws conclusions. In the sections on efficacy, we first review placebo-controlled trials, then studies comparing different dosages of the same agent, then trials comparing agents within the same class, and finally trials comparing the agents under consideration with drugs outside the class or with nondrug therapies.

Evidence Table 1 summarizes the studies included in the analysis, describing in a standardized way the aims and design of each study, characteristics of the patient population, headache diagnostic criteria used, inclusion and exclusion criteria, interventions, treatment protocol, data collected, outcomes measured, and results. Evidence Tables 2 through 11 summarize the evidence for the efficacy of each class of drugs in standard terms, including measures of efficacy (odds ratios or effect sizes) or tests of statistical significance. The results of meta-analyses of multiple studies are also reported in these tables, wherever it was possible to perform such meta-analyses. Evidence Table 12 summarizes the available data from each study on the occurrence of adverse events, in aggregate, and the incidence of specific adverse events.

A description of future research needs and a list of references are provided at the end of the entire report.

Methodology

Topic Questions

The topic questions addressed in the literature review were:

(1) What is the *effect on headache pain and/or headache frequency* of drug treatments taken to prevent migraine headache compared with placebo, alternative drug treatments, and non-drug therapies?

(2) What is the *tolerability* of drug treatments taken to prevent migraine headache compared to placebo, alternative drug treatments, and non-drug therapies?

Criteria for Considering Studies

To be considered for this review, studies were required to be prospective, controlled trials of self-administered drug treatments taken regularly and intended to prevent the occurrence of episodes of headache in patients with migraine. Studies were included only if allocation to treatment groups was randomized or pseudo-randomized (based on some nonrandom process unrelated to the treatment selection or expected response); concurrent cohort comparisons or other nonexperimental designs were excluded. Control groups could comprise placebo, no intervention, usual care, or a specified alternative drug or non-drug treatment.

Search Strategy

Relevant controlled trials were identified by MEDLINE searches using the MeSH term "headache" (exploded) and the search strategy for identifying randomized controlled trials described by Dickersin, Scherer, and Lefebvre (1994) (see Appendix B). The MEDLINE searches included literature indexed from January 1966 through December 1996. Additional search strategies included computerized bibliographical searching of PsycINFO and CINAHL databases; retrospective and prospective hand-searching of the journals *Headache*, *Cephalalgia*, and *Headache Quarterly* from the inception of each (1961, 1981, and 1990, respectively); searching the reference lists of review articles and included studies; searching books related to headache; and consulting experts in the field. We also searched a database of randomized trials in pain relief which is now part of the Cochrane Controlled Trials Register (1997).

Results of Search

Searches of all sources retrieved a total of 6,660 articles (including 352 review articles) on the diagnosis, treatment, and cost of chronic headache (migraine, tension-type, and other types of primary headache). Of these, 2,106 were judged to merit scrutinizing the complete article. Of

the articles reviewed, 1,085 concerned the treatment of chronic headache (rather than diagnosis or cost), and 492 of these articles included at least one preventive drug treatment arm. Of the 492 preventive drug treatment articles reviewed, 283 met all the criteria for consideration in the evidence report (i.e., they were controlled trials conducted on a nonpediatric population of patients with migraine).

Initial Screening and Data Abstraction

Studies identified by the literature search were screened for further review based on criteria focusing on patient population, intervention, study design, and type of outcome data reported. The screen was performed by research nurses specially trained in the application of these criteria; we found excellent inter-rater reliability (kappa = 0.95; 95% confidence interval [CI]: 0.73 to 1.0) among the three screeners following training and in subsequent periodic monitoring during the screening process.

The initial screen was based on the criteria for considering studies for the review and was implemented as lists of keywords that described specific examples to include or exclude. For example, for "patient type," the general rule was that we would accept studies of adults with headache syndromes. This rule was supplemented with lists of appropriate and inappropriate keywords such as the following: headache not otherwise specified, migraine, tension-type headache, tension headache, etc. Excluded were keywords such as "post-lumbar puncture headache." In response to reviewers' questions, the criteria were updated periodically throughout the selection process, based on titles and abstracts actually reviewed. The list of screening criteria is several pages long. Because these criteria applied to the overall headache project and not expressly to this report, they are not included here.

Studies passing the initial screen were reviewed for methodological quality (see below). Efficacy and adverse events data were abstracted from the original reports onto specially designed forms (see Appendix C) by the same research nurses who performed the initial screen. During the data abstraction process, the source of extracted data was indicated on the original published report using a highlighter and handwritten notes. The annotated published report was paired with the data abstraction form, and these were kept together during the remainder of the data management and analysis process. When statistical analyses were performed, key data elements were verified on the original report.

Evaluation of Methodological Quality of Individual Trials

We assessed the internal validity of individual trials using a scale devised by Jadad, Moore, Carroll, et al. (1996) (Exhibit 1). This scale evaluates methodological quality based on the following considerations: the use of random allocation; description of an adequate method of concealment of allocation; the use of double-blinding; description of an adequate method of blinding; and a description of dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial. These criteria were applied during data

abstraction using a standardized form with written definitions (see Appendix C and below). Each trial could score between 0 and 5 points, with higher scores indicating higher quality in the conduct or reporting of the trial.

Each of the items on this quality scale is an accepted criterion that has been empirically validated. The Jadad instrument is one of only a few such scales that has undergone a formal process of development and demonstrated good inter-rater reliability (Moher, Jadad, Nichol, et. al., 1995).

Exhibit 1. Instrument to measure the likelihood of bias in pain research reports

	Question	Response	Score
1	Was the study described as **randomized** (this includes the use of words such as randomly, random and randomization)?	Yes No	1 0
1a	If the method of generating the sequence of randomization was described, was it **adequate** *(table of random numbers, computer-generated, coin tossing, etc.)* or **inadequate** *(allocated alternately, according to date of birth, hospital number, etc.)*?	Not described/NA Adequate Inadequate	0 1 -1
2	Was the study described as **double-blind**?	Yes No	1 0
2a	If the method of blinding was described, was it **adequate** *(identical placebo, active placebo, dummy, etc.)* or **inadequate** *(comparison of tablet vs. injection with no double dummy)*?	Not described/NA Adequate Inadequate	0 1 -1
3	Was there a description of **withdrawals** and **dropouts**?	Yes No	1 0

Source: Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clin Trials 1996;17(1):1-12. Reprinted with permission from Elsevier Science.

The score assigned to each trial is described in the text of the report and in Evidence Table 1. Components of the score have been noted as follows:

Either "not randomized" *or* "randomized," with a "+" after "randomized" if the method of randomization was described and was adequate, and a "-" after "randomized" if the method of randomization was described, but was inadequate.

Either "not double-blind" *or* "double-blind," with a "+" after "double-blind" if the method of blinding was described and was adequate, and a "-" after "double-blind" if the method of blinding was described, but was inadequate.

Either "no description of dropouts" *or* "dropouts described."

Thus, for example, a trial that was explicitly described as "randomized" would receive 1 point; if it did not provide a description of the methods for generating the sequence of randomization, it would not receive a point (0 points); if it was explicitly described as double-blinded, it would receive 1 point; if it provided a description of an adequate method of blinding, it would receive another 1 point (designated with a "plus" sign); if it did not describe dropouts or withdrawals (and we could not determine them from the number of patients included in the efficacy analyses), the study would not receive a point (0 points). This hypothetical trial, therefore, would receive a quality score of "3" and would be described in Evidence Table 1 as "randomized, double-blind+, no description of dropouts."

When describing individual trials in the text of the report, we have consistently identified trials with a quality score of 2 or lower.

Types of Participants

Subjects were required to meet reasonable criteria designed to distinguish migraine from tension-type headache, or if patients with both types of headache were included, results had to be stratified by headache diagnosis. Although the use of a specific set of diagnostic criteria (e.g., Ad Hoc Committee on the Classification of Headache, 1962; Headache Classification Committee of the International Headache Society [IHS], 1988) was not required, diagnoses were required to be based on at least some of the distinctive features of migraine, e.g., nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. Furthermore, secondary headache disorders had to be excluded using reasonable criteria. No further restrictions were placed on studies regarding particular inclusion or exclusion criteria relating to the frequency, duration, or severity of migraine headaches.

Many of the trials reviewed in this report included patients described as having "mixed" migraine and tension-type headaches or "combination" headaches. It was not always clear whether these descriptions referred to patients who had discrete episodes of migraine and discrete episodes of tension-type headache, or to patients with headaches which (in the view of the investigators) combined features of migraine and tension-type headache. As the IHS criteria allow, we considered patients in either of these categories to have migraine. Wherever separate results were reported for migraine and "mixed" or "combination" patients, we described and

analyzed these results separately. Trials and treatment groups including only patients with tension-type headache were excluded from consideration.

Types of Interventions

Each study was required to have at least one arm in which a pharmacological treatment was given regularly during headache-free intervals with the aim of preventing the occurrence of migraine attacks in patients with migraine headaches. Provided that one treatment arm in a study met this criterion, comparator groups could comprise placebo, parenterally administered drug treatments, or behavioral or physical therapies.

We required that the drugs studied be available clinically (in the U.S. or abroad) and included only commercially available dosages. Studies of drugs that have been withdrawn from the U.S. market were excluded.

Outcome Definitions

The interventions considered in this report are preventive in aim, i.e., they focus on reducing the frequency and/or intensity of recurrent migraine headaches and not on aborting or relieving individual acute episodes. We collected trial data on symptomatic outcomes related to head pain (frequency, severity/intensity, and duration) and other symptoms of migraine (nausea, vomiting, photophobia, phonophobia). Secondary outcomes recorded included medication use, functional status (disability), and quality of life. We did not consider physiological or other measures not directly relevant to the patients' symptomatic experience.

We preferred combined measures of headache symptoms such as headache indexes (variously defined combinations of frequency, intensity, and duration). In the absence of a headache index, we recorded headache frequency alone. Studies have shown that headache frequency is significantly correlated with both headache intensity and duration (Penzien, Johnson, Seville, et al., 1994). If neither headache index values nor frequency data were reported, we analyzed data on headache intensity.

Specific Requirements for Outcome Data

Source of Data

We required that outcome data be obtained directly from the patient, not judged by the treating physician or study personnel. We preferred that outcome data be based on daily recording of headache symptoms, rather than on global or retrospective assessments.

Timing of Outcome Measurement

Outcomes were recorded post-treatment and at followup, if available. Post-treatment was considered to be between 8 and 12 weeks after the start of treatment or immediately following

the end of treatment, whichever was later. We considered followup data to be that recorded at the last available time for which the dropout rate was less than 20% and for which data were reported for all treatment groups.

Use of Acute Medication

Many trials permitted the use of medication for acute migraine attacks experienced during the trial period. We recorded descriptions of trial rules concerning the use of medication in the Evidence Tables whenever such information was provided in the studies. We did not otherwise model or adjust for this factor in the analysis.

Analysis of Crossover Trials

Crossover designs are sometimes used for trials of preventive drugs for migraine. In most cases the data reported do not permit analysis of paired within-patient data. We analyzed crossover trials as if they were parallel-group trials, combining data from all treatment periods. If a carry-over effect was found and data were given by period, then we restricted our analysis to period one data only. In rare cases, complete data were reported, and within-patient improvement scores could be calculated.

Data Analysis

Dichotomous Data

Some studies reported treatment success and failure as a dichotomous outcome. In such cases, we required that the threshold for distinguishing between success and failure be clinically significant; for example, we interpreted a 50% or more decrease in headache frequency or headache index as meeting this criterion.

Dichotomous outcomes meeting our definition of a clinically significant threshold were reported in the Evidence Tables as proportions (or response rates for each treatment) which may be directly compared (difference in proportions). For those physical treatment trials that reported outcomes in dichotomous form, we also used these proportions to calculate odds ratios (Fleiss, 1981). An odds ratio estimate of 1 indicates "even odds" or no treatment effect, while an odds ratio greater than 1 indicates greater likelihood of improvement with the tested treatment than the comparator. The 95% CI for the odds ratio can be interpreted as a test of statistical significance; if the confidence limit excludes 1 (null effect), then the treatments are significantly different. The odds ratio is a relative measure of efficacy and should be interpreted along with the response rates and the difference in response rates between groups. The odds ratio approximates the risk ratio at low event rates; however, the response rates among headache studies are high enough so that these are large differences between the odds ratio and risk ratio, with the odds ratio overestimating risk ratio substantially.

Most of the preventive drug treatment trials we reviewed reported continuous outcome data, rather than dichotomous or ordinal; our meta-analysis of those trials was accordingly based on the continuous data.

Ordinal Data

In the few instances in which outcome data were reported on an ordinal scale (e.g., for reduction in headache frequency: none, some, moderate, significant, very significant), we selected a threshold based on the definition of clinically significant improvement (discussed above) and converted these data into a dichotomous outcome.

Continuous Data

General. For outcomes reported on a continuous scale (e.g., mean headache index or mean headache frequency), we identified pre- and post-treatment group mean scores wherever possible. When variance data were also reported, these pre- and post-treatment group mean scores were rescaled and standardized for each treatment condition in each study, as described by Hasselblad (1998). The resulting standardized outcome measures were used to:

- Calculate effect sizes for pair-wise comparisons of preventive drug treatments with placebo for every trial with a placebo arm; and

- Calculate summary effect sizes for each type of treatment considered in the meta-analysis.

Each of these analytical procedures is described in greater detail below.

Many trials reported pre- and post-treatment group means, but did not report data on the variance associated with these means. In such cases, we attempted to calculate or estimate variances based on primary data or test statistics, if these were reported.

When a trial used pre- and post-treatment scores to calculate a change score for each patient and used these within-patient change scores to calculate a group mean change score, then we used these group mean change scores. When only post-treatment data were available for each treatment group, we used these data, relying on allocation to achieve between-group balance.

Throughout the report, wherever we have used the word "significant" to describe results, we mean "statistically significant at an alpha level of 0.05 for the two-sided alternative hypothesis." Wherever we have reported on results that are clinically, rather than statistically, significant, we have explicitly used the word "clinically."

Meta-analysis. As stated above, whenever pre- and post-treatment group means *and* variance data were available, we rescaled and standardized the group mean scores for each treatment condition in each study, as described by Hasselblad (1998). We then included the resulting rescaled and standardized outcome measures from individual studies in a multi-variable, random-effects model to estimate a summary effect size for each type of treatment, controlling for study (Hasselblad, 1998).

For the purposes of this analysis, interventions were grouped into categories based in part on statistical considerations (such as the number of trials of a given intervention) and in part on clinical considerations (such as the way interventions are combined in clinical use; e.g., cognitive-behavioral therapy usually includes relaxation training).

Pair-wise comparisons. The same rescaled and standardized outcome measures used in the meta-analysis were also used to calculate effect sizes for all pair-wise comparisons of a preventive drug treatment versus a placebo or comparator treatment using techniques described by Hasselblad (1998). These effect sizes are reported in Evidence Tables 2 through 11. They show the results of individual trials in the same framework and terms as were used in the meta-analysis and should help the reader interpret both the results of the meta-analysis and the contribution of individual trials to those results.

This type of pair-wise effect size is a unitless index that describes the distance between two group means in terms of the population's standard deviation. These effect sizes are relative, and may best be interpreted by referring to the group mean differences observed in the original measures of the study. Unlike the odds ratio, however, the effect size point estimate provides some information about the magnitude of the treatment difference. For general purposes, effect size point estimates can be interpreted by the following conventional frame of reference: 0.2 is small, 0.5 is medium, and 0.8 or more is a large effect size (Cohen, 1988). An effect size may be interpreted as statistically significant if its 95% CI excludes zero (null effect). The effect size can vary between negative infinity and infinity.

Adverse Events

The incidence of adverse events was recorded and the proportion of patients experiencing adverse events calculated for each treatment group, whenever possible. The difference between rates of adverse events was calculated, along with a 95% CI for the difference. A 95% CI that excludes zero suggests that the rates are significantly different between groups. The identity and rates of specific adverse events reported were summarized for each study, as reported by investigators. Criteria for reporting adverse events vary greatly among trials with regard to terminology used, method of ascertainment, attribution of specific adverse events as drug-related or not, and classification as severe or not.

Alpha-2 Agonists

This section of the report describes trials that have evaluated the efficacy and safety of alpha-2 agonists for the prevention of migraine. Alpha-2 agonists are antihypertensive agents that "block central vasomotor reflexes and diminish vascular reactivity" (Anthony, Lance, and Somerville, 1972). Of the included trials, most concern clonidine hydrochloride; guanfacine, the other drug represented, is pharmacologically similar to clonidine.

Studies Identified

Overview

The review identified 20 publications reporting on 17 separate controlled trials of alpha-2 agonists (Adam, Gore, and Price, 1978; Anthony, Lance, and Somerville, 1972; Behan, 1985; Boisen, Deth, Hübbe, et al., 1978; Bredfeldt, Sutherland, and Kruse, 1989; Das, Ahuja, and Narainaswamy, 1979; Elkind, Webster, Herbertson, et al, 1989a; Elkind, Webster, Herbertson, et al., 1989b; Kallanranta, Hakkarainen, Hokkanen, et al., 1977; Kåss and Nestvold, 1980; Louis, Schoenen, and Hedman, 1985a; Louis, Schoenen, and Hedman, 1985b; Mondrup and Møller, 1977; Ryan, Diamond, and Ryan, 1975; Ryan and Ryan, 1975a; Ryan and Ryan, 1975b; Shafar, Tallett, and Knowlson, 1972; Sjaastad and Stensrud, 1971; Stensrud and Sjaastad, 1976a; Wilkinson, 1970). One of these publications (Kallanranta, Hakkarainen, Hokkanen, et al., 1977) reported results from two separate trials, one comparing clonidine with placebo (Study 1), and another comparing clonidine with practolol (Study 2).

Four publications were excluded from our analysis for the reasons cited in Exhibit 2.

Exhibit 2. Excluded publications: Alpha-2 agonist trials

Excluded publications	Reason for exclusion
Elkind, Webster, Herbertson, et al., 1989b	Abstract of Elkind, Webster, Herbertson, et al., 1989a – Added no new information.
Louis, Schoenen, and Hedman, 1985b	Abstract of Louis, Schoenen, and Hedman, 1985a – Added no new information.
Ryan and Ryan, 1975a	Reported results from one of two sites more fully described in Ryan, Diamond, and Ryan, 1975
Ryan and Ryan, 1975b	Reported preliminary results from first half of trial described in Ryan, Diamond, and Ryan, 1975

Our analysis thus included 16 published reports on 17 separate trials, with 16 of the trials reporting on clonidine and one reporting on guanfacine (Elkind, Webster, Herbertson, et al., 1989a).

Twelve trials compared alpha-2 agonists with placebo, four compared clonidine with a beta-blocker (metoprolol, prindolol, practolol, and propranolol), and one trial each compared clonidine with an anticonvulsant (carbamazepine) and a serotonin antagonist (pizotifen).

The included trials are described in Evidence Table 1.

Study Design and Quality

Two of the 17 included trials were parallel-group in design (Behan, 1985; Elkind, Webster, Herbertson, et al., 1989a); 14 were crossover. One study (Anthony, Lance, and Somerville, 1972) was a partial crossover trial with three interventions. Patients who did not achieve success with one trial medication switched at the end of the first month to one of the others, while those who were successful continued on the initial medication. The investigators reported first-period (1-month) data separately, and we analyzed these data as if the trial were parallel-group in design. One of the crossover trials (Shafar, Tallett, and Knowlson, 1972) compared clonidine with placebo during four 8-week treatment periods. Although the crossover pattern was not described, we assumed that patients received each treatment twice.

Active treatment periods in the included trials ranged from 3 weeks (one trial) to 24 weeks (6 months) (one trial); the average length of the active treatment period was 2.4 months.

Quality scores ranged from 0 (two trials) to 4 (two trials); the average score was 2.4.

Patient Populations

Six trials provided no information about the setting in which patients were recruited. In five cases, patients were recruited from neurology departments or hospital clinics (Anthony, Lance, and Somerville, 1972; Boisen, Deth, Hübbe, et al., 1978; Kallanranta, Hakkarainen, Hokkanen, et al., 1977 [two studies]; Mondrup and Møller, 1977). Patients were recruited from headache clinics in two trials (Behan, 1985; Ryan, Diamond, and Ryan, 1975) and from general practice clinics in two trials (Adam, Gore, and Price, 1978; Bredfeldt, Sutherland, and Kruse, 1989). One trial recruited subjects who were inpatients at hospitals (Wilkinson, 1970), and two recruited patients through physician referrals (Bredfeldt, Sutherland, and Kruse, 1989; Shafar, Tallett, and Knowlson, 1972).

All of the trials reviewed included patients with migraine with or without aura. Most did not explicitly exclude patients who also suffered attacks of tension-type headache. In one study, approximately half of the patients had tension-type as well as migraine headaches (Stensrud and Sjaastad, 1976a). One trial reported that investigators "avoided" including patients with a combination of migraine and tension-type headaches, but did not explicitly exclude such patients (Kåss and Nestvold, 1980). Another trial excluded patients who were unable to distinguish attacks of migraine from tension-type headaches (Louis, Schoenen, and Hedman, 1985a). Four trials referred specifically to the Ad Hoc diagnostic criteria for migraine; none referred to the IHS criteria.

Most of the trials had minimum headache frequency requirements for inclusion. In one study, investigators explicitly recruited patients with migraines of "significant frequency and

severity" (Shafar, Tallett, and Knowlson, 1972). Two trials did not specify any frequency requirements (Kåss and Nestvold, 1980; Stensrud and Sjaastad, 1976a).

Most of the included trials permitted the use of medication for acute attacks of migraine occurring during the trial.

Six of the 17 trials did not report the average age of patients, and two did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 17 to 65, and the percentage of patients who were women ranged from 64% to 89%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 2.

Comparisons With Placebo

Clonidine. Eleven trials compared clonidine with placebo (Adam, Gore, and Price, 1978; Boisen, Deth, Hübbe, et al., 1978; Bredfeldt, Sutherland, and Kruse, 1989; Das, Ahuja, and Narainaswamy, 1979; Kallanranta, Hakkarainen, Hokkanen, et al., 1977; Mondrup and Møller, 1977; Ryan, Diamond, and Ryan, 1975; Shafar, Tallett, and Knowlson, 1972; Sjaastad and Stensrud, 1971; Stensrud and Sjaastad, 1976a; Wilkinson, 1970). Ten trials administered clonidine orally; one (Bredfeldt, Sutherland, and Kruse, 1989) used a transdermal patch.

Three of the 11 trials reported that clonidine was significantly better than placebo, with a reduction in headache frequency observed in Kallanranta, Hakkarainen, Hokkanen, et al., (1977) (Study 1), and a reduction in headache index in Sjaastad and Stensrud (1971) and Stensrud and Sjaastad (1976a). Even these positive studies, however, did not demonstrate large differences between clonidine and placebo. The effect size calculated from Kallanranta, Hakkarainen, Hokkanen, et al. (1977) (Study 1) was a moderate 0.45 (0.05 to 0.85), corresponding to a difference in mean headache frequency of 0.72 headaches per month from a baseline average of nearly three headaches per month in the population studied. Few other studies reported sufficient data to quantify the magnitude of the treatment effect; thus, no meta-analysis of the results was possible.

Guanfacine. A single small (n = 37) study compared two doses of guanfacine to placebo (Elkind, Webster, Herbertson, et al., 1989a). This study reported a statistically significant effect on headache frequency with the higher dose (1.0 mg/day), but no effect with the lower dose (0.5 mg/day) when compared to placebo. No data on the magnitude of the effect were reported.

Comparisons With Beta-blockers

Clonidine was compared with four different beta-blockers in four separate, relatively small trials. Louis, Schoenen, and Hedman (1985a) found that metoprolol reduced headache index significantly better than clonidine ($p<0.05$). Similar proportions of patients reported a greater than 50% reduction in headache frequency (28% and 37% for clonidine and metoprolol, respectively). A small study comparing clonidine and propranolol (Kåss and Nestvold, 1980)

showed reductions in headache frequency that were not significantly different for the two drugs (38% and 62% for clonidine and propranolol, respectively).

Two studies compared clonidine with the beta-blockers practolol and prindolol, both of which have intrinsic sympathomimetic activity. Kallanranta, Hakkarainen, Hokkanen, et al. (1977) (Study 2) reported that clonidine produced a significantly greater reduction in headache frequency than did practolol ($p<0.05$); however, the effect size we calculated suggests a modest benefit of 0.21 (-0.19 to 0.60). No difference in headache frequency was found between clonidine and prindolol in the other trial (Anthony, Lance, and Somerville, 1972).

Comparisons With Other Agents

Two small trials comparing clonidine with pizotifen and carbamazepine found no statistically significant differences in headache frequency between treatments (Anthony, Lance, and Somerville, 1972; Behan, 1985). The single trial of carbamazepine (Anthony, Lance, and Somerville, 1972) reported a large difference in the proportion of patients experiencing a 50% or greater reduction in headache frequency: 53% versus 33% for clonidine and carbamazepine, respectively; this difference, however, was not significantly different.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

The incidence of adverse events in patients taking clonidine in the included trials ranged from 16% to 86%. Withdrawals due to adverse events were relatively uncommon, occurring in 0% to 11% of patients. Specific adverse events associated with clonidine included drowsiness or tiredness, occurring in up to 38% of patients in two studies, and dry mouth, which was reported less frequently, in 2% to 16% of patients. Even less commonly reported were nausea or gastrointestinal effects, and dizziness or vertigo. In trials comparing clonidine to beta-blockers, adverse events occurred at similar rates for both interventions.

The single trial of guanfacine (Elkind, Webster, Herbertson, et al., 1989a) reported no substantial data on adverse events.

Conclusions

The existing trials suggest that clonidine is, at most, mildly effective for the prevention of migraine, but this has not been demonstrated conclusively. The positive placebo-controlled studies do not appear to be systematically different from the negative trials. In comparisons with beta-blockers with intrinsic sympathomimetic activity (practolol and prindolol), for which evidence for efficacy is lacking, clonidine has consistently been less effective, though not to a statistically significant degree.

There is insufficient evidence to conclude that guanfacine is effective for the prevention of migraine (one small, placebo-controlled study with no data on the magnitude of effect).

Adverse events (most commonly drowsiness or tiredness) were observed in a high proportion of patients in trials of clonidine, but the reported symptoms were usually neither serious nor cause for withdrawal from these relatively short-term trials. No information was available on adverse events associated with guanfacine.

Anticonvulsants

A few drugs normally used as anticonvulsants have been employed as migraine preventive agents. The literature review identified controlled trials of divalproex sodium, sodium valproate, carbamazepine, clonazepam, and gabapentin for this indication. This section of the report reviews the evidence for the safety and efficacy of these agents.

Studies Identified

Overview

The literature review identified nine publications reporting on nine separate controlled trials of anticonvulsants used for the prevention of migraine (Anthony, Lance, and Somerville, 1972; Hering and Kuritzky, 1992; Jensen, Brinck, and Olesen, 1994; Klapper, 1994; Klapper, 1996; Mathew, Saper, Silberstein, et al., 1995; Rompel and Bauermeister, 1970; Stensrud and Sjaastad, 1979; Wessely, Baumgartner, Klingler, et al., 1987). All nine publications were included in our analysis.

The included studies reported on the safety and efficacy of the following agents:

Divalproex sodium	3 trials
Sodium valproate	2 trials
Carbamazepine	2 trials
Clonazepam	1 trial
Gabapentin	1 trial

Seven trials compared anticonvulsants with placebo, two compared an anticonvulsant with a beta-blocker, and one compared an anticonvulsant with an alpha-2 agonist.

The included trials are described in Evidence Table 1.

Study Design and Quality

Five of the nine included trials were crossover in design; three were parallel-group. One study (Anthony, Lance, and Somerville, 1972) was a partial crossover trial with three interventions. Patients who did not achieve success with one trial medication switched at the end of the first month to one of the others, while those who were successful continued on the initial medication. The investigators reported first-period (1-month) data separately, and we analyzed these data as if the trial were parallel-group in design.

Active treatment periods in the included trials ranged in length from 1 month (two trials) to 3 months (four trials); the average length of the active treatment periods was 2.2 months.

Quality scores ranged from 1 (one trial) to 5 (one trial); the average score was 3.2.

Patient Populations

Four of the nine included trials provided no information about the setting in which patients were recruited. In three cases patients were drawn from headache clinics (Hering and Kuritzky, 1992; Jensen, Brinck, and Olesen, 1994; Klapper, 1996), in one case from a neurology clinic (Anthony, Lance, and Somerville, 1972), and in one case from headache and neurology clinics (Mathew, Saper, Silberstein, et al., 1995).

The majority of the trials reviewed (seven of nine) included patients with migraine with or without aura. One trial was restricted to patients with migraine without aura (Jensen, Brinck, and Olesen, 1994). Another included only patients with what was described as "typical" migraine (Rompel and Bauermeister, 1970); on the basis of the diagnostic criteria described in the article, we concluded that this referred to migraine with aura. Four trials referred specifically to the IHS diagnostic criteria for migraine, and two referred to the Ad Hoc criteria. All but two of the included trials had minimum migraine headache frequency requirements for inclusion (Rompel and Bauermeister, 1970; Wessely, Baumgartner, Klingler, et al., 1987).

Two trials explicitly excluded patients with chronic daily headache and patients with tension-type headache on 15 or more days per month (Klapper, 1996; Mathew, Saper, Silberstein, et al., 1995). In one case, investigators stated that "more than half" of the patients participating in the trial suffered from interval headaches of the tension type, in addition to their migraines (Stensrud and Sjaastad, 1979).

Klapper (1994) required that patients have no previous experience with the drugs being investigated in the trial (divalproex sodium and propranolol). Two other trials included only patients who had never tried preventive medication or who had failed two or fewer adequate trials of such medication (Klapper, 1996; Mathew, Saper, Silberstein, et al., 1995).

Three trials did not report whether patients were allowed to use medication for acute attacks of migraine occurring during the trial (Anthony, Lance, and Somerville, 1972; Klapper, 1994; Rompel and Bauermeister, 1970); the remaining six permitted the use of such medication.

Four of the nine trials did not report the average age of patients, and one did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 34 to 46, and the percentage of patients who were women ranged from 69% to 89%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 3.

Comparisons With Placebo

Divalproex sodium. Two parallel-group trials of similar design compared divalproex sodium with placebo (Klapper, 1996; Mathew, Saper, Silberstein, et al., 1995). Klapper (1996) tested three doses of divalproex sodium, 1500 mg/day, 1000 mg/day, and 500 mg/day. In

Mathew, Saper, Silberstein, et al. (1995), the dose was individually titrated to achieve a serum level of 70-120 milligrams per liter (mg/L); the average dose taken was 1087 mg/day. In both trials, the active treatment period lasted 12 weeks, including 4 weeks of initial dosage adjustment.

The two trials were consistent in finding all doses of divalproex sodium significantly better than placebo for reducing headache frequency. We were not able to calculate effect sizes from the continuous data reported (variance data were not reported and could not be estimated), but we were able, for each comparison with placebo, to calculate an odds ratio for the number of patients reporting a 50% or greater reduction in headache frequency. The proportion of patients experiencing a 50% or greater reduction in headache frequency was fairly consistent among all the active treatment groups, ranging from 43% to 48%. The resulting odds ratios were all statistically significant in favor of divalproex sodium. The largest point estimate (5.7) was from Mathew, Saper, Silberstein, et al. (1995), which reported a relatively low placebo response rate (14%). Odds ratio point estimates from the Klapper trial (1996) ranged from 2.7 for the 1000-mg dose to 3.1 for the 1500-mg dose, and the confidence intervals were narrower.

Sodium valproate. Sodium valproate is closely related to divalproex sodium. Two crossover trials compared this agent with placebo. Hering and Kuritzky (1992) tested an 800-mg daily dose, administered in two doses; Jensen, Brinck, and Olesen (1994) used a slow-release form of sodium valproate and titrated the dose (1000-1500 mg) to achieve a serum level above 50 mg/L. The latter trial was conducted among patients with migraine without aura only. The length of individual treatment periods was 8 weeks in Hering and Kuritzky (1992) and 12 weeks in Jensen, Brinck, and Olesen (1994).

In both cases, study investigators found that sodium valproate was significantly better than placebo at reducing headache frequency. We were able to calculate an effect size of 0.93 (0.39 to 1.5) from the data reported in one trial (Hering and Kuritzky, 1992) and an odds ratio of 7.1 (2.4 to 21) for the other trial. These confirmed the investigators' findings.

Carbamazepine. A single crossover trial compared carbamazepine (600 mg/day) with placebo (Rompel and Bauermeister, 1970). Though it received a high quality score (5), the trial was inadequately described in many respects. Some results were reported for headache index (not defined) and headache frequency, but no p-values or other measures of statistical significance were provided. We were able to calculate an odds ratio for the percentage of patients achieving "marked or complete improvement" in headache index during the course of the 6-week trial period; the odds ratio was large (12) and statistically significant. There were other problems with the trial: baseline values were based on patient histories; it was not completely certain that the headache index outcomes reported were based on diary data; and the placebo response reported for the above outcome was low (10%).

Clonazepam. Stensrud and Sjaastad (1979) compared clonazepam with placebo. The trial provided no data that we could use to calculate an effect size or odds ratio. Investigators reported that there was no significant difference between clonazepam and placebo for headache index ($p = 0.20$).

Gabapentin. A single parallel-group trial with a low quality score (2) compared gabapentin, in a dose of 900 mg/day, with placebo (Wessely, Baumgartner, Klingler, et al., 1987). Limited

results were reported in abstract form only. The investigators reported, but did not analyze, continuous data on headache frequency. We were not able to use these data to calculate an effect size (variance data were not reported and could not be estimated).

Comparisons With Beta-blockers

The literature review identified two trials comparing an anticonvulsant with a beta-blocking agent (Klapper, 1994; Anthony, Lance, and Somerville, 1972).

Divalproex sodium vs. propranolol. A single, open-label, crossover trial with a low quality score (2) compared divalproex sodium, in an average dose of 1100 mg/day, and propranolol, in an average dose of 140 mg/day (Klapper, 1994). Results were reported in abstract form only. Fifty percent of the 24 patients who started the trial withdrew before completing due to adverse events. The investigators reported mean post-treatment headache frequencies which suggested that divalproex sodium was better than propranolol at reducing headache frequency, but they did not analyze these results, and we were not able to use the reported means to calculate an effect size (variance data were not reported and could not be estimated).

Carbamazepine vs. prindolol. A single trial compared these two agents (Anthony, Lance, and Somerville, 1972). The trial was a partial crossover trial, in which patients who were not successful with their initial medication moved on to another of the study medications after the first month of treatment, while those who did achieve success continued on the initial medication. We analyzed the first-period data (which was reported separately) as if the trial were parallel-group in design. The trial received a low quality score (1).

We were able to calculate an odds ratio for the number of patients with a 50% or greater reduction in headache frequency after 1 month of treatment. The odds ratio was statistically significant in favor of prindolol, which confirmed the investigators' findings.

Comparisons With Alpha-2 Agonists

The literature review identified only one comparison of an anticonvulsant with an alpha-2 agonist. The trial described immediately above (Anthony, Lance, and Somerville, 1972) compared carbamazepine with clonidine. The odds ratio we calculated for headache frequency suggested that clonidine was better than carbamazepine, but not significantly so. Once again, this agrees with the results of investigators' analysis.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Carbamazepine

In the only study comparing carbamazepine with placebo (Rompel and Bauermeister, 1970), the overall percentage of patients reporting adverse events was significantly higher with carbamazepine (63%) than with placebo (23%). Vertigo/giddiness and drowsiness were both

more common with carbamazepine than with placebo (48% vs. 4% and 10% vs. 0%, respectively). One patient (of 48) withdrew due to unspecified adverse events associated with carbamazepine.

One trial was a partial crossover trial of carbamazepine vs. prindolol (Anthony, Lance, and Somerville, 1972). Data on adverse events from this study were reported for the entire trial only; no separate data were reported on the first treatment period. A significantly higher percentage of patients reported adverse events with carbamazepine (53%) than with prindolol (19%). Drowsiness/tiredness/weakness and giddiness/ataxia were more common with carbamazepine (14% vs. 3% and 20% vs. 1%, respectively). Twelve of 51 patients taking carbamazepine (24%) and 8/79 patients taking prindolol (10%) withdrew due to adverse events.

The same trial compared carbamazepine with clonidine (Anthony, Lance, and Somerville, 1972). Investigators found no significant difference in the percentage of patients reporting adverse events with carbamazepine (53%) and clonidine (41%). Giddiness/ataxia was more common with carbamazepine (20% vs. 0%); dry mouth/sore tongue/bad taste was more common with clonidine (14% vs. 0%). Twelve of 51 patients taking carbamazepine (24%) and 8/73 patients taking prindolol (11%) withdrew due to adverse events.

Clonazepam

A single trial compared clonazepam (1 mg/day) with placebo (Stensrud and Sjaastad, 1979). This study also included an extended, uncontrolled trial of clonazepam at higher doses (1-3 mg/day). Data on adverse events were not reported separately for the controlled portion of the trial. The most common adverse events associated with clonazepam were drowsiness and dizziness. Three of 38 patients (8%) withdrew at the end of the controlled trial due to adverse events (lethargy and sleepiness). No data were provided on adverse events associated with placebo.

Divalproex Sodium

Two studies compared divalproex sodium with placebo (Klapper, 1996; Mathew, Saper, Silberstein, et al., 1995). None of the three doses of divalproex sodium used in Klapper (1996) was associated with an adverse event rate significantly higher than placebo. Eighty percent, 76%, 74%, and 86% of patients reported adverse events in the placebo, 500-mg, 1000-mg, and 1500-mg groups, respectively. Almost without exception, rates of individual adverse events were higher in the 1500-mg group than in the lower dose groups. Unspecified "gastrointestinal (GI) events" were the major cause of withdrawals in the divalproex sodium groups (three in the 500-mg group, two in the 1000-mg group, and six in the 1500-mg group); two patients withdrew from the placebo group due to adverse events. Mathew, Saper, Silberstein, et al. (1995) did not report the overall percentages of patients reporting adverse events with divalproex sodium and placebo, but found significantly higher rates of nausea (46% vs. 14%), asthenia (31% vs. 8%), somnolence (30% vs. 5%), vomiting (19% vs. 0%), tremor (13% vs. 0%), and alopecia (13% vs.

0%) in the divalproex sodium group. Nine of 70 patients (13%) withdrew due to adverse events associated with divalproex sodium, 2/37 (5%) due to adverse events associated with placebo.

The one trial that compared divalproex sodium with propranolol (Klapper, 1994) reported data on adverse events only for those patients who withdrew due to adverse events. Of 24 patients evaluated in this crossover trial, nine withdrew while taking divalproex sodium (GI symptoms [three patients], fatigue [two patients], low white blood count [two patients], increasing headaches [one patient], rash [one patient]), and three while taking placebo (fatigue [two patients], increasing headaches [one patient]).

Gabapentin

Gabapentin was compared with placebo in a single trial (Wessely, Baumgartner, Klingler, et al., 1987). Very limited data were reported on adverse events for this treatment comparison. Two of 16 patients (13%) in the gabapentin group and 1/20 (5%) in the placebo group withdrew due to nausea, tiredness, and dizziness (no breakdown by treatment group).

Sodium Valproate

Two trials compared sodium valproate with placebo (Hering and Kuritzky, 1992; Jensen, Brinck, and Olesen, 1994). Neither trial found a significant difference in the overall percentage of patients reporting adverse events with the two treatments. Hering and Kuritzky (1979) reported that 21% of patients reported adverse events while taking sodium valproate, compared with 7% of patients while taking placebo. Three patients not included in this count withdrew due to unspecified adverse events, in one case associated with sodium valproate and in two cases associated with placebo. Jensen, Brinck, and Olesen (1994) reported that 33% of patients experienced adverse events while taking sodium valproate, compared with 16% while taking placebo. There were no striking differences in the occurrence of individual adverse symptoms. Four patients withdrew due to adverse events while taking sodium valproate, two while taking placebo.

Conclusions

Strong and consistent evidence supports the efficacy of divalproex sodium and the related compound sodium valproate for the prevention of migraine. The evidence for the efficacy of other anticonvulsant agents is weaker. Carbamazepine has mixed support from one placebo-controlled trial (suggesting efficacy) and one comparison with prindolol and clonidine (suggesting a smaller effect on headache frequency than either comparator). Neither clonazepam nor gabapentin appears to be an effective migraine preventive drug.

Adverse events -- most commonly dizziness and drowsiness -- were frequently observed with anticonvulsants and were a frequent cause of patient withdrawals from trials.

Antidepressants

This section of the report considers the evidence for the safety and efficacy of antidepressants for the prevention of migraine. The literature review identified trials of the tricyclic antidepressants amitriptyline, clomipramine, and opipramol; the selective serotonin re-uptake inhibitors (SSRIs) femoxetine, fluoxetine, and fluvoxamine; and the tetracyclic antidepressant mianserin. Opipramol, fluoxetine, and mianserin are not available in the US.

The precise relationship between the effect of the above antidepressants on mood and their effect on migraine is unclear, but it is generally thought that the two effects are independent of one another.

Studies Identified

Overview

The literature review identified 21 publications reporting on 17 separate controlled trials of antidepressants used for the prevention of migraine (Adly, Straumanis, and Chesson, 1992; Andersson and Petersen, 1981; Bánk, 1994; Bonuso, Di Stasio, Barone, et al., 1983; Couch and Hassanein, 1976; Couch and Hassanein, 1979; Gomersall and Stuart, 1973; Jacobs, 1972; Kangasniemi, Nyrke, Lang, et al., 1983; Langohr, Gerber, Koletzki, et al., 1985; Mathew, 1981; Monro, Swade, and Coppen, 1984; Monro, Swade, and Coppen, 1985; Nappi, Sandrini, Granella, et al., 1990; Noone, 1980; Orholm, Honoré, and Zeeberg, 1985; Orholm, Honoré, and Zeeberg, 1986; Saper, Silberstein, Lake, et al., 1994; Zeeberg, Orholm, Dalsgaard Nielsen, et al., 1981; Ziegler, Hurwitz, Hassanein, et al., 1987; Ziegler, Hurwitz, Preskorn, et al., 1993).

Three publications were excluded from our analysis for the reasons cited in Exhibit 3.

Exhibit 3. Excluded publications: Antidepressant trials

Excluded publication	Reason for exclusion
Monro, Swade, and Coppen (1984)	Abstract of Monro, Swade, and Coppen (1985); added no new information.
Nappi, Sandrini, Granella, et al. (1990)	Examined patients with chronic headache and depression/dysthymic disorder; included patients with chronic tension-type headache (n = 11) and patients with migraine (n = 27), but did not report results separately by headache type.
Orholm, Honoré, and Zeeberg (1985)	Abstract reporting preliminary results from trial more fully described in Orholm, Honoré, and Zeeberg (1986); added no new information.

Couch and Hassanein (1976) was a 12-month interim report on the trial more fully described in Couch and Hassanein (1979). The interim report provided some information not available in the final report. For that reason, we created combined entries for the two trials in Evidence Tables 1 and 12. The trial will be referred to in the text of this report and in Evidence Table 4 as Couch and Hassanein (1976 and 1979). Finally, Ziegler, Hurwitz, Preskorn, et al. (1993) was a study of predictors of response to treatment in the same study population reported on in Ziegler, Hurwitz, Hassanein, et al. (1987). The principal conclusions of the predictor study are summarized briefly in the entry for the main study in Evidence Table 1.

Our analysis thus included 18 published reports on 16 separate trials. The included studies reported on the safety and efficacy of the following agents:

Amitriptyline	6 trials
Femoxetine	4 trials
Clomipramine	2 trials
Fluoxetine	2 trials
Fluvoxamine	1 trial
Mianserin	1 trial
Opipramol	1 trial

Eleven trials compared antidepressants with placebo; one compared two antidepressants with one another; five trials compared antidepressants with beta-blockers; and one trial compared an antidepressant with timed-release dihydroergotamine (DHE).

The included trials are described in Evidence Table 1.

Study Design and Quality

Ten of the 16 included trials were parallel-group in design; six were crossover. One of the crossover trials (Langohr, Gerber, Koletzki, et al., 1985) included three different interventions, but had only two treatment periods, so that each patient tried only two of the three interventions.

The active treatment periods ranged from 1 month in length (one trial) to 6.25 months (27 weeks) (one trial); the average length of the active treatment period was 2.9 months.

Quality scores ranged from 2 (two trials) to 4 (five trials); the average score was 3.2.

Patient Populations

Seven trials provided no information about the setting in which patients were recruited. In three cases, patients were recruited from general practice settings or by referral from general practitioners (Jacobs, 1972; Orholm, Honoré, and Zeeberg, 1986; Zeeberg, Orholm, Dalsgaard Nielsen, et al., 1981). Noone (1980) recruited patients from two private practices of unspecified type. In one trial (Kangasniemi, Nyrke, Lang, et al., 1983), patients were recruited from a neurologist's private practice, and in two others (Couch and Hassanein, 1976 and 1979; Saper, Silberstein, Lake, et al., 1994) from specialty headache clinics. In the remaining two cases

(Adly, Straumanis, and Chesson, 1992; Gomersall and Stuart, 1973), subjects were recruited through newspaper or other media advertisements.

The majority of the trials reviewed (13 of 16) included patients with migraine with or without aura. Most did not explicitly exclude patients who also suffered attacks of tension-type headache. Four of these 13 trials referred specifically to the Ad Hoc diagnostic criteria for migraine, and 1 referred to the IHS criteria.

Mathew (1981) included patients with migraine only (n = 340) and patients with mixed headache (n = 375) and reported results separately for the two groups; we describe both sets of results below. Saper, Silberstein, Lake, et al. (1994) reported separate results for patients with migraine (n = 58) and patients with chronic daily headache (n = 64); we describe only the migraine results. Finally, Bonuso, Di Stasio, Barone, et al. (1983) compared amitriptyline with timed-release DHE in a population of patients with mixed headache, defined, in this instance, as alternating bouts of migraine and tension-type headache.

Most of the included trials had minimum headache frequency requirements for inclusion. A few required that a certain number or percentage of patients' attacks be severe in intensity (Adly, Straumanis, and Chesson, 1992; Couch and Hassanein, 1976 and 1979; Gomersall and Stuart, 1973; Ziegler, Hurwitz, Hassanein, et al., 1987).

Three trials did not provide any information about whether patients were allowed to use medication for acute attacks of migraine occurring during the trial (Andersson and Petersen, 1981; Jacobs, 1972; Orholm, Honoré, and Zeeberg, 1986); the remaining thirteen trials permitted the use of such medication.

Eight of the 16 trials did not report the average age of patients, and 3 did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 34 to 44, and the percentage of patients who were women ranged from 67% to 96%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 4.

Comparisons With Placebo

Amitriptyline. Three trials compared amitriptyline with placebo (Couch and Hassanein, 1976 and 1979; Gomersall and Stuart, 1973; Ziegler, Hurwitz, Hassanein, et al., 1987). The daily doses of amitriptyline used were 50-150 mg (Ziegler, Hurwitz, Hassanein, et al., 1987), 50-100 mg (Couch and Hassanein, 1976 and 1979), and 30-60 mg (Gomersall and Stuart); the length of the treatment period was 8, 4, and 27 weeks, respectively. Both Couch and Hassanein (1976 and 1979) and Ziegler, Hurwitz, Hassanein, et al. (1987) studied patients who frequently had severe or disabling attacks and reported outcomes that focused on relatively severe attacks.

The three trials were consistent in finding amitriptyline significantly better than placebo. We were able to calculate statistical measures (odds ratios or effect sizes) only for Couch and Hassanein (1976 and 1979) and so could not combine results from more than one trial.

The primary outcome analyzed by Couch and Hassanein (1976 and 1979) was the reduction in mean migraine index from pre- to post-treatment (4 weeks). The migraine index incorporated frequency and duration and included severe and disabling attacks only. Investigators reported that amitriptyline was significantly better than placebo for this outcome ($p<0.01$). The interim report (1976) provided mean scores (reported in Evidence Table 4) for 73 of the 100 patients eventually included in the efficacy analysis. On basis of these data, we were able to calculate an effect size of 0.62 (0.15 to 1.1), which confirms the investigators' findings.

We were also able to calculate an odds ratio of 2.4 (1.1 to 5.4) for the number of patients in each treatment group who reported an improvement of 50% or more in mean migraine index score, which confirms the investigators' finding that amitriptyline was significantly better than placebo for this outcome ($p<0.05$).

Very similar results were reported for another index, the mean total headache index, which included attacks of moderate and mild intensity.

Ziegler, Hurwitz, Hassanein, et al. (1987) used a similar daily dose of amitriptyline (50-150 mg) on a similar group of patients, followed over an 8-week treatment period. Mean weekly headache index scores (incorporating frequency, severity, and duration) were calculated for each intervention, using only headaches with a severity score of 4 or more on scale of 1-10. Investigators found that amitriptyline was significantly better than placebo for this outcome ($p<0.05$). No variance data were reported, and we were unable to estimate variance, so no effect size could be calculated.

Gomersall and Stuart (1973) reported very limited information and used a much lower daily dose of amitriptyline (30-60 mg) than did the other two trials, but still found that amitriptyline was significantly better than placebo for the total number of attacks occurring in the last 26 weeks of each treatment period ($p<0.001$).

Clomipramine. Two small trials compared clomipramine with placebo. They used different daily doses, but were consistent in finding no significant difference between clomipramine and placebo for headache frequency.

A time series analysis (autoregressive integrated moving average [ARIMA]) performed by Langohr, Gerber, Koletzki, et al. (1985) showed no significant difference between clomipramine (max 100 mg/day) and placebo for reduction in headache frequency from pre- to post-treatment (4 weeks) (no p-value reported). We were able to calculate an odds ratio using the conventional data the authors reported for the number of patients with a 50% or greater reduction in headache frequency. The odds ratio was 0.95 (0.25 to 3.6), which is not statistically significant.

Noone (1980) found no significant difference between clomipramine (30 mg/day) and placebo for reduction in headache frequency from pre- to post-treatment (8 weeks) ($p = 0.46$). We were unable to calculate an effect size for this outcome, since median and not mean frequency values were reported.

Femoxetine. Two trials compared femoxetine and placebo (Orholm, Honoré, and Zeeberg, 1985; Zeeberg, Honoré, Dalsgaard-Nielsen, et al., 1981). The two studies involved many of the same researchers, were similar in design, and employed similar analytical strategies. Patients in

both trials were recruited from a general practice setting. The two trials agreed in finding no significant difference between femoxetine and placebo for headache index or frequency.

Fluoxetine. One very small (n = 18) parallel-group trial (Adly, Straumanis, and Chesson, 1992) found that fluoxetine, in a dose ranging from 20 mg every other day to 40 mg/day, was significantly better than placebo at reducing median headache index scores at the end of the 8-week treatment period ($p<0.05$). However, this finding was not repeated in another, larger trial (n = 57 patients completed), employing an analysis of variance (ANOVA) analysis and conducted among patients recruited from a headache clinic, which found no significant differences between fluoxetine (20-40 mg/day) and placebo after 16 weeks of treatment (Saper, Silberstein, Lake, et al., 1994). We were not able to calculate odds ratios or effect sizes for either trial.

Mianserin. The only trial comparing mianserin with placebo (Monro, Swade, and Coppen, 1985) reported that mianserin (30 mg/day for 1 week, then 60 mg/day) reduced headache frequency significantly compared with baseline values ($p<0.05$ at 12 weeks), but was not significantly better than placebo for this outcome (no p-value reported). Similar results were reported for headache severity. We were not able to calculate an odds ratio or effect size on the basis of the data reported in this study.

Opipramol. A single trial compared opipramol with placebo (Jacobs, 1972). The investigators' analysis found that opipramol (150 mg/day) was significantly better than placebo at 12 weeks for mean reduction in number of attacks per patient ($0.05>p>0.02$). We could not calculate an effect size for this outcome, because no variance data were reported and the variance could not be estimated.

Comparisons Among Antidepressants

The literature review identified only one trial comparing one antidepressant with another. Bánk (1994) compared fluvoxamine with amitriptyline. Amitriptyline was administered in a relatively low dose (25 mg/day); the dose of fluvoxamine used was 50 mg/day. The investigators reported that both interventions significantly reduced median headache index scores from pre- to post-treatment (12 weeks) ($p<0.0003$ for fluvoxamine; $p<0.001$ for amitriptyline). They did not directly compare the two treatments for this or any other outcome. We were not able to calculate an effect size for reduction in headache index, since median and not mean scores were reported.

Comparisons With Beta-blockers

Amitriptyline vs. propranolol. Two trials compared amitriptyline and propranolol (Mathew, 1981; Ziegler, Hurwitz, Hassanein, et al., 1987). Mathew (1981) was a large and complicated trial, with eight different treatment arms. We discuss most of the treatment comparisons from this trial below, but describe the amitriptyline vs. propranolol results here.

Mathew (1981) used relatively low daily doses of amitriptyline (25-75 mg) and propranolol (60-160 mg) and followed patients over a 6-month treatment period. Among patients with mixed

migraine and tension-type headache, the study investigator found that amitriptyline was significantly better than propranolol for percentage improvement in headache index scores ($p<0.01$). We calculated an effect size based on pre- and post-treatment mean headache index scores in both groups. The effect size was -0.15 (-0.62 to 0.32), which does not confirm the investigator's finding. In the investigator's analysis, the combination of propranolol + amitriptyline was found to be superior to either drug on its own ($p < 0.01$) in this group of patients.

Among patients with migraine only, Mathew (1981) found that propranolol was significantly better than amitriptyline for percentage improvement in headache index scores; our effect size calculation using mean headache index scores did not confirm this finding (effect size: 0.02 [-0.46 to 0.49]). According to the investigator, propranolol + amitriptyline was not significantly better than propranolol alone ($p<0.50$), but was significantly better than amitriptyline alone for this group of patients.

Ziegler, Hurwitz, Hassanein, et al. (1987) used daily doses of 50-150 mg of amitriptyline and 80-240 mg of propranolol on a group of patients whose migraine headaches were frequently severe or disabling in intensity. Treatment periods were 8 weeks long. Mean weekly headache index scores (incorporating frequency, severity, and duration) were calculated for each intervention, using only headaches with a severity score of 4 or more on scale of 1-10. Investigators reported that there was no significant difference between amitriptyline and propranolol for this outcome ($p>0.05$). No variance data were reported, and we were unable to estimate variance, so no effect size could be calculated.

Investigators also reported the number of patients in both active treatment groups who achieved a 50% or more reduction in mean weekly headache index scores compared with placebo. We were able to use these data to calculate an odds ratio comparing amitriptyline with propranolol for this outcome. The odds ratio was 1.33 (0.47 to 3.8), which is not statistically significant.

Ziegler, Hurwitz, Preskorn, et al. (1993) studied predictors of response to treatment in this same study population. They reported that response to amitriptyline was correlated with female sex and with baseline headaches of shortest duration and highest frequency. Response to propranolol was correlated with attacks of greatest duration at baseline and with low pulse rise with exercise at baseline. Nonspecific response was associated with male sex, most frequent headaches by history, and least frequent headaches during baseline period.

Femoxetine vs. propranolol. Two trials of very similar design compared these two interventions and reached slightly different conclusions (Andersson and Petersen, 1981; Kangasniemi, Nyrke, Lang, et al., 1983). Andersson and Petersen (1981) found no significant difference between the two treatments for reduction in headache index (no p-value reported), and our odds ratio and effect size calculations confirm this finding. Kangasniemi, Nyrke, Lang, et al. (1983) found that propranolol was significantly better than femoxetine at reducing headache index ($p<0.05$). In both studies, the direction of effect favored propranolol-treated patients; however, in only one was the effect statistically significant.

Clomipramine vs. metoprolol. A single trial compared these two interventions (Langohr, Gerber, Koletzki, et al., 1985). A time series analysis (ARIMA) performed by investigators showed that metoprolol (max 100 mg/day) was significantly better than clomipramine (max 100

mg/day) for reduction in headache frequency from pre- to post-treatment (4 weeks) ($p<0.05$). We were able to calculate an odds ratio using the conventional data the authors reported for the number of patients with a 50% or greater reduction in headache frequency. The odds ratio was 0.45 (0.12 to 1.7), which is not statistically significant but is consistent with the investigators' finding, using more powerful statistical techniques permitted by individual patient data, that metoprolol is significantly better than clomipramine.

Comparisons With Other Agents

Amitriptyline vs. timed-release DHE. Bonuso, Di Stasio, Barone, et al. (1983) compared these two treatments in a group of patients with mixed migraine and tension-type headache. Amitriptyline was administered in a dose of 75 mg/day, and DHE in a dose of 10 mg/day. Patients were treated for 2 months. The investigators reported, but did not analyze, mean pre- and post-treatment headache index scores for both groups. The associated effect size of 0.82 (0.08 to 1.6) suggests that amitriptyline had a large and statistically significant effect on headache index when compared to timed-release DHE.

The investigators' analysis of the data on headache duration, stratified by severity, showed that DHE was significantly better than amitriptyline at reducing the number of hours of extremely severe and severe, migraine-type pain; amitriptyline was significantly better than DHE at reducing the number of hours of moderate and mild, tension-type HA-like pain ($p<0.01$ for all comparisons).

Amitriptyline vs. biofeedback alone or in combinations. Mathew (1981) researched the efficacy of amitriptyline alone and combined with several other therapies, both pharmacological and nonpharmacological. The trial compared amitriptyline with a control group (abortive administration of ergotamine + analgesics), biofeedback alone, and propranolol alone. Amitriptyline was also evaluated in the following combinations: amitriptyline + propranolol, amitriptyline + biofeedback, and amitriptyline + propranolol + biofeedback. The final combination evaluated was propranolol + biofeedback. Results were reported separately for patients with migraine and patients with mixed migraine and tension-type headache.

Among patients with migraine, each active treatment group experienced significantly better improvement than did the control group (no p-values reported). The improvement percentages ranged from 35-74% for the active treatment groups, compared with 20% for the control group.

The combination of propranolol + biofeedback yielded the best results: a 74% improvement in mean weekly headache index scores from pre-treatment to the last 3 months of treatment. Adding amitriptyline to this combination did not produce a significant change (73%).

Treatment with biofeedback alone resulted in a 35% improvement. Adding biofeedback to treatment with propranolol or amitriptyline improved both (propranolol, from 62% to 74%; amitriptyline, from 42 to 48%).

Among patients with mixed migraine and tension-type headache, the most effective treatment was the combination of propranolol + amitriptyline + biofeedback, with a 76% improvement in mean weekly headache index scores from pre-treatment to the last 3 months of treatment. Biofeedback alone yielded a 48% improvement. Adding biofeedback to the active drug therapies

produced an improvement in every case (from 52% to 62% for propranolol alone; from 60% to 66% for amitriptyline alone; and from 69% to 76% for propranolol + amitriptyline).

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Amitriptyline

Couch and Hassanein (1979) provided only limited information on adverse events associated with amitriptyline and placebo. Five of 55 amitriptyline patients withdrew due to adverse events, including rash, hypertension, nausea, and numbness in the hands and feet. Two of 61 patients withdrew while taking placebo, both because of chest pain. Dry mouth, bad taste, and drowsiness were all significantly more common with amitriptyline than with placebo.

Gomersall and Stuart (1973) found no significant difference in the number of patients reporting adverse events while on amitriptyline (16/20) versus placebo (13/20). One patient withdrew during treatment with placebo due to increased headache; there were no withdrawals from the amitriptyline group due to adverse events. The most common adverse events with amitriptyline that were less common on placebo were drowsiness and dry mouth.

Bánk (1994) found that more patients reported adverse events with amitriptyline (41%) than with fluvoxamine (23%), but the difference between the two treatments was not statistically significant. Drowsiness was the only adverse event reported with amitriptyline and caused seven patients to withdraw prematurely from the trial. Three patients in the fluvoxamine group withdrew due to adverse events (drowsiness, constipation, and pressure in the abdomen).

Neither of the two trials comparing amitriptyline with propranolol (Mathew, 1981; Ziegler, Hurwitz, Hassanein, et al., 1987) reported substantial data on adverse events.

The only trial comparing amitriptyline with timed-release DHE (Bonuso, Di Stasio, Barone, et al., 1983) reported that the most common adverse events associated with amitriptyline were drowsiness and dry mouth. The most common symptoms associated with DHE were nausea and stomach ache. Three patients in the amitriptyline group and two in the DHE group withdrew due to unspecified adverse events.

Clomipramine

Noone (1980) reported a significantly higher rate of adverse events with clomipramine (60% of patients) than with placebo (10%) among patients who completed the crossover trial. No description was provided of the specific symptoms observed. Two patients withdrew from the trial due to unspecified adverse events associated with clomipramine.

Langohr, Gerber, Koletzki, et al. (1985) found a total of 79 adverse events with clomipramine, compared with 16 with placebo. The most common adverse events observed with clomipramine that were not common with placebo were insomnia (15 patients vs. 2) and sweating (9 vs. 1).

Femoxetine

Two trials compared femoxetine with placebo (Orholm, Honoré, and Zeeberg, 1985; Zeeberg, Honoré, Dalsgaard-Nielsen, et al., 1981). The first of these found no significant difference between the two treatments in overall rates of adverse events (28% vs. 10%), while the second found significantly more adverse events with femoxetine (26% vs. 4%). Tremor, nausea, and changes in mood were all more common with femoxetine than with placebo.

Neither of the two trials comparing femoxetine with propranolol reported overall adverse event rates (Andersson and Petersen, 1981; Kangasniemi, Nyrke, Lang, et al., 1983). Specific adverse events that were more common with propranolol included tiredness (22% vs. 11% and 38% vs. 4% in the two trials, respectively), menstrual disorder (27% vs. 3%), dizziness (42% vs. 13%), and sleep disturbances (21% vs. 4%).

Fluoxetine

Of the two trials comparing fluoxetine with placebo, Adly, Straumanis, and Chesson (1992) reported that three of nine patients in each group reported adverse events. Saper, Silberstein, Lake, et al. (1994) observed significantly more adverse events with fluoxetine than with placebo (84% of patients vs. 66%); however, there was no difference in the number of patients reporting adverse events judged to be severe (8% vs. 4%). Fatigue was common in both groups (25% fluoxetine and 26% placebo), while sleeping problems were more common with fluoxetine (28% vs. 8%), as were tremors (20% vs. 6%) and stomach pain (13% vs. 0%).

Fluvoxamine

See under Amitriptyline, above.

Mianserin

A single trial comparing mianserin with placebo (Monro, Swade, and Coppen, 1985) provided no information on adverse events.

Opipramol

In a single trial comparing opipramol with placebo (Jacobs, 1972), no patients withdrew due to adverse events; no further information on adverse events was provided.

Conclusions

Although the drugs referred to as antidepressants in this section of the report share certain clinical uses, they comprise several distinct drug classes, namely tricyclic antidepressants

(amitriptyline, clomipramine, and opipramol), selective serotonin re-uptake inhibitors (femoxetine, fluoxetine, and fluvoxamine), and tetracyclic antidepressants (mianserin).

Of all these agents, the tricyclic antidepressant amitriptyline has been most frequently studied for the prevention of migraine and is the only antidepressant with reasonably consistent support for efficacy for this indication. Although this has not been demonstrated conclusively, amitriptyline may be more efficacious for patients with mixed migraine and tension-type headache than for patients with migraine alone. A large study by Mathew (1981) found amitriptyline to be significantly better than propranolol for patients with mixed headache, but not as good as propranolol for patients with migraine only.

None of the other agents reviewed in this section of the report -- clomipramine, opipramol, femoxetine, fluoxetine, fluvoxamine, or mianserin -- has sufficient data to support its efficacy, though substantial uncertainty still exists for these agents.

Tolerability was a problem with the tricyclic antidepressants studied, with anticholinergic symptoms frequently reported. It is possible that other tricyclic antidepressants might be equally effective for the prevention of migraine and carry a lower risk of adverse events. In most studies of pain conditions other than migraine, the various tricyclic antidepressants have been shown to be essentially equianalgesic. Within this class, amitriptyline and clomipramine have the strongest sedative and anticholinergic effects and are the most likely to cause orthostatic hypotension. Other tricyclic antidepressants (e.g., nortriptyline or doxepin) are generally associated with fewer adverse events of these types. Although these other tricyclic antidepressants have not been studied for migraine prevention in controlled trials, their analgesic effects in other pain states -- especially neuropathic conditions -- suggest that they may provide effective analgesia in migraine as well, while producing fewer adverse events.

In the relatively short-term trials reviewed here, adverse events were less frequently reported with fluoxetine and other SSRIs than with amitriptyline and clomipramine. However, the particular adverse events most commonly observed with the SSRIs (nausea and sexual dysfunction) may be of greater concern to many migraineurs than the anticholinergic effects associated with tricyclic antidepressants.

Potential adverse events not observed in these trials include drug interactions. Fluoxetine and other SSRIs inhibit the hepatic P450 system which metabolizes many other drugs used for the prevention of migraine, including beta-blockers, tricyclic antidepressants, several of the anticonvulsants, and calcium antagonists. This creates a potential for drug interactions, and perhaps some risk for the development of a serotonin syndrome if SSRIs are used with serotonin agonists.

Beta-blockers

This section of the report reviews the evidence for the efficacy and safety of beta-blockers for the prevention of migraine. A number of beta-blockers have been tested in controlled trials for this indication. The most commonly studied agent is propranolol, followed by metoprolol, atenolol, nadolol, timolol, and pindolol. Less frequently studied for migraine prophylaxis are the beta-blockers acebutolol, alprenolol, and oxprenolol. In the studies reviewed here, beta-blockers were compared with placebo, with a large number of other drugs, and with nonpharmacological treatments for migraine such as acupuncture and biofeedback.

Studies Identified

Overview

The literature review identified 93 publications reporting on 75 separate controlled trials of beta-blockers used for the prevention of migraine. Lücking, Oestreich, Schmidt, et al. (1988) described two separate trials of propranolol compared with flunarizine (Study 1 and Study 2). In two other cases, we combined descriptions from separate publications reporting on the same trial. In one case, two publications reported on a single trial of propranolol, amitriptyline, and placebo (Ziegler, Hurwitz, Hassanein, et al., 1987; Ziegler, Hurwitz, Preskorn, et al., 1993). The 1993 publication was a study of predictors of response in the same population reported on in the 1987 article. In the second case, two different publications reported on the same trial of metoprolol and placebo (Steiner, Cook, Joseph, et al., 1985; Steiner, Joseph, Hedman, et al., 1988). The 1985 publication was an abstract of the 1988 article and provided additional information not available in the later article.

Eighteen publications were excluded from our analysis for the reasons cited in Exhibit 4.

Exhibit 4. Excluded publications: Beta-blocker trials

Excluded publication	Reason for exclusion
Børgesen (1976)	Publication duplicate of Børgesen, Nielsen, and Møller (1974)
Diamond and Medina (1975)	Abstract referring to trial described more fully in Diamond and Medina (1976); no new little information provided.
Diener, Scholz, Dichgans, et al. (1989)	Outcome data reported limited to visual evoked potentials; no headache outcomes. Same population as reported in Gerber, Diener, Scholz, et al. (1991).
Gawel, Kreeft, Nelson, et al. (1991)	Abstract of trial reported more fully in Gawel, Kreeft, Nelson, et al. (1992); added no new information.

Havanka-Kanniainen, Hokkanen, and Myllylä (1987b)	Abstract reporting results from trial described more fully in Havanka-Kanniainen, Hokkanen, and Myllylä (1988); added no new relevant information.
Hedman and Andersen (1987)	Abstract reporting results from trial more fully described in Hedman, Andersen, Andersson, et al. (1988); added no new information.
Hedman, Andersen, Andersson, et al. (1988)	Analysis of secondary outcomes in subset of data reported on in Kangasniemi, Andersen, Andersson, et al. (1987).
Louis, Schoenen, and Hedman, 1985b	Abstract of Louis, Schoenen, and Hedman, 1985a; added no new information.
Ludin (1987)	Abstract reporting preliminary results from trial described more fully in Ludin (1989); added no new information.
Pradalier, Serratrice, Collard, et al. (1989a)	Abstract reporting results of trial described more fully in Pradalier, Serratrice, Collard, et al. (1989b); added no new information.
Ryan, Ryan, and Sudilovsky (1982)	Partial publication duplicate of Ryan, Ryan, and Sudilovsky (1983). The two reports are virtually identical for the controlled portion of the trial; Ryan, Ryan, and Sudilovsky (1983) also includes data on the long-term followup of patients successfully treated during the controlled trial.
Sørensen (1989)	Abstract of trial reported more fully in Sørensen, Larsen, Rasmussen, et al. (1991); added no new information.
Soyka and Oestreich (1987)	Abstract of trial reported more fully in Lücking, Oestreich, Schmidt, et al. (1988) (Study 1); added no new information.
Standnes (1982)	Reports results from one center involved in a multicenter trial; complete results reported in Tfelt-Hansen, Standnes, Kangasneimi, et al. (1984).
Stensrud and Sjaastad (1980b)	Publication duplicate of Stensrud and Sjaastad (1980a).
Sudilovsky, Stern, and Meyer (1986a)	Abstract of trial more fully reported in Sudilovsky, Elkind, Ryan, et al. (1987); added no few information.
Viswanathan, Rajendiran, Manohar, et al. (1991)	Abstract reporting results from 1 week after start of treatment only.
Wörz, Reinhardt-Benmalek, Grotemeyer, et al. (1991)	Abstract reporting results from trial more fully described in Wörz, Reinhardt-Benmalek, Foeh, et al. (1992); added no new information.

Our analysis thus included 75 publications reporting on 74 separate trials of beta-blockers. The included studies are listed below:

Ahuja and Verma (1985)
Albers, Simon, Hamik, et al. (1989)
Al-Qassab and Findley (1993)
Andersson and Petersen (1981)
Andersson, Dahl, Hansen, et al. (1983)
Anthony, Lance, and Somerville (1972)
Baldrati, Cortelli, Procaccianti, et al. (1983)
Behan and Reid (1980)
Børgesen, Nielsen, and Møller (1974)
Briggs and Millac (1979)
Carroll, Reidy, Savundra, et al. (1990)
Dahlöf (1987)
Diamond and Medina (1976)
Ekbom (1975)
Ekbom and Lundberg (1972)
Ekbom and Zetterman (1977)
Formisano, Falaschi, Cerbo, et al. (1991)
Forssman, Henriksson, Johannsson, et al. (1976)
Forssman, Lindblad, and Zbornikova (1983)
Freitag and Diamond (1984)
Gawel, Kreeft, Nelson, et al. (1992)
Gerber, Diener, Scholz, et al. (1991)
Gerber, Schellenberg, Thom, et al. (1995)
Grotemeyer, Scharafinski, Schlake, et al. (1990)
Grotemeyer, Schlake, Husstedt, et al. (1987)
Havanka-Kanniainen, Hokkanen, and Myllylä (1988)
Hesse, Møgelvang, and Simonsen (1994)
Holroyd, France, Cordingley, et al. (1995)
Johannsson, Nilsson, Widelius, et al. (1987)
Johnson, Hornabrook, and Lambie (1986)
Kallanranta, Hakkarainen, Hokkanen, et al. (1977) (Study 2)
Kangasniemi, Andersen, Andersson, et al. (1987)
Kangasniemi and Hedman (1984)
Kangasniemi, Nyrke, Lang, et al. (1983)
Kåss and Nestvold (1980)
Kjærsgåard-Rasmussen, Holt-Larsen, Borg, et al. (1994)
Klapper (1994)
Kuritzky and Hering (1987)
Langohr, Gerber, Koletzki, et al. (1985)
Louis, Schoenen, and Hedman (1985a)
Lücking, Oestreich, Schmidt, et al. (1988) (Studies 1 and 2)
Ludin (1989)
Malvea, Gwon, and Graham (1973)
Mathew (1981)
Mikkelsen, Kjærsgåard, Pedersen, and Christiansen (1986)
Nanda, Johnson, Gray, et al. (1978)
Olerud, Gustavsson, and Furberg (1986)
Olsson, Behring, Forssman, et al. (1984)
Palferman, Gibberd, and Simmonds (1983)
Penzien, Johnson, Carpenter, et al. (1990)
Pita, Higueras, Bolaños, et al. (1977)
Pradalier, Serratrice, Collard, et al. (1989b)
Ryan (1984)
Ryan, Ryan, and Sudilovsky (1983)
Sargent, Solbach, Damasio, et al. (1985)
Shimell, Fritz, and Levien (1990)
Sjaastad and Stensrud (1972)
Solomon (1986)
Sørensen, Larsen, Rasmussen, et al. (1991)
Sovak, Kunzel, Sternbach, et al. (1981)
Steardo, Bonuso, Di Stasio, et al. (1982)
Steiner, Cook, Joseph, et al. (1985)
Steiner, Joseph, Hedman, et al. (1988)
Stellar, Ahrens, Meibohm, et al. (1984)
Stensrud and Sjaastad (1976b)
Stensrud and Sjaastad (1980a)
Sudilovsky, Elkind, Ryan, et al. (1987)
Sudilovsky, Stern, and Meyer (1986b)
Tfelt-Hansen, Standnes, Kangasniemi, et al. (1984)
Vilming, Standnes, and Hedman (1985)
Weber and Reinmuth (1972)
Widerøe and Vigander (1974)
Wörz, Reinhardt-Benmalek, Foeh, et al. (1992)
Ziegler, Hurwitz, Hassanein, et al. (1987)
Ziegler, Hurwitz, Preskorn, et al. (1993)

The included studies reported on the efficacy and safety of the following agents:

Propranolol	46 trials
Metoprolol	15 trials
Nadolol	6 trials
Atenolol	3 trials
Pindolol	3 trials
Timolol	3 trials

Acebutolol	1 trial
Alprenolol	1 trial
Bisoprolol	1 trial
Oxprenolol	1 trial
Practolol	1 trial
Propranolol + amitriptyline	1 trial
Propranolol + amitriptyline + biofeedback	1 trial
Propranolol + analgesics	1 trial
Propranolol + biofeedback	1 trial

Thirty-eight of the trials were placebo-controlled; 3 were dosing studies with no placebo arm; 10 provided comparisons of beta-blockers with one another; 13 compared these agents with calcium antagonists, 6 with antidepressants, 6 with NSAIDs, 4 with alpha-2 agonists, 2 with anticonvulsants, 2 with methysergide, 1 with a serotonin antagonist, and 5 with behavioral or physical treatments.

The included trials are described in Evidence Table 1.

Study Design and Quality

Twenty-six of the 74 included trials were parallel-group in design; 47 were crossover trials; and 1 was a matched-pair trial.

Active treatment periods in the included trials ranged from 1 week (one trial) to 6 months (five trials); the average length of the active treatment periods was 2.6 months.

Quality scores ranged from 0 (one trial) to 5 (one trial); the average score was 3.2.

Patient Populations

Forty-seven of the 74 included trials provided no information about the setting in which patients were recruited. In 13 of the trials, patients were recruited from neurology clinics or departments; in 4 others, from migraine clinics or pain centers (Nanda, Johnson, Gray, et al., 1978; Sovak, Kunzel, Sternbach, et al., 1981; Steiner, Cook, Joseph, et al., 1985; Steiner, Joseph, Hedman, et al., 1988). In three trials, patients were outpatients at either clinics, medical practices, or hospitals (Holroyd, France, Cordingley, et al., 1995; Lücking, Oestreich, Schmidt, et al., 1988 [Studies 1 and 2]). In four trials, patients were referred by physicians (Briggs and Millac, 1979; Hesse, Møgelvang, and Simonsen, 1994; Kangasniemi, Nyrke, Lang, et al., 1983; Kjærsgåard-Rasmussen, Holt-Larsen, Borg, et al., 1994).

Most of the trials reviewed (60 of 74) included patients with migraine with or without aura. Two trials were restricted to patients having migraine with aura (Grotemeyer, Schlake, Husstedt, et al., 1987; Kangasniemi, Andersen, Andersson, et al., 1987); four were restricted to patients having migraine without aura (Baldrati, Cortelli, Procaccianti, et al., 1983; Grotemeyer, Scharafinski, Schlake, et al., 1990; Malvea, Gwon, and Graham, 1973; Tfelt-Hansen, Standnes,

Kangasniemi, et al., 1984). One included patients with mixed migraine and tension-type headaches (Sargent, Solbach, Damasio, et al., 1985). One included patients with tension-type headaches as long as patients could distinguish them from migraine attacks (Stellar, Ahrens, Meibohm, et al., 1984). Twenty-nine trials referred specifically to the Ad Hoc criteria for migraine, and nine referred to the IHS criteria.

Fourteen of the trials excluded patients who had received previous treatment with preventive migraine medications. In five trials, patients were excluded if they could not distinguish migraine from other types of headache attacks (Andersson, Dahl, Hansen, et al., 1983; Kåss and Nestvold, 1980; Louis, Schoenen, and Hedman, 1985a; Olsson, Behring, Forssman, et al., 1984; Vilming, Standnes, and Hedman , 1985). In six trials, patients with "other" or "other vascular" headaches were excluded (Havanka-Kanniainen, Hokkanen, and Myllylä, 1988; Kangasniemi and Hedman, 1984; Olsson, Behring, Forssman, et al., 1984; Ryan, Ryan, and Sudilovsky, 1983; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984; Vilming, Standnes, and Hedman, 1985).

All but 16 of the trials had minimum headache frequency requirements for inclusion. One trial included only patients with a history of two to eight migraines per month; more than 50% of these patients' headaches must also have been accompanied by focal auras (Kangasniemi, Andersen, Andersson, et al., 1987). Ziegler, Hurwitz, Hassanein, et al. (1987) included only patients whose migraine headaches had the following characteristics: more than 50% must have lasted at least 2 hours and more than 50% must have been "disabling" or "severe."

Ten studies did not report whether patients were allowed to use medication for acute attacks of migraine occurring during the trial. Such medications were not permitted in two trials (Behan and Reid, 1980; Sovak, Kunzel, Sternbach, et al., 1981), but were allowed in the remaining 62 trials.

Three trials included only patients who had not previously tried medication for the prevention of migraine (Albers, Simon, Hamik, et al., 1989; Forssman, Henriksson, Johannsson, et al., 1976; Steardo, Bonuso, Di Stasio, et al., 1982). In addition, eight trials excluded patients who had used preventive migraine medications from 2 weeks to 6 months prior to entering the trial (Formisano, Falaschi, Cerbo, et al. , 1991; Holroyd, France, Cordingley, et al., 1995; Kangasniemi, Nyrke, Lang, et al., 1983; Pradalier, Serratrice, Collard, et al., 1989b; Shimell, Fritz, and Levien, 1990; Steiner, Cook, Joseph, et al. , 1985; Steiner, Joseph, Hedman, et al., 1988; Wörz, Reinhardt-Benmalek, Foeh, et al., 1992).

Eighteen of the 74 trials did not report the average age of patients, and 4 did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 32 to 45, and the percentage of patients who were women ranged from 46% to 100%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 5.

Comparisons With Placebo

Propranolol. Propranolol, in doses ranging from 80 to 240 mg/day, was compared with placebo in 21 trials (Ahuja and Verma, 1985; Al-Qassab and Findley, 1993; Børgesen, Nielsen, and Møller, 1974; Dahlöf, 1987; Diamond and Medina, 1976; Forssman, Henriksson, Johannsson, et al., 1976; Johnson, Hornabrook, and Lambie, 1986; Kuritzky and Hering, 1987; Malvea, Gwon, and Graham, 1973; Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986; Palferman, Gibberd, and Simmonds, 1983; Pita, Higueras, Bolaños, et al., 1977; Pradalier, Serratrice, Collard, et al., 1989b; Sargent, Solbach, Damasio, et al., 1985; Solomon, 1986; Stensrud and Sjaastad, 1976b; Stensrud and Sjaastad, 1980a; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984; Weber and Reinmuth, 1972; Widerøe and Vigander, 1974; Ziegler, Hurwitz, Hassanein, et al., 1987).

Three studies (Børgesen, Nielsen, and Møller, 1974; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984; Weber and Reinmuth, 1972) reported the number of patients with a 50% or greater improvement in headache frequency, permitting calculation of odds ratios of 2.3 (0.81 to 6.7), 3.5 (1.8 to 6.7), and 31.5 (5.1 to 195), respectively. Because these results were statistically heterogeneous, and because more data were available for effect sizes, we did not perform a meta-analysis of these odds ratios.

Twelve studies allowed estimation of effect sizes, eight based on headache frequency (Børgesen, Nielsen, and Møller, 1974; Dahlöf, 1987; Johnson, Hornabrook, and Lambie, 1986; Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986; Pita, Higueras, Bolaños, et al., 1977; Pradalier, Serratrice, Collard, et al., 1989b; Sargent, Solbach, Damasio, et al., 1985; Widerøe and Vigander, 1974), and four based on headache indices (Ahuja and Verma, 1985; Forssman, Henriksson, Johannsson, et al., 1976; Stensrud and Sjaastad, 1980a; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984). The 12 effect size estimates were statistically homogeneous (chi-square = 15.0, d.f. = 11, p=0.18) and yielded a combined effect size of 0.55 (0.42 to 0.69). This summary effect size indicates a high degree of certainty that propranolol provides a moderate reduction in headache frequency or index; confidence intervals exclude a small or large effect.

Three placebo-controlled trials of propranolol used a long-acting formulation (Al-Qassab and Findley, 1993; Kuritzky and Hering, 1987; Pradalier, Serratrice, Collard, et al., 1989). Only one of these (Pradalier, Serratrice, Collard, et al., 1989) provided enough data to estimate the magnitude of difference between long-acting propranolol and placebo. These results did not allow us to compare the regular and long-acting formulations of propranolol.

Metoprolol. Four trials compared metoprolol, in doses of 100 mg/day to 200 mg/day, with placebo (Andersson, Dahl, Hansen et al., 1983; Kangasniemi, Andersen, Andersson, et al., 1987; Langohr, Gerber, Koletzki, et al., 1985; Steiner, Joseph, Hedman, et al., 1988). The two trials that used long-acting formulations and relatively high doses (200 mg/day versus 100 mg/day) of metoprolol found statistically significant efficacy compared to placebo (Andersson, Dahl, Hansen et al., 1983; Kangasniemi, Andersen, Andersson, et al., 1987). An effect size estimated from one of these trials (Andersson, Dahl, Hansen et al., 1983) was similar to that of the propranolol meta-analysis: 0.58 (0.08 to 1.1). The other two trials comparing metoprolol with placebo (Langohr, Gerber, Koletzki, et al., 1985; Steiner, Joseph, Hedman, et al., 1988) reported no significant

differences; one (Steiner, Joseph, Hedman, et al., 1988) allowed estimation of an effect size of 0.16 (-0.36 to 0.67).

Odds ratios for improvement could be calculated from one trial of long-acting metoprolol (Andersson, Dahl, Hansen et al., 1983) and one of a regular formulation (Langohr, Gerber, Koletzki, et al., 1985). These odds ratios were 3.9 (1.1 to 14) and 2.1 (0.63 to 7.2), respectively. Only the latter is statistically significant, but each represents a clinically important difference between metoprolol and placebo in the proportion of patients with a 50% or greater reduction in headache frequency or index: 22% and 18%, respectively.

Atenolol. Of the three trials comparing atenolol with placebo (Forssman, Lindblad, and Zbornikova, 1983; Johannsson, Nilsson, Widelius, et al., 1987; Stensrud and Sjaastad, 1980a), two found statistically significant differences (Johannsson, Nilsson, Widelius, et al., 1987; Stensrud and Sjaastad, 1980a). None of these trials reported sufficient data to estimate the magnitude of the treatment differences.

Nadolol. Nadolol, at doses of 80, 160, and 240 mg/day, was compared with placebo in three trials. Two of the trials combined data for all nadolol groups in their statistical analysis, noting similar responses among the different dosage groups. Freitag and Diamond (1984) reported that 32% of patients on nadolol compared with none of the patients on placebo experienced a 50% or greater reduction in headache index, a difference which was not statistically significant. Sudilovsky, Stern, and Meyer (1986b) did find a statistically significant difference, but did not report improvement rates or headache index group means. Ryan, Ryan, and Sudilovsky (1983) reported mean headache frequencies for each dosage group separately, but did not report statistical tests of significance.

Timolol. Timolol, in doses of 20 to 30 mg/day, was compared to placebo in three trials (Briggs and Millac, 1979; Stellar, Ahrens, Meibohm, et al., 1984; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984). Two of these (Stellar, Ahrens, Meibohm, et al., 1984; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984) reported the proportion of patients with a 50% or greater improvement in headache frequency with timolol (43% and 55%, respectively) and with placebo (27% and 30%, respectively). In both trials, the differences between timolol and placebo were statistically significant.

Continuous data on headache frequency or index were summarized in effect sizes for Briggs and Millac (1979) and Tfelt-Hansen, Standnes, Kangasniemi, et al. (1984). Effect size estimates of 0.93 (0.39 to 1.5) and 0.54 (0.22 to 0.85), respectively, were consistent with those calculated for propranolol versus placebo comparisons.

Acebutolol, alprenolol, oxprenolol, and pindolol. Two trials comparing pindolol, in doses of 7.5 mg and 15 mg/day, with placebo each failed to find a statistically significant difference (Ekbom and Lundberg, 1972; Sjaastad and Stensrud, 1972). Sjaastad and Stensrud (1972) reported individual patient data, allowing calculation of an effect size of 0.024 (-0.38 to 0.43) for headache index. While this effect size estimate is negligible, the broad confidence intervals do not exclude a small to moderate clinical effect.

Three other beta-blocking agents with intrinsic sympathomimetic activity -- acebutolol, alprenolol, and oxprenolol -- were investigated in one placebo-controlled trial each (Nanda, Johnson, Gray, et al., 1978; Ekbom, 1975; Ekbom and Zetterman, 1977). None of these trials found a significant benefit to the active drug. The number of patients improving by 50% or more

was not reported. Headache index data were used to calculate effect sizes for the studies of alprenolol and oxprenolol; the effect sizes were -0.5 (-0.58 to 0.47) and 0.15 (-0.36 to 0.65), respectively. These effect sizes are both negligible, but have wide confidence intervals that do not exclude a clinically important effect.

Dosing Studies

Propranolol. Three studies compared long-acting propranolol 80 mg/day with 160 mg/day (Al-Qassab and Findley, 1993; Carroll, Reidy, Savundra, et al., 1990; Havanka-Kanniainen, Hokkanen, and Myllylä, 1988). Although Carroll, Reidy, Savundra, et al. (1990) reported a statistically significant difference favoring the higher dose ($p = 0.03$), this finding was not replicated in the other two studies, where headache frequency was identical with both doses. One of the studies (Havanka-Kanniainen, Hokkanen, and Myllylä, 1988) provided both an odds ratio of 0.71 (0.14 to 3.6) and an effect size estimate of -0.16 (-0.76 to 0.45) for headache frequency.

Nadolol. Three trials compared different doses of nadolol (Ryan, 1984; Ryan, Ryan, and Sudilovsky, 1983; Sudilovsky, Elkind, Ryan, et al., 1987). From one of these -- the only one to provide data on the proportion of patients with at least a 50% improvement in headache index -- we calculated an odds ratio for improvement of 3.5 (1.3 to 9.6) for the 160 mg/day versus 80 mg/day comparison (Sudilovsky, Elkind, Ryan, et al., 1987). Neither of the other studies reported tests of statistical significance or sufficient data to calculate odds ratios or effect sizes.

Comparisons Among Beta-blockers

Metoprolol vs. propranolol. Metoprolol and propranolol were compared in four trials (Gerber, Diener, Scholz, et al., 1991; Kangasniemi and Hedman, 1984; Olsson , Behring, Forssman, et al., 1984; Steardo, Bonuso, Di Stasio, et al., 1982). With one exception, none of the four trials found any significant differences between the two interventions for headache frequency or index. The sole exception was the smallest of the four trials (Steardo, Bonuso, Di Stasio, et al., 1982). This trial used the highest dose of metoprolol (300 mg/day) and found a very low proportion of patients with a 50% or greater reduction in headache frequency on metoprolol: 6% compared with 67% on propranolol. We calculated an effect size of -1.3 (-2.0 to 0.62) based on continuous headache frequency data from this trial; this effect size suggests that although the difference between the two interventions was large, it was not statistically significant.

Nadolol vs. propranolol. Three trials reported comparisons between nadolol and propranolol (Olerud, Gustavsson, and Furberg, 1986; Ryan, 1984; Sudilovsky, Elkind, Ryan, et al., 1987). The same trial that found a significant difference between nadolol 160 mg/day and 80 mg/day reported an odds ratio of 3.5 (1.3 to 9.6) comparing the 37% improvement rate of propranolol-treated patients to the 64% improvement of those taking nadolol 160 mg/day (Sudilovsky, Elkind, Ryan, et al., 1987). The improvement rates were similar in the propranolol and nadolol 80 mg/day arms at 37% and 33% respectively (odds ratio = 0.85 [0.29 to 2.5]).

Other comparisons among beta-blockers. Three other trials provided limited data on comparisons of propranolol with atenolol and timolol, and a comparison of metoprolol with bisoprolol (Stensrud and Sjaastad, 1980a; Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984; Worz, Reinhardt-Benmalek, Foeh, et al., 1992). None of these suggested any clinically important differences between the agents and dosages compared.

Comparisons With Other Treatments

See the chapters on alpha-2 agonists, anticonvulsants, antidepressants, calcium antagonists, methysergide, nonsteroidal anti-inflammatory drugs, and other serotoninergic agents for comparisons between beta-blockers and these other classes of drugs. For the one trial comparing propranolol, amitriptyline, and biofeedback in various combinations (Mathew, 1981), see the chapter on antidepressants. The remaining four trials comparing beta-blockers with a behavioral or physical treatment (Hesse, Møgelvang, and Simonsen, 1994; Holroyd, France, Cordingley, et al., 1995; Penzien, Johnson, Carpenter, et al., 1990; Sovak, Kunzel, Sternbach, et al., 1981) are summarized in Evidence Table 1; the results from these trials are described in the companion report on behavioral and physical treatments for migraine.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12. Similar adverse events were reported for all beta-blockers. They included fatigue, depression, nausea, dizziness, and insomnia.

Propranolol

Of the placebo-controlled trials of propranolol that reported rates of adverse events for both the propranolol and placebo arms, the largest difference in rates was 14% in a study reporting a 42% incidence of adverse events for propranolol and 28% for placebo (Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984).

Many of the studies reported the number of withdrawals due to adverse events. The difference in withdrawal rates in propranolol- and placebo-treated patients ranged from zero (no difference) to 8% higher for propranolol-treated patients.

One of the three placebo-controlled trials of long-acting propranolol reported rates of adverse events for all treatment arms (Pradalier, Serratrice, Collard, et al., 1989). The rates of adverse events and withdrawals due to adverse events were nearly identical for long-acting propranolol and placebo.

Metoprolol

In one placebo-controlled trial, the rate of adverse events appeared higher with metoprolol (Kangasniemi, Andersen, Andersson, et al., 1987). In the other two placebo-controlled trials reporting adverse event rates, there was no difference in withdrawals due to adverse events

between the active treatment and placebo arm (Andersson, Dahl, Hansen, et al., 1983; Steiner, Joseph, Hedman, et al., 1988).

Timolol

Among placebo-controlled trials of timolol, the drug appeared to be well tolerated. In one trial there was no difference in adverse event rates associated with timolol and placebo (Briggs and Millac, 1979). In the other two studies, there were fewer withdrawals due to adverse events in the active treatment groups than in the placebo groups (Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984; Stellar, Ahrens, Meibohm, et al., 1984).

Nadolol

The three placebo-controlled trials of nadolol reported very little information on adverse events. In one (Ryan, Ryan, and Sudilovsky, 1983) a significantly higher adverse event rate was reported for the nadolol 240 mg/day group (50% vs. 25% for placebo).

Atenolol

One of the three placebo-controlled trials of atenolol reported the rate of adverse events for both placebo and active treatment groups (Forssman, Lindblad, and Zbornikova, 1983). There was a 20% higher rate of adverse events with atenolol. There was no difference in withdrawal rate due to adverse events. Another study reported higher rates of withdrawal due to adverse events for the placebo group (Johannsson, Nilsson, Widelius, et al., 1987).

Acebutolol, Alprenolol, Oxprenolol, and Pindolol

Few trials of these agents reported adverse event rates by treatment group. One placebo-controlled trial of pindolol reported higher withdrawals due to adverse events in the active treatment group.

Conclusions

Propranolol, in a daily dose of 120 mg to 240 mg, has strong and consistent support for efficacy in reducing headache frequency and headache index. Timolol, metoprolol, atenolol, and nadolol are also likely to be beneficial, based on trials comparing these agents to placebo or to propranolol. Beta-blockers with intrinsic sympathomimetic activity -- including acebutolol, alprenolol, oxprenolol, and pindolol -- appear to be ineffective for the prevention of migraine.

There is insufficient evidence to conclude that extended-release preparations of propranolol and metoprolol are more or less effective, or more or less well tolerated, than regular formulations of these drugs.

While some studies had high dropout rates, most patients appear to have tolerated the adverse events associated with beta-blockers (principally fatigue, depression, nausea, dizziness, and insomnia). Dropouts were rarely due to adverse events associated with the active treatments.

Calcium Antagonists

Calcium antagonists have been increasingly advocated as a useful class of drugs for the prevention of migraine. Verapamil is the calcium antagonist most frequently used for this purpose in the U.S., though it has been studied for this indication in only a few controlled trials. Flunarizine (which is not available in the U.S.) has been more extensively tested as a migraine preventive agent. Controlled trials of nimodipine, nifedipine, nicardipine, and cyclandelate have also been published. All of these last four agents, except for cyclandelate, are available in the US. This section of the report examines the evidence for the safety and efficacy of these agents.

Studies Identified

Overview

The literature review identified 59 publications reporting on 47 separate controlled trials of calcium antagonists used for the prevention of migraine. Fourteen publications were excluded from our analysis for the reasons cited in Exhibit 5.

Exhibit 5. Excluded publications: Calcium antagonist trials

Excluded publication	Reason for exclusion
Agnoli, Bussone, Manzoni, et al. (1989)	Abstract reporting preliminary results from trial described more fully in Agnoli, Bussone, Mailland, et al. (1991); added no new information.
Diamond, Freitag, and Diamond (1990)	Abstract reporting preliminary results from trial described more fully in Diamond and Freitag (1993); added no new information.
Diener, Scholz, Dichgans, et al. (1989)	Study reported no head pain outcome data. Reported visual evoked potentials (VEPs) in population reported on in Gerber, Diener, Scholz, et al. (1991).
Gawel, Kreeft, Nelson, et al. (1991)	Abstract of trial reported more fully in Gawel, Kreeft, Nelson, et al. (1992); added no new information.
Havanka-Kanniainen, Hokkanen, and Myllylä (1985a)	Abstract of trial reported more fully in Havanka-Kanniainen, Hokkanen, and Myllylä (1987a); added no new information.
Kangasniemi and Tokola (1989)	Abstract describing trial in progress; no results reported.
Ludin (1987)	Abstract reporting preliminary results from trial described more fully in Ludin (1989); added no new information.
Mentenopoulos, Manafi, Logothetis, et al. (1985)	Publication duplicate of Mendenopoulos, Manafi, Logothetis, et al. (1985).

Rascol, Montastruc, and Rascol (1985)	Abstract of trial reported more fully in Rascol, Montastruc, and Rascol (1986); added no new information.
Sandrini, Savoini, Cavallini, et al. (1987)	Abstract of trial reported more fully in Nappi, Sandrini, Savoini, et al. (1987); added no new information.
Sørensen (1989)	Abstract of trial reported more fully in Sørensen, Larsen, Rasmussen, et al. (1991); added no new information.
Sørensen, Hansen, and Olesen (1985)	Abstract of trial reported more fully in Sørensen, Hansen, and Olesen (1986); added no new information.
Soyka and Oestreich (1987)	Abstract of trial reported more fully in Lücking, Oestreich, Schmidt, et al. (1988) (Study 1); added no new information.
Viswanathan, Rajendiran, Manohar, et al. (1991)	Abstract reporting results in unacceptably short time frame (1 week after start of treatment only).

The following 45 publications were included in our analysis:

Agnoli, Bussone, Mailland, et al., 1991
Al Deeb, Biary, Bahou, et al., 1992
Albers, Simon, Hamik, et al., 1989
Ansell, Fazzone, Festenstein, et al., 1988
Bassi, Brunati, Rapuzzi, et al., 1992
Bussone, Baldini, D'Andrea, et al., 1987
Cerbo, Casacchia, Formisano, et al., 1986
Diamond and Freitag, 1993
Formisano, Falaschi, Cerbo, et al., 1991
Freitag, Diamond, and Diamond, 1991
Frenken and Nuijten, 1984
Gawel, 1987
Gawel, Kreeft, Nelson, et al., 1992
Gelmers, 1983
Gerber, Diener, Scholz, et al., 1991
Gerber, Schellenberg, Thom, et al., 1995
Grotemeyer, Schlake, and Husstedt, 1989
Grotemeyer, Schlake, Husstedt, et al., 1987
Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b
Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a
Lamsudin and Sadjimin, 1993
Leandri, Rigardo, Schizzi, et al., 1990
Louis, 1981
Louis and Spierings, 1982
Lücking, Oestreich, Schmidt, et al., 1988
Ludin, 1989
Markley, Cheronis, and Piepho, 1984
Mastrosimone, Iaccarino, and de Caterina, 1992
McArthur, Marek, Pestronk, et al., 1989
Mendenopoulos, Manafi, Logothetis, et al., 1985
Meyer and Hardenberg, 1983
Micieli, Trucco, Agostinis, et al., 1985
Migraine-Nimodipine European Study Group, 1989a
Migraine-Nimodipine European Study Group, 1989b
Nappi, Sandrini, Savoini, et al., 1987
Pini, Ferrari, Guidetti, et al., 1985
Rascol, Montastruc, and Rascol, 1986
Shimell, Fritz, and Levien, 1990
Shukla, Garg, Nag, et al., 1995
Solomon, 1986
Solomon, Steel, and Spaccavento, 1983
Sørensen, Hansen, and Olesen, 1986
Sørensen, Larsen, Rasmussen, et al., 1991
Steardo, Marano, Barone, et al., 1986
Thomas, Behari, and Ahuja, 1991

Freitag, Diamond, and Diamond (1991) was an abstract reporting on the trial more fully described in Diamond and Freitag (1993). The abstract provided data on adverse events that were not reported in the final publication. For that reason, we included the abstract in our analysis and refer to it in the entries for Diamond and Freitag (1993) in Evidence Tables 1 and 12. Lücking, Oestreich, Schmidt, et al. (1988) reported results from two separate trials, which are labeled Study 1 and Study 2 in the text of this report and in the accompanying Evidence Tables.

Our analysis thus included 45 published reports describing 45 separate trials. The included studies reported on the safety and efficacy of the following agents:

Flunarizine	25 trials
Nimodipine	11 trials
Nifedipine	5 trials
Verapamil	3 trials
Cyclandelate	3 trials
Nicardipine	1 trial

Nineteen trials compared calcium antagonists with placebo; 2 were dosing studies with no placebo arm; 3 compared calcium antagonists with one another; 12 trials compared these agents with beta-blockers, 7 with serotonin antagonists, and 3 with other agents.

The included trials are described in Evidence Table 1.

Study Design and Quality

Thirty of the 45 included trials were parallel-group in design; 15 were crossover.

The active treatment periods ranged in length from 1 month (one trial) to 6 months (three trials); the average length of the active treatment period was 3.4 months.

Quality scores ranged from 2 (seven trials) to 5 (two trials); the average score was 3.3.

Patient Populations

Twenty of the 45 included trials provided no information about the setting in which patients were recruited. In eight cases, patients were drawn from headache clinics or headache study centers (Ansell, Fazzone, Festenstein, et al., 1988; Bassi, Brunati, Rapuzzi, et al., 1992; Diamond and Freitag, 1993; Nappi, Sandrini, Savoini, et al., 1987; Pini, Ferrari, Guidetti, et al., 1985; Rascol, Montastruc, and Rascol, 1986; Shukla, Garg, Nag, et al., 1995; Sørensen, Hansen, and Olesen, 1986). Seven different trials recruited patients from neurology clinics or departments (Gelmers, 1983; Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b and 1987a; Migraine-Nimodipine European Study Group, 1989a and 1989b; Sørensen, Larsen, Rasmussen, et al., 1991; Steardo, Marano, Barone, et al., 1986). One trial recruited patients from polyclinic, medical, and neurology departments (Shimell, Fritz, and Levien, 1990), and another from neurology and psychiatric departments (Mendenopoulos, Manafi, Logothetis, et al., 1985). In four trials, patients were recruited from family or general medical practices (Frenken and Nuijten, 1984; Louis, 1981; Louis and Spierings, 1982; Lücking, Oestreich, Schmidt, et al., 1988 [Study 1]). Trial participants were described as hospital outpatients in three studies (Al Deeb, Biary, Bahou, et al., 1992; Lamsudin and Sadjimin, 1993; Lücking, Oestreich, Schmidt, et al., 1988 [Study 2]). Finally, one trial recruited patients through personal referrals and advertisements (McArthur, Marek, Pestronk, et al., 1989).

The majority of the trials reviewed (33 of 45) included patients with migraine with or without aura. Nine trials were restricted to patients with migraine without aura (Agnoli, Bussone,

Mailland, et al., 1991; Bussone, Baldini, D'Andrea, et al., 1987; Grotemeyer, Schlake, and Husstedt, 1989; Leandri, Rigardo, Schizzi, et al., 1990; Micieli, Trucco, Agostinis, et al., 1985; Migraine-Nimodipine European Study Group, 1989b; Nappi, Sandrini, Savoini, et al., 1987; Sørensen, Hansen, and Olesen, 1986; Thomas, Behari, and Ahuja, 1991). Three trials included only patients with migraine with aura (McArthur, Marek, Pestronk, et al., 1989; Mendenopoulos, Manafi, Logothetis, et al., 1985; Migraine-Nimodipine European Study Group, 1989a). Twenty-three trials referred specifically to the Ad Hoc diagnostic criteria for migraine, and eight referred to the IHS criteria.

Five trials explicitly excluded patients who also suffered attacks of tension-type headache or required that patients be able to distinguish between attacks of migraine and tension-type headache (Ansell, Fazzone, Festenstein, et al., 1988; Diamond and Freitag, 1993; Leandri, Rigardo, Schizzi, et al., 1990; Louis, 1981; Micieli, Trucco, Agostinis, et al., 1985). Two trials excluded patients with tension-type headaches on six or more days per month (Migraine-Nimodipine European Study Group, 1989a and 1989b), and one trial excluded patients with daily tension-type headaches (Thomas, Behari, and Ahuja, 1991). One trial included patients with migraine or cluster headache, but reported results separately for the two types of headache (Meyer and Hardenberg, 1983).

Most of the included trials had minimum headache frequency requirements for inclusion. A few required that patients' attacks be moderate to severe in intensity (Frenken and Nuijten, 1984; Louis and Spierings, 1982; Mendenopoulos, Manafi, Logothetis, et al., 1985; Sørensen, Hansen, and Olesen, 1986).

Three trials included only patients who had not previously tried medication for the prevention of migraine (Albers, Simon, Hamik, et al., 1989; Gerber, Schellenberg, Thom, et al., 1995; Steardo, Marano, Barone, et al., 1986). In addition, four trials excluded patients with a history of unsuccessful treatment with preventive agents (Diamond and Freitag, 1993; Gawel, Kreeft, Nelson, et al., 1992; Migraine-Nimodipine European Study Group, 1989a and 1989b).

Seven trials did not report whether patients were allowed to use medication for acute attacks of migraine occurring during the trial (Gawel, 1987; Grotemeyer, Schlake, and Husstedt, 1989; Grotemeyer, Schlake, Husstedt, et al., 1987; Migraine-Nimodipine European Study Group, 1989a and 1989b; Shimell, Fritz, and Levien, 1990; Solomon, 1986); the remaining 38 trials all permitted the use of such medication.

One trial included only migraine patients with low blood pressure, who could not safely take beta-blockers (Grotemeyer, Schlake, and Husstedt, 1989). Another included only patients who experienced vomiting at the beginning of their migraine attacks (Grotemeyer, Schlake, Husstedt, et al., 1987). Otherwise, there were no unusual inclusion or exclusion criteria.

Sixteen of the 45 trials did not report the average age of patients, and five did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 30 to 47, and the percentage of patients who were women ranged from 50% to 90%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 6.

Comparisons With Placebo

Flunarizine. Eight trials compared flunarizine with placebo (Al Deeb, Biary, Bahou, et al., 1992; Diamond and Freitag, 1993; Frenken and Nuijten, 1984; Louis, 1981; Mendenopoulos, Manafi, Logothetis, et al., 1985; Pini, Ferrari, Guidetti, et al., 1985; Sørensen, Hansen, and Olesen, 1986; Thomas, Behari, and Ahuja, 1991). All eight trials used a 10-mg daily dose, though in one case (Pini, Ferrari, Guidetti, et al., 1985), patients were treated with 20 mg/day for the first 2 weeks of the treatment period.

More than half of the trials found a statistically significant benefit for flunarizine compared with placebo in reducing headache frequency or headache index. We were able to calculate effect sizes for all but one of the eight trials (Frenken and Nuijten, 1984). Effect sizes from three trials were statistically significant (Louis, 1981; Mendenopoulos, Manafi, Logothetis, et al., 1985; Sørensen, Hansen, and Olesen, 1986). Results from the seven trials were heterogeneous (chi-square = 13.863; degrees of freedom = 6; p = 0.03). The summary effect size from a meta-analysis was 0.52 (0.24 to 0.80).

Three of the eight trials (Al Deeb, Biary, Bahou, et al., 1992; Diamond and Freitag, 1993; Thomas, Behari, and Ahuja, 1991) reported the number of patients exceeding a 50% improvement threshold. From these data we calculated odds ratios for each of the trials. Two trials (Al Deeb, Biary, Bahou, et al., 1992; Diamond and Freitag, 1993) had odds ratios of 1.3 and were not statistically significant. The smallest study (Thomas, Behari, and Ahuja, 1991), a crossover trial with 15 patients, had an odds ratio of 6.0, which showed a larger effect. We calculated a summary odds ratio of 1.9 (0.7 to 5.0), which was not statistically significant.

One small trial (n = 29) compared two different doses of flunarizine (Bassi, Brunati, Rappuzzi, et al., 1992). Both of the treatment groups in this trial took 10 mg of flunarizine per day for the first week. The dosage was then reduced to 3 mg/day in one group. No significant differences were observed in headache index at 4 months between the two dosage groups.

Nimodipine. Five trials compared nimodipine with placebo (Ansell, Fazzone, Festenstein, et al., 1988; Gelmers, 1983; Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b; Migraine-Nimodipine European Study Group, 1989a and 1989b). All five trials used a 120-mg/day dose of nimodipine.

Two of the five trials found a statistically significant effect (Gelmers, 1983; Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b). Both of the Migraine-Nimodipine European Study Group trials (separately reported trials for migraine with and without aura) had unusually large improvements in the placebo groups, which exceeded those in the nimodipine groups. In these studies, flunarizine was not effective at reducing headache index compared with placebo, for either migraine with or without aura.

Effect size estimates based on headache index were available from two studies (Gelmers, 1983; Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b). The effect sizes from each study

were similar, 0.78 and 0.85, and both were statistically significant. We calculated a summary effect size of 0.82 (0.32 to 1.3).

One crossover trial compared two different doses of nimodipine (60 mg/day and 120 mg/day) (Meyer and Hardenberg, 1983), but did not find any clinically important differences. However, the treatment period observed was short, extending only 2 months.

Verapamil. Verapamil was compared with placebo in three small trials. Two of the three trials used a dose of 240 mg/day (Markley, Cheronis, and Piepho, 1984; Solomon, 1986); the third used a dose of 320 mg/day (Solomon, Steel, and Spaccavento, 1983).

Two of these three crossover studies reported positive findings (Markley, Cheronis, and Piepho, 1984; Solomon, Steel, and Spaccavento, 1983). The two positive studies reported enough data to calculate effect sizes of 1.14 (0.34 to 1.94) and 0.38 (-0.43 to 1.18), respectively. We calculated a summary effect size of 0.78 (0.09 to 1.5), which was consistent with the individual studies' findings of statistically significant effects of moderate size. However, each of these crossover studies had a high dropout rate, which could have exaggerated the estimated effectiveness of treatment.

Nifedipine. Two trials compared nifedipine with placebo (McArthur, Marek, Pestronk, et al., 1989; Shukla, Garg, Nag, et al., 1995). One used a dose of 60-90 mg/day (McArthur, Marek, Pestronk, et al., 1989); the other used a much smaller dose of 15 mg/day (Shukla, Garg, Nag, et al., 1995). In each of these crossover studies, headache frequency or index improved only slightly better during the nifedipine period than it had during the placebo period. Effect size estimates were similar: 0.12 (-0.62 to 0.86) in McArthur, Marek , Pestronk, et al. (1989) and 0.17 (-0.35 to 0.70) in Shukla, Garg, Nag, et al. (1995). The observed effects were small, and the confidence intervals surrounding them were large and failed to exclude either a clinically important benefit or harm associated with nifedipine.

Nicardipine. A single crossover trial compared nicardipine, in a dose of 40 mg/day, with placebo (Leandri, Rigardo, Schizzi, et al., 1990). This study found a large reduction in headache index associated with nicardipine. An effect size of 0.47 (-0.05 to 0.98) was not statistically significant but reflected some loss of power from our analysis (which does not use individual patient data). The investigators' analysis found the effect to be statistically significant.

Comparisons Among Calcium Antagonists

The literature review identified three trials comparing one calcium antagonist with another (Bussone, Baldini, D'Andrea, et al., 1987; Lamsudin and Sadjimin, 1993; Nappi, Sandrini, Savoini, et al., 1987). In every case, relatively less well-established agents were compared with flunarizine.

Nimodipine vs. flunarizine. Bussone, Baldini, D'Andrea, et al. (1987) compared nimodipine with flunarizine. Nimodipine was administered in a dose of 120 mg/day, flunarizine in a dose of 10 mg/day. Twenty-five patients were included in the efficacy analysis. Nimodipine-treated patients had a marginally higher rate of at least a 50% reduction in headache index (43% versus 38%) and a greater reduction in mean headache index. However, neither the

odds ratio for improvement, 1.3 (0.29 to 5.4), nor the effect size (based on mean headache index) of 0.22 (-0.56 to 1.01) was statistically significant.

Nifedipine vs. flunarizine. Lamsudin and Sadjimin (1993) compared nifedipine (20 mg/day) with flunarizine (10 mg/day). Differences observed in headache index between the two groups were negligible and yielded an effect size estimate of -0.08 (-0.66 to 0.50). Although the results of the two groups were equivalent, the confidence intervals did not exclude the possibility of an important benefit of either drug.

Cyclandelate vs. flunarizine. Nappi, Sandrini, Savoini, et al. (1987) compared cyclandelate with flunarizine. Cyclandelate was administered in a dose of 1600 mg/day, flunarizine in a dose of 5 mg/day. Flunarizine had a greater effect on headache index ($p<0.02$). The study did not report the magnitude of the difference.

Comparisons With Beta-blockers

A total of 13 comparisons of calcium antagonists with beta-blockers (either propranolol or metoprolol) were described in the included trials.

Flunarizine vs. propranolol. Five trials compared flunarizine with the beta-blocker propranolol (Gawel, Kreeft, Nelson, et al., 1992; Lücking, Oestreich, Schmidt, et al., 1988 [Study 1 and Study 2]; Ludin, 1989; Shimell, Fritz, and Levien, 1990). All five trials administered flunarizine in a 10 mg/day dose. The dose of propranolol used ranged from 120 mg/day (three trials) to 180 mg/day (one trial). None of these studies found clinically important differences in the outcomes examined. The outcome was usually headache frequency, but some trials also included headache index and headache severity. Effect size estimates were available for four of the five studies (Gawel, Kreeft, Nelson, et al., 1992; Lücking, Oestreich, Schmidt, et al., 1988 [Study 1 and Study 2]; Ludin, 1989) and ranged from -0.16 to 0.13. We calculated a summary effect size of 0 (-0.21 to 0.21), which indicated that the drugs had equivalent effects, as the confidence intervals excluded more than small differences between them.

Flunarizine vs. metoprolol. Two trials compared flunarizine (10 mg/day) with metoprolol (200 mg/day) (Grotemeyer, Schlake, Husstedt, et al., 1987; Sørensen, Larsen, Rasmussen, et al., 1991). Neither of these studies showed statistically significant differences in headache frequency.

Nifedipine vs. propranolol. Nifedipine and propranolol were compared in two trials. In one (Albers, Simon, Hamik, et al., 1989), nifedipine was administered in a dose of 60-90 mg/day and propranolol in a dose of 120-180 mg/day. In the other trial (Gerber, Diener, Scholz, et al., 1991), patients were treated for 1 month at a relatively low dose (20 mg/day of nifedipine; 80 mg/day of propranolol), then for 2 months at a relatively high dose (40 mg/day of nifedipine; 160 mg/day of propranolol). Their dosage was then successively reduced over the next 3 months (to 10 mg/day of nifedipine and 40 mg/day of propranolol).

The Albers, Simon, Hamik, et al. (1989) trial had a large imbalance in baseline headache frequency between groups and had a greater reduction in headache frequency in the propranolol group. We calculated an effect size of -0.68 (-1.64 to 0.27). The trial was too small ($n = 19$) for the difference to be statistically significant. Gerber, Diener, Scholz, et al. (1991) reported finding no statistically significant differences. The investigators did not report headache frequency

means or other data that might have allowed us to estimate the magnitude or direction of any trend.

Nifedipine vs. metoprolol. The trial described immediately above (Gerber, Diener, Scholz, et al., 1991) also compared nifedipine with metoprolol. Metoprolol was administered in a dose of 100, 200, and 50 mg/day during the low-dose, high-dose, and final phases of the trial, respectively. Metoprolol was reported to have exceeded nifedipine in reducing headache frequency ($p<0.05$), although no data were reported on the magnitude of this effect.

Nimodipine vs. propranolol. A single small trial ($n = 19$) compared nimodipine with propranolol (Formisano, Falaschi, Cerbo, et al., 1991). Both drugs were administered in a dose of 120 mg/day. Reductions in headache frequency were similar between groups. We calculated an effect size of -0.13 (-1.0 to -0.78) for the comparison between the treatments.

Verapamil vs. propranolol. Solomon (1986) compared verapamil (240 mg/day) with propranolol (120 mg/day). Fifteen patients completed the crossover trial and were included in the efficacy analysis. Mean headache frequency was marginally lower during propranolol periods (4.5 versus 5), but this difference was not statistically significant (no p-value reported).

Cyclandelate vs. propranolol. A single trial compared cyclandelate with propranolol. The 4-month treatment period was broken into a 2-month low-dose phase (1200 mg/day of cyclandelate; 120 mg/day of propranolol) and a 2-month high-dose phase (1600 mg/day of cyclandelate; 160 mg/day of propranolol). A higher proportion of patients had at least a 50% reduction in headache frequency on cyclandelate (71% versus 53%), but this difference was not statistically significant. We calculated an odds ratio of 2.2 (0.77 to 6.4) for the comparison between these treatments.

Comparisons With Serotonin Antagonists

The seven trials described below compared calcium antagonists with pizotifen.

Flunarizine vs. pizotifen. Flunarizine and pizotifen were compared in three trials (Cerbo, Casacchia, Formisano, et al., 1986; Louis and Spierings, 1982; Rascol, Montastruc, and Rascol, 1986). Cerbo, Casacchia, Formisano, et al. (1986) used a relatively high dose of flunarizine (15 mg/day) and a relatively low dose of pizotifen (1.5 mg/day). The other two trials administered flunarizine in a dose of 10 mg/day and pizotifen in doses of 2-3 mg/day (Louis and Spierings, 1982) or 2.19 mg/day (Rascol, Montastruc, and Rascol, 1986).

We were not able to calculate odds ratios or effect sizes for any of these trials. The results reported by investigators were consistent across the three trials. They found no statistically significant difference between flunarizine and pizotifen for a reduction in headache frequency at 4 months, and no statistically significant difference between the two treatments for a reduction in headache index at 2 months.

Nimodipine vs. pizotifen. Three trials compared nimodipine (120 mg/day) with pizotifen 1.5 mg/day (Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a; Micieli, Trucco, Agostinis, et al., 1985) or pizotifen 3 mg/day (Gawel, 1987). None of these trials found any clinically important or statistically significant differences between the two drugs. Two studies (Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a; Gawel, 1987) reported enough data to calculate

effect sizes of 0.11 (-0.31 to 0.54) and -0.11 (-0.64 to 0.42), respectively. These effect sizes yielded a summary or combined estimate of -0.02 (-0.41 to 0.45), which suggested equivalent effects but did not exclude the possibility of a small or moderate superiority of either drug.

Cyclandelate vs. pizotifen. A single trial compared cyclandelate (1600 mg/day) with pizotifen (1.5 mg/day) (Mastrosimone, Iaccarino, and de Caterina, 1992). This study found a statistically significant effect on headache index favoring cyclandelate ($p<0.001$). The study did not report any data with which to estimate the magnitude of the effect.

Comparisons With Other Agents

A single trial each (described below) compared flunarizine with dihydroergokryptine (DEK), methysergide, and etilefrine pivalate.

Flunarizine vs. DEK. Agnoli, Bussone, Mailland, et al. (1991) compared flunarizine (5 mg/day) with DEK (20 mg/day). The proportion of patients reporting at least 50% reduction in headache frequency was small in both groups (10% for flunarizine and 7% for DEK). The odds ratio of 1.4 (0.30 to 6.7), which favored flunarizine, was not statistically significant. The investigators analyzed mean headache frequency at 6 months and reported finding a statistically significant benefit favoring DEK. However, despite the fact that mean headache frequency was not reported, the improvement rate data suggested that the magnitude of this difference may have been relatively small.

Flunarizine vs. methysergide. Flunarizine (10 mg/day) and methysergide (6 mg/day) were compared in Steardo, Marano, Barone, et al. (1986). Both drugs were associated with similar reductions in headache frequency. The authors reported that the difference was not statistically significant.

Flunarizine vs. etilefrine pivalate. Grotemeyer, Schlake, and Husstedt (1989) compared flunarizine with etilefrine pivalate. Flunarizine was administered in a dose of 5 mg/day, etilefrine pivalate in a dose of 20 mg/day. This study reported similar reductions in mean headache frequency between the two groups, but investigators did not report having performed tests of statistical significance.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Flunarizine

The adverse events most frequently reported in the flunarizine trials were sedation, weight gain, and abdominal pain. Additional adverse events were observed in a very few instances and may be attributable to the drug. These effects included tiredness, depression, giddiness, and galactorrhea. The rates of adverse events varied widely among the studies. The greatest difference between flunarizine and placebo in the adverse events rate was 14%, observed in a trial that reported the highest adverse events rate (44.4%) in the placebo group (Frenken and Nuitjen, 1984). Of the five studies that described whether or not withdrawals were due to

adverse events, only four actually attributed any withdrawals to adverse events (Al Deeb, Biary, Bahou, et al., 1992; Diamond and Freitag, 1993; Sørensen, Hansen, and Olesen, 1986; Thomas, Behari, and Ahuja, 1991). The largest difference between withdrawal rates due to adverse events in the flunarizine and placebo arms was 6% (Thomas, Behari, and Ahuja, 1991).

Nimodipine

Six trials of nimodipine were reviewed (Ansell, Fazzone, Festenstein, et al., 1988; Gelmers, 1983; Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b; Migraine-Nimodipine European Study Group, 1989a and 1989b; Meyer and Hardenberg, 1983). The adverse event most frequently reported in these trials was abdominal discomfort. The rates of adverse events varied widely among the trials. The greatest difference in adverse events rates between nimodipine and placebo was 10.4%, observed in a trial that reported the highest adverse events rate (17.4%) in the placebo group (Migraine-Nimodipine European Study Group, 1989b).

All six trials described whether or not withdrawals were due to adverse events. In only two trials were any withdrawals actually attributed to adverse events (Migraine-Nimodipine European Study Group, 1989a and 1989b). In these two trials, the withdrawal rate due to adverse events was higher in the placebo arm than in the active treatment arm.

Nifedipine

The single placebo-controlled trial of nifedipine was marked by a high incidence of dizziness, edema, and flushing (McArthur, Marek, Pestronk, et al., 1989). These adverse events frequently led to the discontinuation of treatment.

Verapamil

Three trials reported adverse events data for placebo-controlled trials of verapamil (Markley, Cheronis, and Piepho, 1984; Solomon, 1986; Solomon, Steel, and Spaccavento, 1983). The adverse event most frequently reported in these trials was constipation. Although no adverse events were reported by Solomon (1986), Markley, Cheronis, and Piepho (1984) reported a 43% incidence of constipation on verapamil, which led to a 7% withdrawal rate.

Nicardipine

The single placebo-controlled trial of nicardipine (Leandri, Rigardo, Schizzi, et al., 1990) attributed a slightly greater frequency of headache and dizziness to nicardipine with than to placebo, although precise rates for all adverse events were not reported. However, withdrawals attributed to adverse events were actually more frequent in the placebo arm.

Conclusions

Flunarizine has strong and consistent evidence from eight placebo-controlled trials for efficacy in migraine prevention. This evidence is strengthened by comparisons with propranolol, another drug whose efficacy is well-established for migraine prevention, which demonstrate reasonable equivalence.

Other calcium antagonists have been less thoroughly studied. Nimodipine had mixed results in placebo-controlled studies. Of six such trials, four reported nonsignificant differences, but two with sufficient information to quantify the magnitude of benefit suggested a clinically important and statistically significant benefit. This latter conclusion must be interpreted with caution.

Nifedipine had consistently poor results in four trials, two-placebo-controlled and two comparisons with propranolol.

Verapamil is the calcium antagonist most commonly used for migraine prevention in the US. Two small placebo-controlled trials suggested that this phenylalkylamine calcium antagonist is effective in migraine prevention. However, both trials were plagued by high dropout rates. Our best estimate of the efficacy of this agent therefore carries substantial uncertainty.

Nicardipine has a single positive trial supporting its efficacy. The effect size from this trial was intermediate between those associated with the other dihydropyridine calcium antagonists, nifedipine and nimodipine.

Cyclandelate has not been tested in placebo-controlled trials for migraine prevention, but it has been compared with several drugs of established efficacy, viz. flunarizine, propranolol, and pizotifen. Cyclandelate was found to be less effective than flunarizine, but more effective than pizotifen; the comparison with propranolol was uninformative. The uncertainty regarding the efficacy of this agent is still considerable, given the lack of placebo-controlled trials.

The adverse event rates reported for calcium antagonists varied widely between studies, even between studies of the same dose of the same drug, and provide little in the way of reliable information on the risk of adverse events associated with these agents.

Since flunarizine and cyclandelate are not available in the US, verapamil, nicardipine, nifedipine, and nimodipine are the only calcium antagonists available that have actually been studied as treatments for migraine. Extended-release preparations of verapamil (Calan SR®) and nifedipine (Adalat CC® or Procardia XL®) may be better-tolerated than regular verapamil and nifedipine, but these preparations have not been studied for migraine prevention.

Ergots

Ergot alkaloids, some of which are used to treat acute attacks of migraine, have also been studied as preventive agents. The literature review identified controlled trials of dihydroergotamine (DHE); dihydroergokryptine (DEK); ergotamine tartrate; and the combination agent, Cafergot comp.® (ergotamine + caffeine + butalbital + belladonna alkaloids). This section of the report reviews the evidence for the safety and efficacy of these agents.

Studies Identified

Overview

The literature review identified 17 publications reporting on 15 separate controlled trials of ergots used for the prevention of migraine (Agnoli, Bussone, Mailland, et al., 1991; Agnoli, Bussone, Manzoni, et al., 1989; Autret and de Chasteigner, 1987; Barrie, Fox, Weatherall, et al., 1968; Bonuso, Di Stasio, Barone, et al., 1983; Bousser, Chick, Fuseau, et al., 1988; Buscaino, Sorge, Bussone, et al., 1991; Cangi, Boccuni, Zanotti, et al., 1989; Canonico, Scapagnini, Genazzani, et al., 1989; Demarez, Darbeau, and Cauquil, 1987; Fiorini, Sances, Martignoni, et al., 1991; Frediani, Grazzi, Zanotti, et al., 1991; Kallos and Kallos-Deffner, 1971; Martucci, Manna, Mattesi, et al., 1983; Neuman, Demarez, Harmey, et al., 1986; Stensrud, Skaug, and Sjaastad, 1971; Stieg, 1977).

Four publications were excluded from our analysis for the reasons cited in Exhibit 6.

Exhibit 6. Excluded publications: Ergot trials

Excluded publication	Reason for exclusion
Agnoli, Bussone, Manzoni, et al. (1989)	Abstract reporting preliminary results from trial described more fully in Agnoli, Bussone, Mailland, et al. (1991); added no new information.
Demarez, Darbeau, and Cauquil (1987)	Abstract reporting on the trial described more fully in Neuman, Demarez, Harmey, et al. (1986). While the full report described 1-month results only, the abstract reported some 2-month efficacy data for the active treatment group; however, no 2-month results were reported for the comparator group (placebo).
Stensrud, Skaug, and Sjaastad (1971)	Placebo-controlled trial of investigational drug (MY-25 = 1-methyl-ergotamine-bitartrate) that was never brought to market.
Stieg (1977)	Trial included both migraine and tension-type headache patients (n's not reported); no separate results were reported for migraine patients.

Thirteen publications reporting on 13 separate trials were thus included in our analysis. The included studies reported on the safety and efficacy of the following agents:

Dihydroergotamine	7 trials
Dihydroergokryptine	5 trials
Cafergot comp.®	1 trial
Ergotamine	1 trial

Seven trials compared ergots with placebo, two compared different doses of a single ergot agent, one compared two ergots with one another, two compared ergots with methysergide, and one trial each compared ergots with an antidepressant and a calcium antagonist.

The included trials are described in Evidence Table 1.

Study Design and Quality

Seven of the 13 included trials were crossover in design; 6 were parallel-group. Three of the crossover trials were analyzed as if they were parallel-group in design for reasons described in Evidence Table 1 (Barrie, Fox, Weatherall, et al., 1968; Fiorini, Sances, Martignoni, et al., 1991; Frediani, Grazzi, Zanotti, et al., 1991).

Active treatment periods in the included trials ranged in length from 1 month (two trials) to 6 months (one trial); the average length of the active treatment periods was 2.3 months.

Quality scores ranged from 1 (one trial) to 4 (three trials); the average score was 2.9.

Patient Populations

Eleven of the 13 included trials provided no information about the setting in which patients were recruited. In the remaining two cases patients were drawn from headache clinics (Barrie, Fox, Weatherall, et al., 1968; Martucci, Manna, Mattesi, et al., 1983).

The majority of the trials reviewed (7 of 13) included patients with migraine without aura only. Three trials included patients with both types of migraine (with and without aura) (Barrie, Fox, Weatherall, et al., 1968; Bousser, Chick, Fuseau, et al., 1988; Neuman, Demarez, Harmey, et al., 1986); one of these (Barrie, Fox, Weatherall, et al., 1968) also included patients with hemiplegic migraine and mixed migraine + tension-type headache. One trial included only patients with mixed migraine + tension-type headache (Bonuso, Di Stasio, Barone, et al., 1983). Two trials included only women whose migraines occurred in connection with the menstrual cycle (Fiorini, Sances, Martignoni, et al., 1991; Kallos and Kallos-Deffner, 1971); neither of these trials used a stringent definition of menstrual migraine. Four trials referred specifically to the Ad Hoc diagnostic criteria for migraine, and two referred to the IHS criteria. All but three of the included trials dealing with nonmenstrual headaches had minimum migraine headache frequency requirements for inclusion (Bonuso, Di Stasio, Barone, et al., 1983; Frediani, Grazzi, Zanotti, et al., 1991; Martucci, Manna, Mattesi, et al., 1983). The two trials focusing on menstrual migraine did not state this explicitly, but appeared to require that participants regularly experience migraine headaches at the same point in their menstrual cycles.

Two trials explicitly excluded patients with daily headaches (Autret and de Chasteigner, 1987; Buscaino, Sorge, Bussone, et al., 1991).

Four trials excluded patients who had used migraine preventive therapy during some period of time leading up to the trial (Bousser, Chick, Fuseau, et al., 1988; Buscaino, Sorge, Bussone, et al., 1991; Martucci, Manna, Mattesi, et al., 1983; Neuman, Demarez, Harmey, et al., 1986). One of these trials (Buscaino, Sorge, Bussone, et al., 1991) reported that 40% of patients included had used some type of preventive medication in the more distant past, with varying results. The single trial of Cafergot comp.® included only patients who had used the drug before with good results (Kallos and Kallos-Deffner, 1971).

The two trials restricted to women who experienced migraine attacks in connection with their menstrual cycle did not report whether patients were permitted to use medication for acute attacks occurring during the trial. In one of these trials, preventive medication was taken on a daily basis throughout the menstrual cycle (Fiorini, Sances, Martignoni, et al., 1991); in the other, it was taken only around the time of the expected migraine attack (Kallos and Kallos-Deffner, 1971). The other eleven included trials all permitted the use of medication for acute attacks.

Six trials did not report the average age of patients, and three did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 33 to 47, and the percentage of patients who were women ranged from 45% to 100%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 7.

Comparisons With Placebo

Cafergot comp.®. Cafergot comp.® (ergotamine + caffeine + butalbital + belladonna alkaloids) was compared with placebo in a crossover trial among women with migraines associated with the menstrual cycle (Kallos and Kallos-Deffner, 1971). All 20 patients included in the efficacy analysis had used the drug in the past with good results. One capsule was taken twice a day during the perimenstrual period for two menstrual cycles. Mean headache frequency for the two cycles was lower with Cafergot comp.® than with placebo (0.35 attacks vs. 1.55 attacks, respectively), but investigators reported no test of statistical significance.

DHE. Three trials compared timed-release DHE in a dose of 10 mg per day with placebo (Autret and de Chasteigner, 1987; Martucci, Manna, Mattesi, et al., 1983; Neuman, Demarez, Harment, et al., 1986). Each of these studies found significantly lower headache index or headache frequency scores for the DHE-treated patients. In two cases (Autret and de Chasteigner, 1987; Neuman, Demarez, Harment, et al., 1986), we were able to calculate effect sizes which confirmed the investigators' findings.

One trial comparing timed-release DHE 10 mg + aspirin 80 mg with placebo also reported a significant reduction in headache frequency compared to placebo; our effect size calculations confirmed this result (0.62 [0.16 to 1.1]).

DEK. Two trials, one among patients with migraine associated with menstruation (Fiorini, Sances, Martignoni, et al., 1991) and the other among patients with common migraine

(Canonico, Scapagnini, Genazzani, et al., 1989), compared DEK 20 mg daily with placebo. Both reports were abstracts and provided limited information. Fiorini, Sances, Martignoni, et al. (1991) found a nearly two-fold reduction in headache index with DEK that was highly statistically significant. The effect size that we calculated from the first-period headache index data was, however, not statistically significant. Canonico, Scapagnini, Genazzani, et al. (1989) appeared to have a treatment-period interaction which confounded the assessment of efficacy.

Dosing Studies

Buscaino, Sorge, Bussone, et al. (1991) compared two different DHE dosing regimens (two 5-mg doses and a single 10-mg dose per day). No difference in headache index was observed between the two groups.

Two different doses of ergotamine (1 mg daily and 0.5 mg daily) were compared by Barrie, Fox, Weatherall, et al. (1968). For reasons described in Evidence Table 1, we analyzed the 1-month data from this trial. At the end of 1 month of treatment, 47% of patients in both dosage groups reported a reduction in headache severity in comparison to baseline values.

Comparisons Among Ergots

Frediani, Grazzi, Zanotti, et al. (1991) compared timed-release DHE 10 mg daily and DEK 20 mg daily in a crossover trial; because of a significant carry-over effect, investigators analyzed only the first-period data. DHE and DEK groups showed similar reductions in headache index and headache frequency compared to baseline values; no direct statistical comparisons of the two agents were reported.

Comparisons With Other Agents

DHE vs. amitriptyline. Bonuso, Di Stasio, Barone, et al. (1983) compared timed-release DHE 10 mg daily with amitriptyline 75 mg daily in a group of patients with mixed migraine + tension-type headache. Patients were treated for two months. The investigators reported, but did not analyze, mean pre- and post-treatment headache index scores for both groups. Using these data, we calculated an effect size of -0.82 (-1.6 to -0.08) for the DHE vs. amitriptyline comparison, which suggests that amitriptyline was significantly better than DHE for this outcome.

The investigators' analysis of the data on headache duration, stratified by severity, showed that DHE was significantly better than amitriptyline at reducing the number of hours of extremely severe and severe, migraine-type pain; amitriptyline was significantly better than DHE at reducing the number of hours of moderate and mild, tension-type-headache-like pain ($p<0.01$ for all comparisons).

DEK vs. flunarizine. Agnoli, Bussone, Mailland, et al. (1991) compared DEK (20 mg/day) with flunarizine (5 mg/day). The proportion of patients reporting a 50% or more reduction in headache frequency was small in both groups (7% for DEK and 10% for flunarizine). The resulting odds ratio favoring flunarizine (0.71 [0.15 to 3.4]) was not statistically significant. The

investigators analyzed mean headache frequency at 6 months and reported a statistically significant benefit favoring DEK; however, the data on the proportion of patients reporting a 50% or more improvement suggest that the magnitude of this difference may be relatively small (post-treatment mean headache frequencies were reported only in graphical form and could not be reliably read off the graph).

DEK and ergotamine vs. methysergide. Two separate trials compared DEK (Cangi, Boccuni, Zanotti, et al., 1989) and ergotamine (Barrie, Fox, Weatherall, et al., 1968) with methysergide. Neither trial demonstrated any significant differences between the ergots tested and methysergide.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Information provided about adverse events in the included trials was very limited, especially since several of the reports (five) were abstracts. The most commonly reported adverse events for all the ergot drugs -- including DHE, DEK, and ergotamine -- were gastrointestinal symptoms, including dyspepsia, epigastric pain, nausea, and vomiting.

Conclusions

Dihydroergotamine appears to be efficacious for migraine prevention when used daily in a dose of 10 mg, based on four placebo-controlled trials with consistent findings. A single trial suggested that DHE may be less effective than amitriptyline for patients with mixed migraine + tension-type headache. The efficacy of dihydroergokryptine is less certain, but is supported by one placebo-controlled study in women with menstrual migraine and by one direct comparison each with flunarizine and methysergide. Cafergot comp.® and ergotamine do not have support for efficacy in migraine prevention.

The limited data on adverse events reported in trials of ergots suggest that unwanted gastrointestinal symptoms are common with these drugs.

Methysergide

This section of the report examines the evidence from controlled trials for the safety and efficacy of methysergide. Methysergide is a semi-synthetic ergot alkaloid which is structurally related to methylergonovine. It was one of the first drugs to be used and studied for the prevention of migraine. The use of methysergide has, however, been limited by reports of retroperitoneal fibrosis with long-term, uninterrupted administration.

Studies Identified

Overview

The literature review identified 18 publications reporting on 17 separate controlled trials of methysergide for the prevention of migraine (Andersson, 1973; Barrie, Fox, Weatherall, et al., 1968; Behan and Reid, 1980; Cangi, Boccuni, Zanotti, et al., 1989; Forssman, Henriksson, and Kihlstrand, 1972; Herrmann, Horowski, Dannehl, et al., 1977; Hudgson, Foster, and Newell, 1967; Lance, Fine, and Curran, 1963; Pedersen and Møller, 1966; Presthus, 1971; Ryan, 1968; Shekelle and Ostfeld, 1964; Sicuteri, 1959; Sicuteri, 1973; Steardo, Bonuso, Di Stasio, et al., 1982; Steardo, Marano, Barone, et al., 1986; Titus, Dávalos, Alom, et al., 1986; Titus, Dávalos, and Codina, 1985).

Two publications were excluded from our analysis for the reasons cited in Exhibit 7.

Exhibit 7. Excluded publications: Methysergide trials

Excluded publication	Reason for exclusion
Sicuteri (1959)	Allocation to treatment groups neither randomized nor quasi-randomized.
Titus, Dávalos, and Codina (1985)	Abstract reporting on trial more fully described in Titus, Dávalos, Alom, et al. (1986); added no new information.

Our analysis thus included 16 published reports on 16 separate trials. Four of the included trials compared methysergide with placebo; seven compared it with a serotonin antagonist; two with a beta-blocker; and one each with dihydroergokryptine (DEK), ergotamine, the progestogen, flumedroxone (Demigran®), and flunarizine.

The included trials are described in Evidence Table 1.

Study Design and Quality

Nine of the 16 included trials were crossover in design; 5 were parallel-group. One of the crossover trials (Barrie, Fox, Weatherall, et al., 1968) had an orthogonally-balanced design. We

were only able to use the data from the first period of this trial for reasons that are explained in Evidence Table 1, and so treated it as if it were a parallel-group trial. Two additional publications require comment. One (Cangi, Boccuni, Zanotti, et al., 1989) was an abstract reporting parallel-group interim results from a then ongoing, longer-term crossover trial. The other (Lance, Fine, and Curran, 1963) reported on a partial crossover trial with two interventions. Patients who did not achieve success with the first trial medication switched at the end of the first month to the other, while those who were successful continued on the initial medication. The investigators reported first-period (1-month) data separately, and we analyzed these data as if the trial were parallel-group in design.

Active treatment periods in the included trials ranged in length from 1 month (two trials) to 6 months (two trials); the average length of the active treatment periods was 2.9 months.

Quality scores ranged from 1 (one trial) to 4 (6 trials); the average score was 3.1.

Patient Populations

Only 4 of the 16 included reports provided information about the setting in which patients were recruited. In two of the four cases, patients were drawn from neurology departments (Pedersen and Møller, 1966; Steardo, Marano, Barone, et al., 1986); in the other two, patients were recruited from headache clinics (Barrie, Fox, Weatherall, et al., 1968; Lance, Fine, and Curran, 1963).

Thirteen of the 16 trials reviewed included patients with migraine with or without aura. One trial was restricted to patients with migraine without aura (Cangi, Boccuni, Zanotti, et al., 1989). Another included only patients with what was described as "typical" migraine, without further clarification (Hudgson, Foster, and Newell, 1967). Barrie, Fox, Weatherall, et al. (1968) included patients with common, classic, and hemiplegic migraine, and patients with mixed migraine + tension-type headache. One trial referred specifically to the IHS diagnostic criteria for migraine; six referred to the Ad Hoc criteria.

Ten trials had minimum migraine headache frequency requirements for inclusion (Barrie, Fox, Weatherall, et al., 1968; Behan and Reid, 1980; Cangi, Boccuni, Zanotti, et al., 1989; Forssman, Henriksson, and Kihlstrand, 1972; Herrmann, Horowski, Dannehl, et al., 1977; Hudgson, Foster, and Newell, 1967; Lance, Fine, and Curran, 1963; Pedersen and Møller, 1966; Ryan, 1968; Steardo, Marano, Barone, et al., 1986). Four of these also required that patients' headaches regularly be "severe" or "incapacitating" in intensity (Behan and Reid, 1980; Herrmann, Horowski, Dannehl, et al., 1977; Hudgson, Foster, and Newell, 1967; Lance, Fine, and Curran, 1963).

One trial explicitly excluded patients with tension-type headache or mixed migraine + tension-type headache (Titus, Dávalos, Alom, et al., 1986). As noted above, Barrie, Fox, Weatherall, et al. (1968) included a small number of patients with mixed migraine + tension-type headache. Another trial included patients with several types of headache, but reported results separately for migraine patients (Lance, Fine, and Curran, 1963). Two trials included one patient each with cluster headache (Forssman, Henriksson, and Kihlstrand, 1972; Shekelle and Ostfeld, 1964).

Two trials included only patients who had never tried migraine-preventive medication before (Steardo, Bonuso, Di Stasio, et al., 1982; Steardo, Marano, Barone, et al., 1986). One included only patients who had used such medication at some point in the past (Hudgson, Foster, and Newell, 1967). The remaining 13 trials provided no information on this point.

Four trials did not report whether patients were allowed to use medication for acute attacks of migraine occurring during the trial (Hudgson, Foster, and Newell, 1967; Lance, Fine, and Curran, 1963; Sicuteri, 1973; Titus, Dávalos, Alom, et al., 1986). One trial prohibited the use of such medication (Behan and Reid, 1980), and another permitted it only in "exceptionally severe" cases (Andersson, 1973). In the remaining 10 trials, patients were allowed to use medication to treat acute attacks of migraine.

Eleven of the 16 included trials did not report the average age of patients; 6 did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 30 to 43, and the percentage of patients who were women ranged from 52% to 84%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 8.

Comparisons With Placebo

Four placebo-controlled trials of methysergide used doses of 4 to 6 mg per day over 4- to 6-week treatment periods (Lance, Fine, and Curran, 1963; Pedersen and Møller, 1966; Ryan, 1968; Shekelle and Ostfeld, 1964). Two trials described results in terms of the proportion of patients with a 50% or greater reduction in headache frequency (Lance, Fine, and Curran, 1963; Pedersen and Møller, 1966). These studies reported similar response rates among placebo-treated patients (21% and 27%, respectively). The response rates during methysergide treatment were also similar (68% and 57%, respectively). The resulting odds ratios of 8.1 and 3.6 were both statistically significant, as was the combined odds ratio estimate of 5.1 (1.9 to 13).

Pedersen and Møller (1966) also reported decreased headache frequency based on an analysis of within-patient differences in headache frequency between placebo and methysergide periods. We calculated an effect size of 0.22 (-0.04 to 0.47) for the comparison between these treatments. A similar analysis by Shekelle and Ostfeld (1964) in a smaller crossover study showed a statistically significant reduction in headache frequency after treatment with methysergide. We calculated an effect size of 1.02 (0.48 to 1.6) for this trial. A combined estimate of the effect size was 0.56 (-0.20 to 1.3).

Comparisons With Serotonin Antagonists

Four trials compared methysergide with pizotifen (Andersson, 1973; Forssman, Henriksson, and Kihlstrand, 1972; Presthus, 1971; Ryan, 1968). The doses of methysergide used were consistent across the four trials (between 3-4 mg/day), while the doses of pizotifen ranged from

1.5 to 4 mg/day. One trial reported the proportion of patients with a greater than 50% reduction in headache frequency compared with baseline (Andersson, 1973). Response rates were lower than those seen in the placebo-controlled trials (31% for the methysergide arm and 38% for the pizotifen arm). The difference between the two treatments was not statistically significantly, and the odds ratio estimate of 0.73 (0.31 to 1.7) favored pizotifen.

Two studies comparing methysergide with pizotifen reported sufficient data to calculate effect sizes, both based on headache frequency. Andersson (1973) allowed the calculation of an effect size of -0.17 (-0.57 to 0.23), which favored pizotifen, but failed to reach statistical significance. Presthus (1971) reported individual patient data on headache frequency, which allowed the calculation of an effect size of -0.29 (-0.76 to 0.17), which was very similar to the estimate from Andersson (1973). A combined effect size from the two trials was -0.22 (-0.60 to 0.16).

Two trials comparing methysergide with oxitriptan (5-hydroxytryptophan [HTP]) offered little information on the relative effectiveness of the two drugs. Sicuteri (1973) found no difference between the two treatments for headache index; a calculated effect size of 0.09 was negligible, and the 95% confidence interval was quite broad, ranging from -0.53 to 0.71. Results from Titus, Dávalos, Alom, et al. (1986) did not improve the precision of the estimate, as the proportion of patients with at least a 50% reduction in headache frequency was 75% for methysergide and 71% for oxitriptan. The odds ratio of 1.2 (0.47 to 3.2) did not exclude a clinically important benefit of either drug.

A single study comparing methysergide with lisuride over 3 months (Herrmann, Horowski, Dannehl, et al., 1977) found similar proportions of patients with a 50% or greater improvement in headache frequency (51% and 53%, respectively). An odds ratio of 0.93, with a confidence interval ranging from 0.46 to 1.9, did not exclude a clinically important benefit of either drug.

Comparisons With Beta-blockers

Methysergide was compared to propranolol in two controlled trials (Behan and Reid, 1980; Steardo, Bonuso, Di Stasio, et al., 1982), one of which also included a metoprolol treatment arm (Steardo, Bonuso, Di Stasio, et al., 1982). The two comparisons of methysergide with propranolol each found a substantial difference in the proportion of patients with a 50% or greater reduction in headache frequency, resulting in similar odds ratios of 0.58 (0.23 to 1.5) and 0.64 (0.20 to 2.0). The combined odds ratio was 0.61 (0.25 to 1.5), which favored propranolol, but was not statistically significant. Headache frequency data from Steardo, Bonuso, Di Stasio, et al. (1982) were used to calculate an effect size of -0.51 (-1.1 to 0.06), which suggested a moderate effect favoring propranolol that narrowly missed being statistically significant.

In contrast to placebo-controlled trials of beta-blockers, in which the effectiveness of propranolol and metoprolol and various other agents without intrinsic sympathomimetic activity was similar, Steardo, Bonuso, Di Stasio, et al. (1982) found that propranolol was significantly more effective than metoprolol at reducing headache frequency. This may have been due to the relatively high dose of metoprolol used in this study (300 mg/day) and to the high proportion of dropouts due to adverse events (especially in the metoprolol arm). The large odds ratio of 18

(2.2 to 153) and the effect size of 0.81 (0.16 to 1.5) calculated on the basis of data from this trial may overstate the certainty of the effectiveness of methysergide relative to metoprolol.

Comparisons With Other Agents

One trial each compared methysergide with DEK (Cangi, Boccuni, Zanotti, et al., 1989), ergotamine (Barrie, Fox, Weatherall, et al., 1968), flumedroxone (Demigran®) (Hudgson, Foster, and Newell, 1967), and flunarizine (Steardo, Marano, Barone, et al., 1986). None of these trials demonstrated any significant differences between methysergide and the comparator drug.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Methysergide was associated with more adverse events than was placebo in each placebo-controlled trial. Gastrointestinal complaints -- including nausea, vomiting, abdominal pain, and diarrhea -- were most common, followed by dizziness, giddiness, drowsiness, lassitude, and paresthesia (an abnormal spontaneous sensation, such as that of burning or numbness). Some studies reported leg symptoms, including restlessness or pain, as the most common side effect of treatment with methysergide.

In comparisons with pizotifen, methysergide had no more frequent adverse events. Weight gain was more common with pizotifen, nausea with methysergide.

The trials reviewed here were too short to detect the fibrotic complications that have been observed with long-term, uninterrupted administration of methysergide. Fibrotic changes in the retroperitoneal, pleuropulmonary, cardiac, and other tissues may have serious consequences. Retroperitoneal fibrosis has been associated with vascular insufficiency of the lower limbs and ureteral obstruction; cardiac fibrosis involving the aortic root or aortic or mitral valves can lead to valvular heart disease; and pleuropulmonary fibrosis can lead to pulmonary effusion or pulmonary insufficiency. The manufacturer's labeling suggests that the drug be discontinued for 3-4 weeks after each 6-month course of treatment.

Conclusions

Four placebo-controlled trials suggested that methysergide is moderately effective at reducing headache frequency. These trials were all conducted in the 1960s using earlier or no diagnostic criteria for migraine, and their generalizability to patients diagnosed under the more precise diagnostic criteria of the IHS is uncertain.

In direct comparisons with other migraine preventive agents, methysergide appeared to be no more effective than pizotifen or propranolol. Although the four trials directly comparing methysergide to pizotifen did not demonstrate a statistically significant difference between the two drugs, they supported the conclusion that methysergide is not better than pizotifen to any clinically important degree. Similarly, two direct comparisons of propranolol and methysergide reported lower headache frequency with propranolol; although not statistically significant, the reported differences between the two drugs suggest that methysergide is not better than

propranolol to any clinically significant degree. A single trial comparing methysergide and metoprolol reported an unusually low response to metoprolol and may have exaggerated the effectiveness of methysergide relative to this agent.

A handful of trials comparing methysergide to other drugs (oxitriptan, lisuride, DEK, ergotamine, flumedroxone [Demigran®], and flunarizine) were too small to demonstrate equivalence and failed to demonstrate any statistically significant differences.

Short-term adverse events (principally gastrointestinal complaints) led to discontinuation of treatment in up to 20% of patients treated with methysergide in the reviewed trials. The risk of adverse events associated with the long-term use of methysergide (particularly fibrotic changes in the retroperitoneal, pleuropulmonary, cardiac, and other tissues) is, however, probably a greater deterrent to the use of this agent.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used both for the prevention of migraine and for the treatment of acute attacks. A companion report summarizes the evidence for the safety and efficacy of NSAIDs for the treatment of acute attacks. The present report considers their use for the prevention of migraine. The literature review identified controlled trials of naproxen, naproxen sodium, aspirin, tolfenamic acid, fenoprofen, flurbiprofen, indobufen, indomethacin, ketoprofen, lornoxicam, and mefenamic acid for this indication.

Studies Identified

Overview

The literature review identified 30 publications reporting on 26 separate controlled trials of NSAIDs used for the prevention of migraine. Seven publications were excluded from our analysis for the reasons cited in Exhibit 8.

Exhibit 8. Excluded publications: NSAID trials

Excluded publication	Reason for exclusion
Buring, Peto, and Hennekens (1990)	Assessment based on annual retrospective report.
Carasso, Peled, and Yehuda (1992)	Test drug (flufenamic acid) used for both prevention of migraine episodes and treatment of acute attacks, but results for these two uses not separately reported.
Carrieri, Orefice, and Sorge (1985)	Preliminary report of trial described more fully in Carrieri, Orefice, and Sorge (1988).
Mongini, Bona, Garnero, et al. (1993)	Fewer than five patients (with migraine) per treatment group.
Solomon, Freitag, Mehta, et al. (1987)	Abstract reporting results from trial more fully described in Diamond, Solomon, Freitag, et al. (1987); added no new information.
Solomon and Kunkel (1991)	Abstract reporting results from trial more fully described in Solomon and Kunkel (1993); added no new information.
Welch (1986)	Publication duplicate of Welch, Ellis, and Keenan (1985).

The following 23 publications, reporting on 23 separate controlled trials, were included in our analysis:

Anthony and Lance, 1968
Baldrati, Cortelli, Procaccianti, et al., 1983
Bellavance and Meloche, 1990
Carrieri, Orefice, and Sorge, 1988
Couch, Bearss, and Verhulst, 1987
Diamond, Solomon, Freitag, et al., 1987
Grotemeyer, Scharafinski, Schlake, et al., 1990
Johnson, Hornabrook, and Lambie, 1986
Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994
Lindegaard, Övrelid, and Sjaastad, 1980
Masel, Chesson, Peters, et al., 1980
Mikkelsen and Falk, 1982
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986
O'Neill and Mann, 1978
Ryan and Ryan, 1981
Sances, Martignoni, Fioroni, et al., 1990
Sargent, Solbach, Damasio, et al., 1985
Solomon and Kunkel, 1993
Stensrud and Sjaastad, 1974
Sternieri, Bussone, Manzoni, et al., 1991
Szekely, Merryman, Croft, et al., 1989
Welch, Ellis, and Keenan, 1985
Ziegler and Ellis, 1985

The included studies reported on the safety and efficacy of the following agents:

Naproxen or naproxen sodium	7 trials
Aspirin	5 trials
Tolfenamic acid	3 trials
Fenoprofen	2 trials
Flurbiprofen	1 trial
Indobufen	1 trial
Indomethacin	1 trial
Ketoprofen	1 trial
Lornoxicam	1 trial
Mefenamic acid	1 trial

Twenty trials compared NSAIDs with placebo, six compared NSAIDs with beta-blockers, and one compared an NSAID with a serotonin antagonist.

The included trials are described in Evidence Table 1.

Study Design and Quality

Fourteen of the included trials were crossover in design; nine were parallel-group. In two crossover trials (Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994; Lindegaard, Övrelid, and Sjaastad, 1980), first-period data were analyzed as if the trial were parallel-group (see Evidence Table 1 for details).

Active treatment periods in the included trials ranged in length from 1 month (one trial) to 3 months (13 trials); the average length of the active treatment periods was 2.5 months.

Quality scores ranged from 1 (one trial) to 4 (nine trials); the average score was 3.2.

Patient Populations

In six of the included trials patients were recruited from neurology clinics or departments (Anthony and Lance, 1968; Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994; Lindegaard, Övrelid, and Sjaastad, 1980; Masel, Chesson, Peters, et al., 1980; Mikkelsen and Falk, 1982;

Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986). The remaining 17 trials provided no information about the setting in which patients were recruited.

The majority of the trials reviewed (19 of 23) included patients with migraine with or without aura. One of these 19 trials explicitly excluded patients with mixed migraine + tension-type headache (Ryan and Ryan, 1981); another explicitly included them (Sargent, Solbach, Damasio, et al., 1985). Four trials were restricted to patients with migraine without aura (Baldrati, Cortelli, Procaccianti, et al., 1983; Grotemeyer, Scharafinski, Schlake, et al., 1990; Sances, Martignoni, Fioroni, et al., 1990; Sternieri, Bussone, Manzoni, et al., 1991). Two trials focused on migraine attacks occurring in conjunction with the menstrual cycle (Sances, Martignoni, Fioroni, et al., 1990; Szekely, Merryman, Croft, et al., 1989). Ten trials referred specifically to the Ad Hoc diagnostic criteria for migraine, and four referred to the IHS criteria. All but one of the included trials had minimum migraine headache frequency requirements for inclusion (Couch, Bearss, and Verhulst, 1987).

Four trials explicitly excluded patients with headaches other than migraine (Bellavance and Meloche, 1990; Diamond, Solomon, Freitag, et al., 1987; Sances, Martignoni, Fioroni, et al., 1990; Sternieri, Bussone, Manzoni, et al., 1991); another excluded patients with frequent tension-type headaches (Solomon and Kunkel, 1993). Szekely, Merryman, Croft, et al. (1989) included one patient each with tension-type and "cluster-like" headaches.

The two trials examining the use of NSAIDs in the perimenstrual period (Sances, Martignoni, Fioroni, et al., 1990; Szekely, Merryman, Croft, et al., 1989) permitted no other medication for the treatment of acute attacks of migraine. Three trials did not report whether patients were allowed to use such medication (Anthony and Lance, 1968; Baldrati, Cortelli, Procaccianti, et al., 1983; Couch, Bearss, and Verhulst, 1987). The remaining 18 trials permitted the use of other medication for acute attacks, but frequently prohibited the use of NSAIDs for this purpose.

Thirteen of the 23 trials did not report the average age of patients, and two did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 30 to 42, and the percentage of patients who were women ranged from 42% to 100%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 9.

Comparisons With Placebo

Naproxen and naproxen sodium. Naproxen or naproxen sodium were studied in seven placebo-controlled trials, naproxen in a dose of 500 mg/day (Lindegaard, Övrelid, and Sjaastad, 1980), and naproxen sodium in a dose of 1100 mg/day (Bellavance and Meloche, 1990; Sances, Martignoni, Fioroni, et al., 1990; Sargent, Solbach, Damasio, et al., 1985; Szekely, Merryman, Croft, et al., 1989; Welch, Ellis, and Keenan, 1985; Ziegler and Ellis, 1985). The duration of these trials ranged from 6 weeks to 3 months. Four trials were crossover in design; however, at

least one of these found a carry-over effect, so we analyzed first-period data only (Lindegaard, Övrelid, and Sjaastad, 1980).

One small trial reported the number of patients reporting a 50% or greater improvement in headache index as 6% in the placebo arm and 33% in the naproxen arm (Sances, Martignoni, Fioroni, et al., 1990). An odds ratio for improvement of 7.7 (0.87 to 69) was not statistically significant.

Five trials reported sufficient data to calculate effect sizes (Lindegaard, Övrelid, and Sjaastad, 1980; Sances, Martignoni, Fioroni, et al., 1990; Sargent, Solbach, Damasio, et al., 1985; Welch, Ellis, and Keenan, 1985; Ziegler and Ellis, 1985). The five effect sizes were statistically homogeneous (chi-square = 1.06; degrees of freedom = 4; p = 0.90). The summary effect size was 0.29 (0.01 to 0.57), indicating a small clinical effect that was statistically significant.

Aspirin and aspirin + dipyridamole. Two trials compared aspirin 1300 mg/day with placebo (O'Neill and Mann, 1978; Ryan and Ryan, 1981). The small crossover trial by O'Neill and Mann (1978) showed a dramatic reduction in headache frequency. Individual patient data reported in the trial allowed us to calculate an effect size of 1.7 (1.1 to 2.2) based on within-patient aspirin-placebo differences in headache frequency. The large difference was not replicated by Ryan and Ryan (1981), which found a small reduction in headache frequency, the statistical significance of which was not commented upon.

Two studies provided comparisons of aspirin + dipyridamole with placebo (Masel, Chesson, Peters, et al., 1980; Ryan and Ryan, 1981); Ryan and Ryan (1981) also compared aspirin + dipyridamole with aspirin alone. The reduction in headache frequency in the aspirin + dipyridamole group was greater than that observed in the aspirin-only or in the placebo group in Ryan and Ryan (1981); however, no tests of significance were performed or reported. The other trial, a small crossover study (Masel, Chesson, Peters, et al., 1980), reported a statistically significant decline of about 33% in median headache frequency in the aspirin + dipyridamole group, while median headache frequency in the placebo group increased.

Fenoprofen. Two studies compared fenoprofen with placebo, both testing fenoprofen doses of 600 mg/day and 1800 mg/day (Couch, Bearss, and Verhulst, 1987; Diamond, Solomon, Freitag, et al., 1987). Although similar reductions in headache index in all groups were observed by Couch, Bearss, and Verhulst (1987), the other study found a large difference in the proportion of patients reporting a greater than 50% improvement in headache index in the high-dose (59%) and low-dose (31%) fenoprofen groups, and in the high-dose fenoprofen (59%) and placebo groups (32%). These differences were statistically significant.

Tolfenamic acid. Tolfenamic acid was compared with placebo in two trials of similar design by the same group of investigators (Mikkelsen and Falk, 1982; Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986). Both crossover trials found a statistically significant result favoring tolfenamic acid. Effect sizes of 0.38 (-0.12 to 0.88) and 0.44 (0.17 to 0.79) suggested a moderate effect. A summary effect size of 0.42 (0.05 to 0.78) was statistically significant and suggested moderate clinical importance. Individual patient data from these trials showed an average reduction of 2.5 attacks per 12 weeks between tolfenamic acid and placebo periods.

Other NSAIDs. One trial each compared six other NSAIDs (flurbiprofen, indobufen, indomethacin, ketoprofen, lornoxicam, mefenamic acid) with placebo.

A single crossover study comparing flurbiprofen 200 mg/day with placebo found a trend toward lower headache frequency on flurbiprofen ($0.05<p<0.10$) (Solomon and Kunkel, 1993). Indobufen 400 mg/day was compared with placebo in a small parallel-group trial that found a significant effect on headache index at 3 months (Carrieri, Orefice, and Sorge, 1988). Indomethacin at 75 mg/day was compared with placebo in a trial of only 1 month's duration (Anthony and Lance, 1968). This trial found identical proportions of patients in the indomethacin and placebo groups reporting a greater than 50% reduction in headache frequency or severity (37%). Ketoprofen at a dose of 150 mg/day was found to reduce headache index compared with placebo ($p<0.05$) in a 6-week trial (Stensrud and Sjaastad, 1974). Lornoxicam at a dose of 12 mg/day for 2 months reduced headache frequency significantly ($p<0.05$) (Sternieri, Bussone, Manzoni, et al., 1991). Mefenamic acid, in a small crossover study, compared with placebo at 3 months, showed a significant reduction in headache frequency (Johnson, Hornabrook, and Lambie, 1986).

Comparisons With Beta-blockers

Aspirin vs. metoprolol. Aspirin 1500 mg/day was compared with metoprolol 200 mg/day in a crossover study with 3- month treatment periods (Grotemeyer, Scharafinski, Schlake, et al., 1990). Metoprolol-treated patients were more likely to experience a greater than 50% reduction in headache frequency (67% versus 14%). The aspirin-treated patients had lower mean headache severity, although this difference was not statistically significant.

Aspirin vs. propranolol. Aspirin 975 mg/day and propranolol 120 mg/day were compared in a small crossover trial (Baldrati, Cortelli, Procaccianti, et al., 1983). The proportion of patients with a greater than 50% reduction in headache index was identical in the aspirin and propranolol groups (75%). An effect size of -0.01 (-0.58 to 0.55) for headache index also suggested that the two drugs had a similar effect. The wide confidence intervals did not exclude a moderate benefit of either drug.

Mefenamic acid vs. propranolol. Mefenamic acid 1500 mg/day was compared with propranolol 240 mg/day in a small crossover study in which headache frequency was very similar between periods (Johnson, Hornabrook, and Lambie, 1986). The effect size of 0.06 (-0.61 to 0.74) provided little precision in comparing these drugs.

Naproxen sodium vs. propranolol. Sargent, Solbach, Damasio, et al. (1985) compared naproxen sodium 1100 mg/day with propranolol 120 mg/day. The investigators found a trend toward reduced headache frequency in the propranolol-treated patients. The effect size was -0.37 (-0.80 to 0.05), which excluded the probability that naproxen reduced headache frequency more than did propranolol.

Tolfenamic acid vs. propranolol. Two studies compared tolfenamic acid 300 mg/day with propranolol 120 mg/day (Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994; Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986). In each trial, the effect size favored propranolol, but was not statistically significant.

Comparisons With Serotonin Antagonists

The literature review identified only one comparison of an NSAID with a serotonin antagonist. Naproxen sodium 1100 mg/day and pizotifen 1.5 mg/day were compared by Bellavance and Meloche (1990) in a 3-month parallel-group trial. Both drugs reduced headache index to similar degrees, and the differences between them were not statistically significant.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Between 13% and 26% of patients taking naproxen or naproxen sodium reported adverse events, and between 2% and 10% withdrew from trials due to adverse events. Rates of adverse events for the other NSAIDs were generally similar to these. Although adverse event rates in NSAID groups were consistently higher than those in placebo groups, the differences were not statistically significant except in trials of flurbiprofen (Solomon and Kunkel, 1993) and lornoxicam (Sternieri, Bussone, Manzoni, et al., 1991), where rates were 16% and 17% higher than placebo, respectively.

The most common adverse events in all the NSAID trials were gastrointestinal. Although most trials combined all gastrointestinal symptoms into a single category, some listed specific adverse events such as nausea, vomiting, gastritis, and blood in the stool. Among trials of all agents, rates of gastrointestinal adverse events ranged from 3% to 45%.

Other specific adverse events that were reported in association with NSAIDs included dizziness, drowsiness, central nervous system symptoms, fatigue, insomnia, and dysuria.

Conclusions

Multiple trials of naproxen or naproxen sodium consistently showed a moderate reduction in headache symptoms compared with placebo. Some of the other NSAIDs studied -- including flurbiprofen, indobufen, ketoprofen, lornoxicam, mefenamic acid, and tolfenamic acid -- appeared to have similar moderate effects, but fewer studies supported the efficacy of these agents. The effects of aspirin, aspirin + dipyridamole, fenoprofen, and indomethacin are less certain. The reviewed trials of these agents described unusually large or small effects that have not been replicated.

In comparisons with beta-blockers, NSAIDs generally had effects which, while not statistically different, appeared to be slightly smaller than those associated with beta-blockers. NSAIDs were certainly not superior to beta-blockers to any clinically important degree.

Gastrointestinal adverse events were common with NSAIDs, and often led to withdrawal from trials. The relatively short-term trials reviewed here were inadequate to assess adverse events that may be associated with the long-term use of NSAIDs.

Other Serotoninergic Agents

Many of the drugs tested for efficacy in migraine prevention affect serotonin systems or serotonin metabolism, most notably, methysergide, ergotamine, and dihydroergotamine. This section of the report describes trials evaluating the efficacy and safety of other drugs that affect serotoninergic systems or serotonin metabolism for the prevention of migraine. The most frequently studied of these agents are pizotifen, which acts as an antiserotonin and an antihistamine (Arthur and Hornabrook, 1971), and lisuride, which "acts at a central level as a partial serotoninergic blocker" and is antiserotoninergic at a peripheral level (Nattero, Biale, and Savi, 1991). Other serotonin antagonists reported on here are iprazochrome (Divascan®, Migrenon®); tropisetron hydrogen chloride (ICS 205-930, Navoban®, Novaban®), a potent 5-HT(3) receptor antagonist usually used as an antinauseant; and oxitriptan. Oxitriptan (L-5-HTP, the levorotatory enantiomer of 5-hydroxytryptophan) is a precursor to serotonin (5-HT).

None of the serotoninergic agents covered in this section of the report (pizotifen, lisuride, iprazochrome, oxitriptan, and tropisetron) is currently available in the US.

Studies Identified

Overview

The literature review identified 47 publications reporting on 44 separate controlled trials of serotonin antagonists used for the prevention of migraine. One publication (Ferrari, Wilkinson, Hirt, et al., 1991) described two separate trials of the same drug (Studies 1 and 2).

Eight publications were excluded from our analysis for the reasons cited in Exhibit 9.

Exhibit 9. Excluded publications: Trials of other serotoninergic agents

Excluded publications	Reason for exclusion
Capildeo and Rose, 1982	Provided no data allowing comparisons of the two dosing regimens studied (daily vs. nightly regimens with same dose of active drug).
Chappell, Bay, and Botzum, 1991	Sergolexole maleate is not commercially or clinically available.
De Benedittis and Massei, 1985	Separate results for migraine provided only on a graph from which it was difficult to obtain precise data.
Havanka-Kanniainen, Hokkanen, and Myllylä, 1985a	Abstract of Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a; provided no new information.
Rascol, Montastruc, and Rascol, 1985	Abstract of Rascol, Montastruc, and Rascol, 1986; provided no new information.

Somerville and Herrmann, 1976	Abstract of Somerville and Herrmann, 1978; provided no new information .
Sulman, Pfeifer, and Superstine, 1981	Org GC 94 is not commercially or clinically available.
Titus, Dávalos, and Codina, 1985	Abstract of Titus, Dávalos, Alom, et al., 1986; provided no new information

Our analysis thus included 39 publications (listed below) reporting on 40 separate trials.

Andersson, 1973
Arthur and Hornabrook, 1971
Behan, 1985
Bellavance and Meloche, 1990
Bono, Criscuoli, Martignoni, et al., 1982
Carroll and Maclay, 1975
Cerbo, Casacchia, Formisano, et al., 1986
De Benedittis and Massei, 1986
Ferrari, Wilkinson, Hirt, et al., 1991 (Studies 1 and 2)
Forssman, Henriksson, and Kihlstrand, 1972
Gawel, 1987
Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a
Herrmann, Horowski, Dannehl, et al., 1977
Herrmann, Krištof, and Sastre y Hernandez, 1978
Hübbe, 1973
Hughes and Foster, 1971
Kangasniemi, 1979
Kangasniemi, Falck, Långvik, et al., 1978
Krakowski and Engisch, 1973
Lance and Anthony, 1968
Lawrence, Hossain, and Littlestone, 1977
Louis and Spierings, 1982
Mastrosimone, Iaccarino, and de Caterina, 1992
Mathew, 1978
Micieli, Trucco, Agostinis, et al., 1985
Nattero, Biale, and Savi, 1991
Osterman, 1977
Presthus, 1971
Rascol, Montastruc, and Rascol, 1986
Ryan, 1971
Ryan, 1968
Sances, Martignoni, Rosettino, et al., 1989
Sicuteri, 1973
Sjaastad and Stensrud, 1969
Somerville and Herrmann, 1978
Titus, Dávalos, Alom, et al., 1986
Vilming, Standnes, and Hedman, 1985
Wilkinson, Agnoli, Gerber, et al., 1989
Zuddas, Mulas, Del Zompo, et al., 1985

The included studies reported on the efficacy and safety of the following agents:

Pizotifen	26 trials
Lisuride	6 trials
Oxitriptan	4 trials
Iprazochrome	2 trials
Tropisetron	2 trials

Twenty of the trials were placebo-controlled; 4 compared one of the above agents with another; and 18 compared them with agents from different classes.

The included trials are described in Evidence Table 1.

Study Design and Quality

Twenty-two of the 40 included trials were parallel-group in design; 18 were crossover trials.

Active treatment periods in the included trials ranged from 1 month (three trials) to 6 months (two trials); the average length of the active treatment periods was 2.9 months.

Quality scores ranged from 1 (one trial) to 5 (two trials); the average score was 3.4.

Patient Populations

Twenty-nine of the 40 included trials provided no information about the setting in which patients were recruited. In four cases patients were drawn from neurology clinics (Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a; Hübbe, 1973; Lance and Anthony, 1968; Osterman, 1977), in three cases from a headache clinic or pain research center (Behan, 1985; De Benedittis and Massei, 1986; Rascol, Montastruc, and Rascol, 1986), and in two cases from general practice clinics (Lawrence, Hossain, and Littlestone, 1977; Louis and Spierings, 1982). In two trials patients were referred by physicians (Arthur and Hornabrook, 1971; Kangasniemi, 1979).

Many of the trials reviewed (25 of 40) included patients with migraine with or without aura. In one trial 25 of 26 patients had migraine with aura (Hughes and Foster, 1971), and in two trials patients had migraine without aura (Micieli, Trucco, Agostinis, et al., 1985; Nattero, Biale, and Savi, 1991). Two trials included patients with migrainous neuralgia (Arthur and Hornabrook, 1971; Hughes and Foster, 1971), two were restricted to women having migraine during or close to the time of their menstrual cycles (Sances, Martignoni, Rosettino, et al., 1989; Zuddas, Mulas, Del Zompo, et al., 1985). Fifteen trials referred specifically to the Ad Hoc criteria for migraine, and one referred to the IHS criteria.

All but 13 of the trials had minimum headache frequency requirements for inclusion. Six trials included only patients with severe headaches (Arthur and Hornabrook, 1971; Bellavance and Meloche, 1990; Herrmann, Krištof, and Sastre y Hernandez, 1978; Hughes and Foster, 1971; Kangasniemi, 1979; Lance and Anthony, 1968). Two excluded patients with headache indexes below a certain threshold (defined differently in each trial) (Bono, Criscuoli, Martignoni, et al., 1982; De Benedittis and Massei, 1986). In one study, several patients had been hospitalized for migraine (Sjaastad and Stensrud, 1969).

One trial explicitly excluded patients with tension-type or "tension-vascular" headaches (Titus, Dávalos, Alom, et al., 1986), and one excluded patients with tension-type headaches that could not be clearly distinguished from migraine (Vilming, Standnes, and Hedman, 1985). Patients were excluded from trials for having the following types of headaches (one trial in all but one case): "other types of headache" (Bellavance and Meloche, 1990), "other vascular headaches" (Vilming, Standnes, and Hedman, 1985), "headaches resulting from head trauma or cervical spondylosis" (Somerville and Herrmann, 1978), and "complicated or ophthalmoplegic migraine" (Ferrari, Wilkinson, Hirt, et al., 1991 [Studies 1 and 2]).

In four trials patients were excluded for taking concomitant migraine medications (Ferrari, Wilkinson, Hirt, et al., 1991 [Studies 1 and 2]; Ryan, 1971; Wilkinson, Agnoli, Gerber, et al., 1989). Patients were not allowed to take migraine prophylactic medications in one trial (Lawrence, Hossain, and Littlestone, 1977). The two trials described in Ferrari, Wilkinson, Hirt,

et al. (1991) also excluded patients who were receiving prophylactic nonpharmacological treatments (e.g., acupuncture or psychotherapy). One trial excluded patients who had used any investigational drugs in the month preceding the trial (Ryan, 1971). This was the only trial that required patients to have had no previous experience with the drugs being investigated in the trial. None of the trials was restricted to patients who had never tried preventive medication.

Twenty-seven trials permitted patients to use medication for acute attacks of migraine occurring during the trial; 11 trials did not specify whether patients were allowed to use such medications. One trial permitted patients to use ergotamine preparations or morphine only in exceptionally severe cases (Andersson, 1973), and in one trial patients were asked to discontinue or minimize the use of analgesics (De Benedittis and Massei, 1986). Patients in another trial were not permitted to take acute medications that might obscure the efficacy of the study drug (pizotifen) (Arthur and Hornabrook, 1971).

Fourteen of the 40 trials did not report the average age of patients, and 9 did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 31 to 47, and the percentage of patients who were women ranged from 52% to 100%.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 10.

Comparisons With Placebo

Pizotifen. Eleven trials compared pizotifen and placebo using, in doses of 1.5 mg to 6 mg daily for a period of 4 to 12 weeks (Arthur and Hornabrook, 1971; Bellavance and Meloche, 1990; Carroll and Maclay, 1975; Hughes and Foster, 1971; Krakowski and Engisch, 1973; Lance and Anthony, 1968; Lawrence, Hossain, and Littlestone, 1977; Osterman, 1977; Ryan, 1968; Ryan, 1971; Sjaastad and Stensrud, 1969). Four of the trials showed a statistically significant efficacy, while two reported nonsignificant effects that favored pizotifen. Five studies did not report any information on tests of statistical significance of the efficacy of pizotifen relative to placebo.

The proportion of patients experiencing a 50% or greater improvement in headache frequency or headache index with pizotifen was 40% and 48% in the two trials reporting this outcome (Arthur and Hornabrook, 1971; Lance and Anthony, 1968), while the corresponding placebo response rates were 12% and 36%, respectively. The trial with the higher placebo response rate (Lance and Anthony, 1968) counted a 50% or greater reduction in either headache frequency or intensity as a positive treatment response. Odds ratios from the two trials favored pizotifen at 5.2 (1.9 to 14.3) and 1.6 (0.53 to 5.1).

Four studies allowed translation of outcomes into effect sizes (Krakowski and Engisch, 1973; Lawrence, Hossain, and Littlestone, 1977; Osterman, 1977; Sjaastad and Stensrud, 1969). These four studies produced similar effect size estimates (test for homogeneity: chi-square = 0.88; d.f.

= 3; p = 0.83) which, when combined, yielded a summary effect size of 0.91 (0.50 to 1.3), indicating a large clinical effect that is highly statistically significant.

Lisuride. Four trials compared lisuride with placebo, using doses of 0.075 mg to 0.15 mg daily for a period of 3 to 6 months (Herrmann, Krištof, and Sastre y Hernandez, 1978; Sances, Martignoni, Resetting, et al., 1989; Somerville and Herrmann, 1978; Zuddas, Mulas, Del Zompo, et al., 1985). All four studies reported the statistically significant efficacy of lisuride, though only one trial reported sufficient data to permit any quantitative estimate of the drug's efficacy (Sances, Martignoni, Rosettino, et al., 1989). The effect size of 0.76 (0.12 to 1.4) from this trial indicates a moderate to large effect and is statistically significant.

A single trial compared the two doses of lisuride used in the placebo-controlled trials (Wilkinson, Agnoli, Gerber, et al., 1989). The proportion of patients with a 50% or greater improvement in headache frequency was 37% both for patients receiving 0.15 mg/day and patients receiving 0.075 mg/day. However, the broad confidence intervals surrounding the resulting odds ratio (0.98 [0.42 to 2.3]) do not exclude the possibility of a clinically important dose-response relationship.

Oxitriptan. Oxitriptan was compared with placebo in three small crossover trials using doses ranging from 300 mg to 2000 mg/day (De Benedittis and Massei, 1986; Kangasniemi, Falck, Långvik, et al., 1978; Mathew, 1978). None of the three trials found a significant improvement in headache index with oxitriptan. Two provided quantitative data that permitted calculation of effect sizes (De Benedittis and Massei, 1986; Kangasniemi, Falck, Långvik, et al., 1978). The effect size estimates were 0.08 (-0.42 to 0.58) and 0.45 (-0.54 to 1.4), resulting in a combined estimate of 0.19 (-0.44 to 0.83). Neither the individual estimates nor the combined estimate is precise enough to exclude the possibility of a clinically important effect, positive or negative.

Tropisetron. Tropisetron was compared with placebo in two studies described in a single report (Ferrari, Wilkinson, Hirt, et al., 1991 [Studies 1 and 2]). The first, a dose-ranging study, failed to find effectiveness of either the 25 or 50 mg/day doses tested; however, a better response to the lower dose (25 mg) spurred a followup placebo-controlled study of 15 mg/day (Study 2). In this trial, the response rate to the 15 mg/day dose (57%) was higher than the response rate to the 25 or 50 mg/day doses tested in Study 1 (37% and 29%, respectively), and the placebo response rates were similar, at 35% compared with 40%. However, the difference of 22% in the response rate between the 15 mg/day dose and placebo was not statistically significant.

Iprazochrome. A single crossover study that compared iprazochrome 15 mg/day for 8 weeks with placebo found no difference in post-treatment headache index (Osterman, 1977).

Comparisons Among Serotonin Antagonists

Pizotifen vs. iprazochrome. Two crossover studies compared pizotifen, in doses of 1.5 mg or 3 mg/day, to iprazochrome 15 mg/day (Osterman, 1977; Kangasniemi, 1979). The study using the higher dose of pizotifen over 8 weeks (Osterman, 1977) showed that pizotifen doubled the proportion of patients with a 50% or greater reduction in headache frequency compared to iprazochrome, from 22% to 44%. The associated odds ratio of 2.8 (0.86 to 9.1) was not statistically significant. Continuous headache index data from this trial produced an effect size of

0.73 (0.18 to 1.3), indicating a moderate to large clinical effect that is statistically significant. The other study (Kangasniemi, 1979), which used a dose of 1.5 mg/day of lisuride, found a smaller benefit in headache index, with an effect size of 0.26 (-0.22 to 0.73).

Pizotifen vs. lisuride. A single crossover trial compared pizotifen 4.5 mg/day and lisuride (Nattero, Biale, Savi, et al., 1991). A relatively high dose of lisuride was used (0.225 mg/day). The trial demonstrated a marginally higher proportion of patients experiencing a 50% or greater reduction in headache frequency with lisuride compared with pizotifen (35% vs. 23%, respectively); however, the 12% difference between the two therapies was not statistically significant. The associated odds ratio of 0.57 (0.22 to 1.5) does not exclude the possibility of a clinically important benefit of either agent.

Pizotifen vs. oxitriptan. A single study compared pizotifen, in a low dose of 1.4 mg/day, with oxitriptan (Bono, Criscuoli, Martignoni, et al., 1982). This study found that pizotifen was significantly better in reducing headache index, but did not report sufficient data to estimate the magnitude of this benefit.

Comparisons With Calcium Antagonists

Pizotifen vs. flunarizine. Pizotifen and flunarizine were compared in three trials (Cerbo, Casacchia, Formisano, et al., 1986; Louis and Spierings, 1982; Rascol, Montastruc, and Rascol, 1986). Cerbo, Casacchia, Formisano, et al. (1986) used a relatively low dose of pizotifen (1.5 mg/day) and a relatively high dose of flunarizine (15 mg/day). The other two trials administered flunarizine in a dose of 10 mg/day and pizotifen in doses of 2-3 mg/day (Louis and Spierings, 1982), or in an average dose of 2.19 mg/day (Rascol, Montastruc, and Rascol, 1986).

None of these small studies found a statistically significant difference in headache frequency at 4 months between pizotifen- and flunarizine-treated patients. None reported sufficient quantitative data to allow calculation of an odds ratio for improvement or an effect size.

Pizotifen vs. nimodipine. Three trials compared pizotifen at 1.5 mg to 3 mg/day with nimodipine 120 mg/day (Gawel, 1987; Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a; Micieli, Trucco, Agostinis, et al., 1985). None of these trials found any clinically important or statistically significant differences between the two drugs. Two studies (Gawel, 1987; Havanka-Kanniainen, Hokkanen, and Myllylä, 1987a) reported enough data to calculate effect sizes of 0.11 (-0.42 to 0.64) and -0.11 (-0.54 to 0.31); these effect sizes yielded a combined estimate of 0.02 (-0.45 to 0.41), which suggests equivalent effects, but does not exclude the possibility of a small or moderate superiority of either drug.

Pizotifen vs. cyclandelate. A single trial compared pizotifen 1.5 mg/day to cyclandelate 1600 mg/day over 3 months (Mastrosimone, Iaccarino, and de Caterina, 1992). The study reported that cyclandelate-treated patients had a significantly lower total pain index than those treated with pizotifen ($p<0.001$); however, neither mean scores nor the proportion of patients improving was reported, so the magnitude of benefit could not be assessed.

Comparisons With Methysergide

Pizotifen vs. methysergide. Four trials compared pizotifen with methysergide (Andersson, 1973; Forssman, Henriksson, and Kihlstrand, 1972; Presthus, 1971; Ryan, 1968). The doses of pizotifen used ranged from 1.5 mg to 4 mg/day, while doses of methysergide were consistent across the four trials (between 3-4 mg/day). One trial reported the proportion of patients with a greater than 50% reduction in headache frequency compared to baseline (Andersson, 1973). Response rates were lower than those seen in the placebo-controlled trials: 38% for the pizotifen arm and 31% for the methysergide arm. The difference between the two treatments was not significant, and the odds ratio estimate of 1.4 (0.59 to 3.2) favored pizotifen.

Two studies reported sufficient data to calculate effect sizes, both based on headache frequency. Andersson (1973) allowed calculation of an effect size of 0.17 (-0.23 to 0.57), which favored pizotifen but failed to reach statistical significance. Presthus (1971) reported individual patient data on headache frequency which allowed calculation of an effect size of 0.29 (-0.17 to 0.76), which is very similar to the estimate from Andersson (1973). The combined effect size for the two trials was 0.22 (-0.16 to 0.60).

Oxitriptan vs. methysergide. Two trials comparing oxitriptan with methysergide provided little information on the relative effectiveness of the two agents (Sicuteri, 1973; Titus, Dávalos, Alom, et al., 1986). Sicuteri (1973) found no difference in headache index; an effect size point estimate of -0.09, based on data from the trial, was negligible, and the 95% confidence intervals associated with this point estimate were quite broad, ranging from -0.71 to 0.53. Data from Titus, Dávalos, Alom, et al. (1986) did not improve the precision of the estimate, since the proportion of patients with a 50% or greater reduction in headache frequency (overall or for severe headaches) was 75% for methysergide and 71% for oxitriptan. The corresponding odds ratio of 0.82 (0.31 to 2.2) does not exclude a clinically important benefit of either drug.

Lisuride vs. methysergide. A single study comparing lisuride with methysergide over 3 months (Herrmann, Horowski, Dannehl, et al., 1977) found similar proportions of patients with a 50% or greater improvement in headache frequency: 53% and 51%, respectively. The associated odds ratio of 1.1 (0.53 to 2.2) does not exclude a clinically important benefit of either drug.

Comparisons With Other Classes of Drugs

Pizotifen, in doses of 1.5 mg to 3 mg/day was compared with clonidine (Behan, 1985), prochlorperazine (Hübbe, 1973), metoprolol (Vilming, Standnes, and Hedman, 1985), and naproxen sodium (Bellavance and Meloche, 1990). None of these studies reported any statistically significant differences between pizotifen and the comparator treatment, and none reported sufficient quantitative data to allow the calculation of an odds ratio for improvement or an effect size.

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Pizotifen

Adverse events were reported for between 25% and 91% of patients taking pizotifen in seven trials that reported overall adverse event rates (Arthur and Hornabrook, 1971; Bellavance and Meloche, 1990; Forssman and Kihlstrand, 1972; Gawel, 1987; Krakowski and Engisch, 1973; Mastrosimone, Iaccarino, and de Caterina, 1992; Rascol, Montastruc, and Rascol, 1986). Withdrawals due to adverse events ranged from 0% to 10% of patients on pizotifen.

The specific adverse event observed most frequently with pizotifen was weight gain, occurring in 17 trials in 10% to 78% of patients. The high degree of variability in the rate of weight gain reported in different studies may be explained by the use of different thresholds for reporting weight gain as an adverse event. Osterman (1977) stratified the weight gain results, reporting that while 78% of patients on pizotifen reported a weight gain of at least 1.5 kg, 30% experienced a weight gain of more than 4 kg.

Drowsiness or somnolence was observed in 15 of the trials at rates ranging from 5% to 60%. Gastrointestinal side effects -- such as increased appetite, nausea, dyspepsia, vomiting, and diarrhea -- were observed in many trials. Dizziness or vertigo was described in eight studies at rates ranging from 2% to 27%. Fatigue was reported in seven trials at rates between 4% and 19%, and depression in four studies at rates between 5% and 13% of participants.

Lisuride

None of the seven trials including a lisuride treatment arm reported overall adverse event rates. Withdrawals occurred in 10% to 18% of patients taking lisuride in the four trials that reported the number of withdrawals due to adverse events. Specific adverse events (and rates) reported in more than one study included nonspecific gastrointestinal effects (5%-50%), nausea (3%-5%), vertigo (2%-24%), and drowsiness (3%-12%).

Oxitriptan

Of the four trials including an oxitriptan arm, one reported a total adverse event rate of 16% vs. 19% with placebo (De Benedittis and Massei, 1986), and another reported that no adverse events were reported with oxitriptan or placebo (Kangasniemi, Falck, Långvik, et al., 1978). No withdrawals due to adverse events associated with oxitriptan were reported in three trials (De Benedittis and Massei, 1986; Kangasniemi, Falck, Långvik, et al., 1978; Sicuteri, 1973); no information on withdrawals was provided in the fourth (Mathew, 1978). Specific adverse events reported with oxitriptan included gastric distress in one study (16%). Other effects reported occurred in less than 3% of subjects and included weight gain, nausea, diarrhea, pyrosis, and drowsiness.

Tropisetron

The two studies of tropisetron noted high rates of constipation occurring in the majority of patients (Ferrari, Wilkinson, Hirt, et al., 1991 [Studies 1 and 2]). In each of these trials, 8% of

patients withdrew due to adverse events, for reasons including constipation, nausea and vomiting, hypoglycemia, and skin reaction. Other adverse events not requiring withdrawal occurred, but were not identified.

Iprazochrome

Neither of the two trials with an iprazochrome treatment arm reported overall rates of adverse events (Kangasniemi, 1979; Osterman, 1977). In both trials, iprazochrome was associated with a smaller number of adverse events than was pizotifen. In Osterman (1977), there were no significant differences in the adverse events reported with iprazochrome and with placebo.

Conclusions

There is strong and consistent evidence from 11 placebo-controlled trials and 19 comparisons with other agents suggesting that pizotifen, in doses of 1.5 mg to 4 mg/day, is effective for the prevention of migraine attacks. Pizotifen has been shown in direct comparative trials to be more effective than placebo, iprazochrome, and oxitriptan. In comparisons with drugs known to be efficacious (e.g., flunarizine and metoprolol), pizotifen has been found to be no less effective. However, in the trials reviewed here, pizotifen was generally poorly tolerated, commonly causing substantial weight gain or drowsiness, and was associated with a high incidence of patient withdrawals due to adverse events.

Lisuride has consistent support from four placebo-controlled trials showing significant benefit, and from direct comparisons with pizotifen and methysergide, in which lisuride was no less effective. Lisuride was associated with a lower incidence of adverse events than was pizotifen, and a lower rate of patient withdrawal due to adverse events.

None of the other drugs considered in this section of the report (iprazochrome, oxitriptan, or tropisetron) has been shown to be effective compared to placebo. Iprazochrome and oxitriptan have been shown to be less effective than pizotifen.

Other Treatments

This section of the report reviews the evidence for the safety and efficacy of two distinct types of treatment for which the literature review identified only a few trials each: hormonal treatments (estrogens and progestogens) and the herbal remedy, feverfew.

As a disorder, migraine frequently begins at puberty in both men and women. In many women, migraine attacks occur in conjunction with the menstrual cycle throughout the reproductive years, and the character and frequency of attacks are often affected by pregnancy and menopause. There is also a strong epidemiological association of migraine with female sex. For all these reasons, researchers have explored the possibility that hormonal treatments might be useful for the prevention of migraine. Estrogens and progestogens, in particular, have been studied among various subsets of migraineurs, including women whose migraine attacks are somehow correlated with the menstrual cycle; women whose attacks are not associated with the menstrual cycle; and, in a few studies, men.

Feverfew (tanacetum parthenium) is a medicinal plant whose leaves have become a popular treatment for the prevention of migraine.

Studies Identified

Overview

The literature review identified six publications reporting on six separate controlled trials of estrogens or progestogens used for the prevention of migraine (Bradley, Hudgson, Foster, et al., 1968; Dennerstein, Morse, Burrows, et al., 1988; Hudgson, Foster, and Newell, 1967; Lundberg, 1969; Ryan, 1978; Smits, van der Meer, Pfeil, et al., 1993) and two publications reporting on two separate controlled trials of feverfew (Johnson, Kadam, Hylands, et al., 1985; Murphy, Heptinstall, and Mitchell, 1988). All eight trials were included in our analysis.

The hormonal trials reported on the safety and efficacy of the following agents:

Flumedroxone	3 trials
Estradiol	2 trials
Norgestrel + estradiol	1 trial

Five of the six hormonal trials were placebo-controlled; the sixth compared flumedroxone with methysergide. Both feverfew trials were placebo-controlled.

The trials are described in Evidence Table 1.

Study Design and Quality

Five of the hormonal treatment trials were crossover in design; one (Lundberg, 1969) was parallel-group. One of the feverfew trials was crossover (Murphy, Heptinstall, and Mitchell, 1988), and the other parallel-group (Johnson, Kadam, Hylands, et al., 1985).

Active treatment periods in the hormonal treatment trials ranged in length from 1 month (one trial) to 4 months (one trial); the average length of the active treatment periods was 2.5 months. Active treatment periods in the two feverfew trials were 4 and 6 months.

Quality scores for the hormonal treatment trials ranged from 2 (one trial) to 5 (one trial); the average score was 3.2. For the two feverfew trials, quality scores were 4 and 3.

Patient Populations

Four of the six trials of hormonal treatments provided no information about the setting in which patients were recruited. In one of the remaining two cases, patients were drawn from a menstrual disorders clinic (Dennerstein, Morse, Burrows, et al., 1988); in the other, patients were said only to have been referred to the investigator (Lundberg, 1969). One of the feverfew trials recruited patients from a migraine self-help group and through media advertising (Murphy, Heptinstall, and Mitchell, 1988); the other drew patients from a migraine clinic (Johnson, Kadam, Hylands, et al., 1985).

Among the hormonal treatment trials, Bradley, Hudgson, Foster, et al. (1968) included male and female patients with "typical" migraine (which was not defined). Trial results were reported and analyzed separately for men, women with a history of more frequent migraines around the time of menstruation, and women with no such history. Dennerstein, Morse, Burrows, et al. (1988) included only women with migraine attacks of severe intensity that regularly occurred during the 7 days encompassing menstruation. Smits, van der Meer, Pfeil, et al. (1993) included only women with "pure menstrual migraine," defined as attacks of migraine without aura (as defined by the IHS criteria), regularly occurring no earlier than 2 days before menstruation and no later than the last day of menstruation, with no attacks during the rest of the menstrual cycle. The remaining three trials did not focus on migraine attacks associated with the menstrual cycle: Hudgson, Foster, and Newell (1967) treated a group of patients (sexual mix not described) with frequent, severe attacks of "typical" migraine (again, not defined); Lundberg (1969) included men and women with migraine with or without aura; and Ryan (1978) treated a group of women described only as having migraine of moderate to severe intensity. The feverfew trials both included patients with migraine with aura or migraine without aura. Most of the trials had minimum frequency requirements for inclusion. Apart from Smits, van der Meer, Pfeil, et al. (1993), none of the trials referred to the Ad Hoc or IHS diagnostic criteria.

Three of the hormonal treatment trials included patients who had tried preventive therapy at some point in the past (Dennerstein, Morse, Burrows, et al., 1988; Hudgson, Foster, and Newell, 1967; Lundberg, 1969). Another trial (Smits, van der Meer, Pfeil, et al., 1993) permitted patients on preventive medication to continue taking it during the trial, provided they had been taking it for at least 3 months before the trial started and did not change the medication during the trial. Two of the hormonal treatment trials did not state whether patients were permitted to take medication for acute attacks occurring during the trial (Bradley, Hudgson, Foster, et al., 1968; Hudgson, Foster, and Newell, 1967); the remaining four permitted the use of such medication.

One of the feverfew trials included only patients who had been taking the herb daily for at least 3 months prior to the start of the trial (Johnson, Kadam, Hylands, et al., 1985); this trial also permitted the use of both acute and preventive medications. In the other feverfew trial (Murphy,

Heptinstall, and Mitchell, 1988), only 29% of those who completed the trial had used feverfew before, and no acute or preventive medications were permitted during the trial.

Three of the hormonal treatment trials did not report the average age of patients, and one did not report the number of patients who were women. Among those trials that did report such information, the average age of patients ranged from 35 to 40, and the percentage of patients who were women ranged from 64% to 100%. Average ages in the feverfew trials were 46 and 48. In one trial, 74% of patients were women; the other trial did not report on the number of patients who were women.

Evidence for Efficacy

Efficacy data from the trials reviewed in this section of the report are summarized in Evidence Table 11.

Hormonal Treatments

Estradiol. Estradiol was compared with placebo in two trials (Dennerstein, Morse, Burrows, et al., 1988; Smits, van der Meer, Pfeil, et al., 1993). Dennerstein, Morse, Burrows, et al. (1988) studied 19 women with menstrual migraines, randomizing them to receive either a percutaneous estradiol gel (1.5 mg/day) or a placebo gel to be used beginning at least 2 days before an anticipated headache and continuing for 7 days thereafter. Headache frequency during the 7-day perimenstrual period (which did not necessarily correspond precisely with the days of estradiol administration) was lower among women treated with the active preparation. We calculated an effect size for this outcome based on individual patient data reported by the investigators; the effect size was 0.71 (0.26 to 1.2), which is statistically significant in favor of estradiol.

The other trial of estradiol (Smits, van der Meer, Pfeil, et al., 1993) was also conducted among women with menstrual migraine; but, in this case, patients were selected according to a more stringent definition of menstrual migraine, and a much lower dose of estradiol was used. Patients were randomized to receive a patch delivering 50 micrograms of estradiol daily or a placebo patch. The patch was to be applied 2 days before the anticipated onset of menstruation, with another patch to be applied 4 days later. Headache frequency (measured as the number of menstrual cycles accompanied by a migraine attack) did not differ significantly between those cycles in which estradiol was used and those in which placebo was used; 59% of cycles on estradiol and 69% of cycles on placebo were associated with migraine.

Flumedroxone. Two placebo-controlled trials provided data on the efficacy of the drug flumedroxone, a modified oral progestogen designed to have reduced progestogenic effects (Bradley, Hudgson, Foster, et al., 1968; Lundberg, 1969). Bradley, Hudgson, Foster, et al. (1968) randomized patients to receive either 30 mg of a micronized preparation of flumedroxone or placebo daily for 3 months. The investigators' analysis was stratified to consider separately three patient subgroups: men, women without menstrual exacerbation of headache, and women with menstrual exacerbation of headache. Headache index was reduced with flumedroxone compared to placebo only among women with menstrual exacerbation of their headaches ($p<0.05$). With 18 patients, this was the largest of the three subgroups studied.

Lundberg (1969) compared flumedroxone 10 mg daily with placebo in a parallel-group trial. The investigator found a highly significant improvement ($p<0.0005$) in headache frequency associated with flumedroxone; however, the definition used for improvement (fewer headaches than during the pre-treatment period) did not meet our 50% or greater threshold.

Flumedroxone, in a dose of 15 mg/day, was also compared with methysergide in a single crossover study (Hudgson, Foster, and Newell, 1967). The patient population of this trial was poorly characterized: the sexual distribution was not described, and participants were said to suffer from frequent, severe attacks of "typical" migraine, which was not defined. Mean headache frequency was lower with methysergide than with flumedroxone (2.8 vs. 4.3 attacks per month, respectively). No statistical comparison was made by the investigators, and insufficient data were reported to allow us to calculate an effect size.

Ovral® (norgestrel 0.5 mg + ethinyl estradiol 0.005 mg). A combination oral contraceptive (Ovral®) was compared with no treatment in a randomized crossover trial conducted among 40 women with migraine (Ryan, 1978). There was no explicit requirement that patients' migraines be associated with their menstrual cycle. One Ovral® tablet was administered daily for 3 weeks, followed by no treatment for 1 week, during each month of the 2-month active treatment periods. Headache index scores were worse during treatment with Ovral® than during the no-treatment period (48.70 vs. 32.85, respectively). No tests of statistical significance were reported.

Feverfew

Two trials compared feverfew with placebo or no treatment (Johnson, Kadam, Hylands, et al., 1985; Murphy, Heptinstall, and Mitchell, 1988). The trials differed from one another in several important respects.

Johnson, Kadam, Hylands, et al. (1985) recruited patients through a headache clinic who had not only previously tried feverfew, but had been using the herb daily for at least 3 months. The investigators randomized these patients either to continue taking 50 mg of the freeze-dried, pulverized, and encapsulated herb daily, or to take a matching placebo. This small trial (15 patients completed the trial) found an increase in headache frequency among those taking placebo, and little change in those maintained on feverfew. The difference was highly statistically significant, even with a small sample size, with an effect size of 2.3 (1.0 to 3.6).

A subsequent trial was conducted in a larger population of migraineurs recruited from a migraine self-help group and through media advertising (Murphy, Heptinstall, and Mitchell, 1988). Only 29% of the 59 patients who completed the trial and were included in the efficacy analysis had used feverfew before; 8% (5/59) were using the herb at the time of entry into the study. This crossover study reported a highly significant difference in headache frequency between feverfew and placebo periods; however, the magnitude of the difference between the two treatments was much smaller than that observed in the trial discussed immediately above: 1.1 headaches per 2-month treatment period, which yielded an effect size of 0.56 (0.19 to 0.93).

Adverse Events

The available data on adverse events are summarized in Evidence Table 12.

Hormonal Treatments

Adverse events were only slightly more frequent with estradiol than with placebo. In Dennerstein, Morse, Burrows, et al. (1988), amenorrhea was the most commonly reported adverse event (9% of patients on estradiol vs. 0% on placebo). In Smits, van der Meer, Pfeil, et al. (1993), where an estradiol patch was used, itching in the area of the patch was the most common adverse event associated with estradiol that was not reported with placebo (9% vs. 0%). Very few withdrawals were caused by adverse events associated with estradiol.

Progestogenic adverse events -- particularly polymenorrhea, nausea, and mastitis -- were much more frequent with flumedroxone than with placebo in Bradley, Hudgson, Foster, et al. (1968). Six of 14 (43%) women of reproductive age included in the trial reported polymenorrhea. Among male patients taking flumedroxone, adverse events included drowsiness, dyspepsia, and decreased libido. Another placebo-controlled study, using a lower dose of flumedroxone (Lundberg, 1969), provided incomplete information on adverse events, but noted that menstrual disturbances were the most common adverse events, occurring in 8/30 women (27%).

In the only trial comparing the two interventions, adverse events were significantly more frequent during treatment with flumedroxone (23% of patients) than during treatment with methysergide (3% of patients). Thirteen percent of patients (5/40) reported polymenorrhea with flumedroxone (vs. 0% with methysergide).

Limited information was provided on adverse events in the only trial of Ovral® (norgestrel + ethinyl estradiol) (Ryan, 1978). A high proportion of patients (70%) reported one or more adverse events in association with Ovral®. The frequency of individual adverse events was not reported, but at least the following were observed: nausea, vomiting, abdominal cramping, depression, drowsiness, and dry mouth.

Feverfew

Johnson, Kadam, Hylands, et al. (1985) reported that more adverse events were experienced by those patients in the placebo group (i.e., those from whom feverfew was withdrawn) than by those continuing with active treatment. Adverse events reported on withdrawal of feverfew included nervousness, and tension-type and other non-migrainous headaches. Other adverse events were infrequent and were reported in similar proportions by patients in the placebo and feverfew groups.

Murphy, Heptinstall, and Mitchell (1988) described a different constellation of adverse events, but reported that these symptoms were no more common during treatment with feverfew than during treatment with placebo. Mouth ulceration was remarkably common, occurring in 22% of patients during treatment with feverfew and in 14% during treatment with placebo. Other adverse events were infrequently reported.

Conclusions

Hormonal Treatments

Data on the use of estrogens and progestogens for migraine prevention are relatively poor, with only a few relatively small trials and marked variation in subject population, dosages employed, and clinical results. The trials of estradiol used perimenstrually in a gel or patch form suggest that a relatively high dose of this hormone may be efficacious in women whose migraine attacks are associated with their menstrual cycles. The trials using lower doses of estradiol perimenstrually or mixed estradiol/progestogen oral contraceptives in a cyclic fashion do not support efficacy for migraine prevention.

Three trials of flumedroxone indicate that this agent can be efficacious, particularly among women whose migraine headaches are associated with their menstrual cycle. The use of this agent is, however, limited by the frequency of polymenorrhea and other adverse events.

The data reviewed in this section of the report do not support the efficacy of estrogens or progestogens in women whose migraines are not associated with their menstrual cycle, or in male migraineurs.

Feverfew

Two trials provide evidence that feverfew is efficacious for migraine prevention. One study among a self-selected population of feverfew users showed that withdrawal of feverfew led to a statistically significant increase in headache frequency. Another, more traditional, trial suggested that feverfew was efficacious among a more generalizable population of migraineurs. Although the magnitude of benefit was smaller in this second trial, the effect size estimate obtained was similar to those associated with other migraine preventive medications.

Future Research

Further research is required into the safety and efficacy of currently available drugs if their use for the long-term prevention of migraine attacks is to be optimized. The recommendations described below may be made.

Conduct and Reporting of Trials

(1) The generalizability of the results of trials conducted among patients in headache specialty centers to primary care populations is uncertain. More trials should be conducted among patients recruited from general practice settings.

(2) The diagnosis of migraine -- even when made according to specific criteria such as the IHS criteria for migraine with aura and migraine without aura -- encompasses a wide range of symptomatology. Researchers should be as precise as possible in describing any operational inclusion or exclusion criteria they employed in addition to headache diagnosis, such as headache frequency, severity, and chronicity.

(3) The use of medications for the treatment of acute migraine episodes during the trial of preventive therapy was handled in a variety of ways in different studies. Because effective treatment of acute migraine attacks can significantly affect headache severity and duration measures, the uncontrolled use of such medications can confound the results of a preventive trial. Future studies should measure and describe the use of medications for the treatment of acute migraine attacks.

(4) More head-to-head comparisons of preventive treatments should be performed in order to help clinicians and patients make informed choices among the many available therapies. Such comparative trials are particularly important for older drugs.

(5) Future trials should use common scales for measuring pain outcomes, if possible. The IHS recommends the use of headache frequency per 4-week observation period as the primary measure of efficacy (International Headache Society Committee on Clinical Trials in Migraine, 1991). The consistent adoption of this recommendation in trials of migraine preventive drugs would greatly facilitate future meta-analyses.

(6) Because many preventive drugs are poorly tolerated, future trials should expand the scope of the clinically relevant outcomes measured. Overall or disease-specific quality-of-life measures, along with careful assessment and complete reporting of adverse events, would help in evaluating the overall efficacy of the treatment.

(7) Adverse events should be reported for all patients taking study medication, including those who withdraw prematurely. The number of patients experiencing adverse events with each intervention should be reported, and the specific adverse events reported should be described.

New Directions for Research

(8) Adverse events associated with long-term use of some migraine preventive agents have been identified (e.g., fibrotic complications associated with methysergide, weight gain with flunarizine, and gastrointestinal symptoms with many NSAIDs). The relatively short-term clinical trials reviewed in this report do not effectively capture these adverse events. New approaches to ascertaining long-term or rare complications of treatment are needed.

(9) The real-life management of headache disorders often involves multiple simultaneous interventions, including an acute drug treatment plan (which might include an initial and rescue medication), a preventive drug treatment plan, behavioral therapy or other self-management education, or skills training. Such multidisciplinary interventions, usually delivered in specialty clinics, have been reported to show dramatic response rates in uncontrolled studies. Testing these bundled multiple interventions in a prospective, controlled trial may provide more understanding of how to care for patients with chronic headache disorders than do the short-term, single intervention preventive drug studies reviewed here.

(10) Further research is needed regarding the delivery of migraine care, in general, and of preventive therapies, in particular. It is important to ascertain whether there are patterns of use of different migraine treatment approaches in different settings and among different types of providers (e.g., generalists versus specialists).

(11) Limited data suggest that most patients do not remain on migraine preventive drugs for long-term use; however, little is known about the reasons for discontinuing the drugs or about the effect of this discontinuation on patients' headaches. Preventive drug treatments for migraine are often undertaken with the expectation that after a period of successful treatment (e.g., 6 to 12 months), treatment can be discontinued without the patient's headaches either worsening or returning to the same intensity experienced prior to treatment. Further research on the effects of withdrawing migraine preventive treatments would help address the issue of whether to discontinue or taper treatment and the best timeframe for doing so.

(12) Few studies have attempted to identify predictors of response or nonresponse to particular migraine preventive drugs, leaving physicians with little guidance for choosing among efficacious agents. Particularly informative would be tests of association between treatment response and patient-level factors, such as headache characteristics,

demographic characteristics, or response (or nonresponse) to other drugs for the acute or preventive treatment of migraine. Furthermore, protocols describing particular selection criteria or order of drug trials in individual patients could be tested in a controlled fashion.

References

Ad Hoc Committee on the Classification of Headache of the National Institute of Neurological Diseases and Blindness. Classification of headache. JAMA 1962;179:717-8.

Adam EI, Gore SM, Price WH. Double-blind trial of clonidine in the treatment of migraine in a general practice. J R Coll Gen Pract 1978;28(195):587-90.

Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache 1992;32(2):101-4.

Agnoli A, Bussone G, Mailland F, Manzoni GC, Martucci N, Nappi G. Dihydroergokryptine vs. flunarizine in the basic treatment of migraine without aura. Cephalalgia 1991;11(Suppl 11):216-7.

Agnoli A, Bussone G, Manzoni GC, Martucci N, Nappi G. Dihydroergokryptine (DEK) versus flunarizine (FLU) in common migraine: a multicentre double-blind study. Cephalalgia 1989;9(Suppl 10):373-4.

Ahuja GK, Verma AK. Propranolol in prophylaxis of migraine. Indian J Med Res 1985;82:263-5.

al Deeb SM, Biary N, Bahou Y, al Jaberi M, Khoja W. Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population). Headache 1992;32(9):461-2.

Albers GW, Simon LT, Hamik A, Peroutka SJ. Nifedipine versus propranolol for the initial prophylaxis of migraine. Headache 1989;29(4):215-8.

Al-Qassab HK, Findley LJ. Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo-controlled study. Cephalalgia 1993;13(2):128-31.

Andersson PG. BC-105 and deseril in migraine prophylaxis: a double-blind study. Headache 1973;13(2):68-73.

Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Kristensen TN, de Fine Olivarius B. Prophylactic treatment of classical and non-classical migraine with metoprolol: a comparison with placebo. Cephalalgia 1983;3(4):207-12.

Andersson PG, Petersen EN. Propranolol and femoxetine, a 5HT-uptake inhibitor, in migraine prophylaxis: a double-blind crossover study. Acta Neurol Scand 1981;64(4):280-8.

Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, Wozniak I. Nimodipine in migraine prophylaxis. Cephalalgia 1988;8(4):269-72.

Anthony M, Lance JW. Indomethacin in migraine. Med J Aust 1968;1(2):56-7.

Anthony M, Lance JW, Somerville B. A comparative trial of prindolol, clonidine, and carbamazepine in the interval therapy of migraine. Med J Aust 1972;1(26):1343-6.

Anthony M, Lord GD, Lance JW. Controlled trials of cimetidine in migraine and cluster headache. Headache 1978;18(5):261-4.

Arthur GP, Hornabrook RW. The treatment of migraine with BC 105 (pizotifen): a double-blind trial. N Z Med J 1971;73(464):5-9.

Autret A, De Chasteigner C. DHE methane sulfonate with programmed liberation: preliminary results of a controlled study in common migraine. Cephalalgia 1987;7(Suppl 6):451-2.

Baldrati A, Cortelli P, Procaccianti G, Gamberini G, D'Alessandro R, Baruzzi A, Sacquegna T. Propranolol and acetylsalicylic acid in migraine prophylaxis: double-blind crossover study. Acta Neurol Scand 1983;67(3):181-6.

Bánk J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache 1994;34(8):476-8.

Barrie MA, Fox WR, Weatherall M, Wilkinson MI. Analysis of symptoms of patients with headaches and their response to treatment with ergot derivatives. Q J Med 1968;37(146):319-36.

Bassi P, Brunati L, Rapuzzi B, Alberti E, Mangoni A. Low-dose flunarizine in the prophylaxis of migraine. Headache 1992;32(8):390-2.

Baxter RC, Marsden CD, Parkes JD, Zilkha KJ. Amantadine in migraine. Lancet 1972;2(774):429.

Behan PO. Prophylactic treatment for migraine: a comparison of pizotifen and clonidine. Cephalalgia 1985;5(Suppl 3):524-5.

Behan PO, Reid M. Propranolol in the treatment of migraine. Practitioner 1980;224(1340):201-3.

Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotyline, and placebo in migraine prophylaxis. Headache 1990;30(11):710-5.

Boisen E, Deth S, Hübbe P, Jansen J, Klee A, Leunbach G. Clonidine in the prophylaxis of migraine. Acta Neurol Scand 1978;58(5):288-95.

Bono G, Criscuoli M, Martignoni E, Salmon S, Nappi G. Serotonin precursors in migraine prophylaxis. Adv Neurol 1982;33:357-63.

Bonuso S, Di Stasio E, Barone P, Steardo L. Timed-release dihydroergotamine in the prophylaxis of mixed headache: a study versus amitriptyline. Cephalalgia 1983;3(Suppl 1):175-8.

Børgesen SE. Treatment of migraine with propranolol. Postgrad Med J 1976;52 (Suppl 4[0]):163-5.

Børgesen SE, Nielsen JL, Møller CE. Prophylactic treatment of migraine with propranolol: a clinical trial. Acta Neurol Scand 1974;50(5):651-6.

Bousser MG, Chick J, Fuseau E, Soisson T, Thevenet R. Combined low-dose acetylsalicylic acid and dihydroergotamine in migraine prophylaxis: a double-blind, placebo-controlled crossover study. Cephalalgia 1988;8(3):187-92.

Bradley WG, Hudgson P, Foster JB, Newell DJ. Double-blind controlled trial of a micronized preparation of flumedroxone (Demigran) in prophylaxis of migraine. Br Med J 1968;3(617):531-3.

Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients: a randomized crossover trial. J Fam Pract 1989;29(2):153-6; discussion 157-8.

Briggs RS, Millac PA. Timolol in migraine prophylaxis. Headache 1979;19(7):379-81.

Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. JAMA 1990;264(13):1711-3.

Burns C. Migraine in a rural practice (1958-1963): a five-year study of a controlled clinical trial. J Coll Gen Pract 1965;10(3):230-8.

Buscaino GA, Sorge F, Bussone G, Frediani F, et al. Preventive treatment of headache with slow-release dihydroergotamine: comparison of dosage protocols. Curr Ther Res 1991;49(6):925-35.

Bussone G, Baldini S, D'Andrea G, Cananzi A, Frediani F, Caresia L, Ferro Milone F, Boiardi A. Nimodipine versus flunarizine in common migraine: a controlled pilot trial. Headache 1987;27(2):76-9.

Cangi F, Boccuni M, Zanotti A, Mailland F, Sicuteri F. Dihydroergokryptine (DEK) in migraine prophylaxis in a double-blind study vs. methysergide. Cephalalgia 1989;9(Suppl 10):448-9.

Canonico PL, Scapagnini U, Genazzani E, Zanotti A. Dihydroergokryptine (DEK) in the prophylaxis of common migraine: double-blind clinical study vs. placebo. Cephalalgia 1989;9(Suppl 10):446-7.

Capildeo R, Rose FC. Single-dose pizotifen, 1.5 mg nocte: a new approach in the prophylaxis of migraine. Headache 1982;22(6):272-5.

Carasso RL, Peled O, Yehuda S. Flufenamic acid in prostaglandin migraine. In: Diamond S and Maliszewski M, editors. Sexual aspects of headaches. Madison (CT): International Universities Press Inc.; 1992. p. 141-7.

Carasso RL, Yehuda S. The prevention and treatment of migraine with an analgesic combination. Br J Clin Pract 1984;38(1):25-7.

Carrieri P, Orefice G, Sorge F. Indobufen, a new antiaggregant drug, in the treatment of migraine: a double-blind study compared with placebo. Cephalalgia 1985;5(Suppl 3):546-7.

Carrieri PB, Orefice G, Sorge F. A double-blind placebo-controlled trial of indobufen in the prophylaxis of migraine. Acta Neurol Scand 1988;77(6):433-6.

Carroll JD, Maclay WP. Pizotifen (BC 105) in migraine prophylaxis. Curr Med Res Opin 1975;3(2):68-71.

Carroll JD, Reidy M, Savundra PA, Cleave N, McAinsh J. Long-acting propranolol in the prophylaxis of migraine: a comparative study of two doses. Cephalalgia 1990;10(2):101-5.

Cerbo R, Casacchia M, Formisano R, Feliciani M, Cusimano G, Buzzi MG, Agnoli A. Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis. Cephalalgia 1986;6(1):15-8.

Chappell AS, Bay JM, Botzum GD. Sergolexole maleate and placebo for migraine prophylaxis. Cephalalgia 1991;11(Suppl 11):170-1.

Clarke CE, MacMillan L, Sondhi S, Wells NE. Economic and social impact of migraine. Q J Med 1996;89(1):77-84.

Cochrane Controlled Trials Register [computer program]. In: The Cochrane Library, CD-ROM for Windows (IBM-PC) version. London: BMJ Publishing Group; 1997.

Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale (NJ): L. Erlbaum Associates; 1988.

Couch JR, Bearss CM, Verhulst S. Fenoprofen in migraine prophylaxis. Headache 1987;27(5):289.

Couch JR, Hassanein RS. Migraine and depression: effect of amitriptyline prophylaxis. Trans Am Neurol Assoc 1976;101:234-7.

Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol 1979;36(11):695-9.

Dahlöf C. No clearcut longterm prophylactic effect of one month of treatment with propranolol in migraineurs. Cephalalgia 1987;7(Suppl 6):459-60.

Das SM, Ahuja GK, Narainaswamy AS. Clonidine in prophylaxis of migraine. Acta Neurol Scand 1979;60(4):214-7.

De Benedittis G, Massei R. Serotonin precursors in chronic primary headache: a double-blind cross-over study with L-5-hydroxytryptophan vs. placebo. J Neurosurg Sci 1985;29(3):239-48.

De Benedittis G, Massei R. 5-HT precursors in migraine prophylaxis: a double-blind cross-over study with L-5-hydroxytryptophan versus placebo. Clin J Pain 1986;2:123-9.

Demarez JP, Darbeau D, Cauquil J. Dihydroergotamine prophylaxis of migraine. Cephalalgia 1987;7(Suppl 6):448-51.

Dennerstein L, Laby B, Burrows GD, Hyman GJ. Headache and sex hormone therapy. Headache 1978;18(3):146-53.

Dennerstein L, Morse C, Burrows G, Oats J, Brown J, Smith M. Menstrual migraine: a double-blind trial of percutaneous estradiol. Gynecol Endocrinol 1988;2(2):113-20.

Diamond S, Freitag FG. A double-blind trial of flunarizine in migraine prophylaxis. Headache Quarterly 1993;4(2):169-72.

Diamond S, Freitag FG, Diamond ML. Flunarizine in migraine therapy. Clin Pharmacol Ther 1990;47(2):165.

Diamond S, Medina JL. Controlled study of prophylaxis of migraine with propranolol. Clin Pharmacol Ther 1975;17(2):232.

Diamond S, Medina JL. Double-blind study of propranolol for migraine prophylaxis. Headache 1976;16(1):24-7.

Diamond S, Solomon GD, Freitag FG, Mehta ND. Fenoprofen in the prophylaxis of migraine: a double-blind, placebo-controlled study. Headache 1987;27(5):246-9.

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309(6964):1286-91.

Diener HC, Scholz E, Dichgans J, Gerber WD, Jack A, Bille A, Niederberger U. Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials. Ann Neurol 1989;25(2):125-30.

Edmeads J, Findlay H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: a Canadian population survey. Can J Neurol Sci 1993;20(2):131-7.

Ekbom K. Alprenolol for migraine prophylaxis. Headache 1975;15(2):129-32.

Ekbom K, Lundberg PO. Clinical trial of LB-46 (d, 1-4-(2-hydroxy-3-isopropyl-aminopropoxy)indol: an adrenergic beta-receptor blocking agent in migraine prophylaxis. Headache 1972;12(1):15-7.

Ekbom K, Zetterman M. Oxprenolol in the treatment of migraine. Acta Neurol Scand 1977;56(2):181-4.

Elkind AH, Webster C, Herbertson RK. Efficacy of guanfacine in a double-blind parallel study for migraine prophylaxis. Cephalalgia 1989a;9(Suppl 10):369-70.

Elkind AH, Webster C, Herbertson RK. Efficacy of guanfacine in a double-blind parallel study for migraine prophylaxis. Clin Pharmacol Ther 1989b;45(2):162.

Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache 1991;31(5):298-301.

Ferrari MD, Wilkinson M, Hirt D, Lataste X, Notter M. Efficacy of ICS 205-930, a novel 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist, in the prevention of migraine attacks: a complex answer to a simple question. Pain 1991;45(3):283-91.

Fioroni L, Sances G, Martignoni E, Facchinetti F, Nappi G, Genazzani AR. Perimenstrual headache prophylaxis with dihydroergokriptine. Cephalalgia 1991;11(Suppl 11):199-200.

Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons, Inc.; 1981.

Formisano R, Falaschi P, Cerbo R, Proietti A, Catarci T, D'Urso R, Roberti C, Aloise V, Chiarotti F, Agnoli A. Nimodipine in migraine: clinical efficacy and endocrinological effects. Eur J Clin Pharmacol 1991;41(1):69-71.

Forssman B, Henriksson KG, Johannsson V, Lindvall L, Lundin H. Propranolol for migraine prophylaxis. Headache 1976;16(5):238-45.

Forssman B, Henriksson KG, Kihlstrand S. A comparison between BC 105 and methysergide in the prophylaxis of migraine. Acta Neurol Scand 1972;48(2):204-12.

Forssman B, Lindblad CJ, Zbornikova V. Atenolol for migraine prophylaxis. Headache 1983;23(4):188-90.

Frediani F, Grazzi L, Zanotti A, Mailland F, Zappacosta BM, Bussone G. Dihydroergokryptine versus dihydroergotamine in migraine prophylaxis: a double-blind clinical trial. Cephalalgia 1991;11(3):117-21.

Freitag FG, Diamond S. Nadolol and placebo comparison study in the prophylactic treatment of migraine. J Am Osteopath Assoc 1984;84(4):343-7.

Freitag FG, Diamond S, Diamond M. A placebo-controlled trial of flunarizine in migraine prophylaxis. Cephalalgia 1991;11(Suppl 11):157-8.

Frenken CW, Nuijten ST. Flunarizine, a new preventive approach to migraine: a double-blind comparison with placebo. Clin Neurol Neurosurg 1984;86(1):17-20.

Gawel M. A double-blind, cross-over study of nimodipine versus pizotyline in common and classical migraine. Cephalalgia 1987;7(Suppl 6):453-4.

Gawel M, Kreeft J, Nelson R, Simard D. Flunarizine is comparable to propanolol in the prophylaxis of migraine with and without aura. Cephalalgia 1991;11(Suppl 11):156.

Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. Can J Neurol Sci 1992;19(3):340-5.

Gelmers HJ. Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache 1983;23(3):106-9.

Gennari C, Chierichetti MS, Gonnelli S, Vibelli C, Montagnani M, Piolini M. Migraine prophylaxis with salmon calcitonin: a cross-over double-blind, placebo-controlled study. Headache 1986;26(1):13-6.

Gerber WD, Diener HC, Scholz E, Niederberger U. Responders and non-responders to metoprolol, propranolol, and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. Cephalalgia 1991;11(1):37-45.

Gerber WD, Schellenberg R, Thom M, Haufe C, Bolsche F, Wedekind W, Niederberger U, Soyka D. Cyclandelate versus propranolol in the prophylaxis of migraine: a double-blind placebo-controlled study. Funct Neurol 1995;10(1):27-35.

Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 1973;36(4):684-90.

Grotemeyer KH, Scharafinski HW, Schlake HP, Husstedt IW. Acetylsalicylic acid vs. metoprolol in migraine prophylaxis: a double-blind cross-over study. Headache 1990;30(10):639-41.

Grotemeyer KH, Schlake HP, Husstedt IW. Etilefrine pivalate vs. dihydroergotamine and flunarizine in prophylactic treatment of migraine in patients with low blood pressure: a randomized double-blind study. Cephalalgia 1989;9(Suppl 10):433-4.

Grotemeyer KH, Schlake HP, Husstedt IW, Rolf LH. Metoprolol versus flunarizine: a double blind cross-over study. Cephalalgia 1987;7(Suppl 6):465-6.

Hasselblad V. Meta-analysis of multitreatment studies. Med Decis Making 1998;18:37-43.

Havanka-Kanniainen H, Hokkanen E, Myllylä V. Efficacy of nimodipine in comparison with pizotifen (Sandomigrin) in the prophylaxis of migraine. Cephalalgia 1985a;5(Suppl 3):530-1.

Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in the prophylaxis of migraine. Cephalalgia 1985b;5(1):39-43.

Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in comparison with pizotifen in the prophylaxis of migraine. Cephalalgia 1987a;7(1):7-13.

Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Long-acting propranolol in migraine prophylaxis. Clin Pharmacol Ther 1987b;41(2):203.

Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Long-acting propranolol in the prophylaxis of migraine: comparison of the daily doses of 80 mg and 160 mg. Headache 1988;28(9):607-11.

Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. Cephalalgia 1988;8(Suppl 7):1-96.

Hedman C, Andersen AR. Effects of the B_1-selective adrenoceptor antagonist metoprolol on the symptomatology of classic migraine attacks. Cephalalgia 1987;7(Suppl 6):461-2.

Hedman C, Andersen AR, Andersson PG, Gilhus NE, Kangasniemi P, Olsson JE, Strandman E, Nestvold K, Olesen J. Symptoms of classic migraine attacks: modifications brought about by metoprolol. Cephalalgia 1988;8(4):279-84.

Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 1992;12(2):81-4.

Herrmann WM, Horowski R, Dannehl K, Kramer U, Lurati K. Clinical effectiveness of lisuride hydrogen maleate: a double-blind trial versus methysergide. Headache 1977;17(2):54-60.

Herrmann WM, Krištof M, Sastre M, Sastre M. Preventive treatment of migraine headache with a new isoergolenyl derivative. J Int Med Res 1978;6(6):476-82.

Hesse J, Møgelvang B, Simonsen H. Acupuncture versus metoprolol in migraine prophylaxis: a randomized trial of trigger point inactivation. J Intern Med 1994;235(5):451-6.

Holroyd KA, France JL, Cordingley GE, Rokicki LA, Kvaal SA, Lipchik GL, McCool HR. Enhancing the effectiveness of relaxation-thermal biofeedback training with propranolol hydrochloride. J Consult Clin Psychol 1995;63(2):327-30.

Hübbe P. The prophylactic treatment of migraine with an antiserotonin pizotifen. Acta Neurol Scand 1973;49(1):108-14.

Hudgson P, Foster JB, Newell DJ. Controlled trial of demigran in the prophylaxis of migraine. Br Med J 1967;2(544):91-3.

Hughes RC, Foster JB. BC 105 in the prophylaxis of migraine. Curr Ther Res Clin Exp 1971;13(1):63-8.

International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine. 1st ed. Cephalalgia 1991;11(1-12).

Jacobs H. A trial of opipramol in the treatment of migraine. J Neurol Neurosurg Psychiatry 1972;35(4):500-4.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clin Trials 1996;17(1):1-12.

Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 1994;44(4):647-51.

Johannsson V, Nilsson LR, Widelius T, Javerfalk T, Hellman P, Akesson JA, Olerud B, Gustafsson CL, Raak A, Sandahl G, et al. Atenolol in migraine prophylaxis: a double-blind cross-over multicentre study. Headache 1987;27(7):372-4.

Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. Br Med J (Clin Res Ed) 1985;291(6495):569-73.

Johnson RH, Hornabrook RW, Lambie DG. Comparison of mefenamic acid and propranolol with placebo in migraine prophylaxis. Acta Neurol Scand 1986;73(5):490-2.

Jorgensen PB, Weightman D, Foster JB. Comparison of migraleve and buclizine in prophylaxis of migraine. Curr Ther Res Clin Exp 1974;16(12):1276-80.

Kallanranta T, Hakkarainen H, Hokkanen E, Tuovinen T. Clonidine in migraine prophylaxis. Headache 1977;17(4):169-72.

Kallos P, Kallos-Deffner L. Clinical and experimental evaluation of a new ergot-derivative (ergostine) in the treatment of migraine. Headache 1971;11(2):68-73.

Kangasniemi P. Placebo, 1-isopropylnoradrenochrome-5-monosemicarbazono, and pizotifen in migraine prophylaxis. Headache 1979;19(4):219-22.

Kangasniemi P, Andersen AR, Andersson PG, Gilhus NE, Hedman C, Hultgren M, Vilming S, Olesen J. Classic migraine: effective prophylaxis with metoprolol. Cephalalgia 1987;7(4):231-8.

Kangasniemi P, Falck B, Långvik VA, Hyyppa MT. Levotryptophan treatment in migraine. Headache 1978;18(3):161-5.

Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine: a double-blind study. Cephalalgia 1984;4(2):91-6.

Kangasniemi PJ, Nyrke T, Lang AH, Petersen E. Femoxetine--a new 5-HT uptake inhibitor--and propranolol in the prophylactic treatment of migraine. Acta Neurol Scand 1983;68(4):262-7.

Kangasniemi P, Tokola R. Flunarizine in the prophylaxis of migraine patients without aura. Cephalalgia 1989;9(Suppl 10):425.

Kåss B, Nestvold K. Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine: a comparative trial. Acta Neurol Scand 1980;61(6):351-6.

Kjærsgåard Rasmussen MJ, Holt Larsen B, Borg L, Soelberg Sørensen P, Hansen PE. Tolfenamic acid versus propranolol in the prophylactic treatment of migraine. Acta Neurol Scand 1994;89(6):446-50.

Klapper J. Divalproex sodium for migraine prophylaxis. Unpublished manuscript. 1996.

Klapper JA. An open label cross-over comparison of divalproex sodium and propranolol HCl in the prevention of migraine headaches. Headache Quarterly 1994;5(1):50-3.

Krakowski AJ, Engisch R. A new agent for chemotherapy of migraine headaches: a controlled study. Psychosomatics 1973;14(5):302-8.

Kuritzky A, Hering R. Prophylactic treatment of migraine with long acting propranolol: a comparison with placebo. Cephalalgia 1987;7(Suppl 6):457-8.

Lamsudin R, Sadjimin T. Comparison of the efficacy between flunarizine and nifedipine in the prophylaxis of migraine. Headache 1993;33(6):335-8.

Lance JW, Anthony M. Clinical trial of a new serotonin antagonist, BC105, in the prevention of migraine. Med J Aust 1968;1(2):54-5.

Lance JW, Fine RD, Curran DA. An evaluation of methysergide in the prevention of migraine and other vascular headaches. Med J Aust 1963;(June):814-8.

Langohr HD, Gerber WD, Koletzki E, Mayer K, Schroth G. Clomipramine and metoprolol in migraine prophylaxis: a double-blind crossover study. Headache 1985;25(2):107-13.

Lawrence ER, Hossain M, Littlestone W. Sanomigran for migraine prophylaxis: controlled multicenter trial in general practice. Headache 1977;17(3):109-12.

Leandri M, Rigardo S, Schizzi R, Parodi CI. Migraine treatment with nicardipine. Cephalalgia 1990;10(3):111-6.

Lindegaard KF, Övrelid L, Sjaastad O. Naproxen in the prevention of migraine attacks: a double-blind placebo-controlled cross-over study. Headache 1980;20(2):96-8.

Loh L, Nathan PW, Schott GD, Zilkha KJ. Acupuncture versus medical treatment for migraine and muscle tension headaches. J Neurol Neurosurg Psychiatry 1984;47(4):333-7.

Louis P. A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. Headache 1981;21(6):235-9.

Louis P, Schoenen J, Hedman C. Metoprolol v. clonidine in the prophylactic treatment of migraine. Cephalalgia 1985a;5(3):159-65.

Louis P, Schoenen J, Hedman C. Metoprolol versus clonidine in the prophylactic treatment of migraine. Cephalalgia 1985b;5(Suppl 3):520-1.

Louis P, Spierings EL. Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: a double-blind study. Cephalalgia 1982;2(4):197-203.

Lücking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. Cephalalgia 1988;8(Suppl 8):21-6.

Ludin HP. A comparative trial with flunarizine and propranolol in migraine. Cephalalgia 1987;7(Suppl 6):469-70.

Ludin HP. Flunarizine and propranolol in the treatment of migraine. Headache 1989;29(4):219-24.

Lundberg PO. Prophylactic treatment of migraine with flumedroxone. Acta Neurol Scand 1969;45(3):309-26.

Malvea BP, Gwon N, Graham JR. Propranolol prophylaxis of migraine. Headache 1973;12(4):163-7.

Markley HG, Cheronis JC, Piepho RW. Verapamil in prophylactic therapy of migraine. Neurology 1984;34(7):973-6.

Martelletti P, Bussone G, Centonze V, Ferrari A, Frediani F, Giacovazzo M, Micieli G, Nappi G, Polito A, Sternieri E. Activity of cromolyn sodium in dietary migraine: a double-blind placebo-controlled multicenter trial. Cephalalgia 1991;11(Suppl 11):148-9.

Martucci N, Manna V, Mattesi P, Troiani G, Manzoni GC, Lanfranchi M, Bono G, Micieli G. Ergot derivatives in the prophylaxis of migraine: a multicentric study with a timed-release dihydroergotamine formulation. Cephalalgia 1983;3(Suppl 1):151-5.

Masel BE, Chesson AL, Peters BH, Levin HS, Alperin JB. Platelet antagonists in migraine prophylaxis: a clinical trial using aspirin and dipyridamole. Headache 1980;20(1):13-8.

Mastrosimone F, Iaccarino C, de Caterina G. Efficacy and tolerance of cyclandelate versus pizotifen in the prophylaxis of migraine. J Med 1992;23(1):1-16.

Mathew NT. 5-Hydroxytryptophane in the prophylaxis of migraine: a double-blind study. Headache 1978;18:111.

Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache 1981;21(3):105-9.

Mathew NT, Saper JR, Silberstein SD, Rankin L, Markley HG, Solomon S, Rapoport AM, Silber CJ, Deaton RL. Migraine prophylaxis with divalproex. Arch Neurol 1995;52(3):281-6.

Matts SG. Metoclopramide in the treatment of migraine. Practitioner 1974;212(1272):887-90.

McArthur JC, Marek K, Pestronk A, McArthur J, Peroutka SJ. Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. Neurology 1989;39(2 Pt 1):284-6.

Mendenopoulos G, Manafi T, Logothetis I, Bostantjopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia 1985;5(1):31-7.

Mentenopoulos G, Manafi T, Logothetis J, Bostantzopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia 1985;5(Suppl 2):135-40.

Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache 1983;23(6):266-77.

Micieli G, Cavallini A, Martignoni E, Covelli V, Facchinetti F, Nappi G. Effectiveness of salmon calcitonin nasal spray preparation in migraine treatment. Headache 1988;28(3):196-200.

Micieli G, Trucco M, Agostinis C, Mancuso A, Papalia F, et al. Nimodipine vs. pizotifen in common migraine: results of a double-blind cross-over trial. Cephalalgia 1985;5(Suppl 3):532-533.

Migraine-Nimodipine European Study Group (MINES). European multicenter trial of nimodipine in the prophylaxis of classic migraine (migraine with aura). Headache 1989a;29(10):639-42.

Migraine-Nimodipine European Study Group (MINES). European multicenter trial of nimodipine in the prophylaxis of common migraine (migraine without aura). Headache 1989b;29(10):633-8.

Mikkelsen BM, Falk JV. Prophylactic treatment of migraine with tolfenamic acid: a comparative double-blind crossover study between tolfenamic acid and placebo. Acta Neurol Scand 1982;66(1):105-11.

Mikkelsen B, Pedersen KK, Christiansen LV. Prophylactic treatment of migraine with tolfenamic acid, propranolol, and placebo. Acta Neurol Scand 1986;73(4):423-7.

Minervini MG, Pinto K. Captopril relieves pain and improves mood depression in depressed patients with classical migraine. Cephalalgia 1987;7(Suppl 6):485-6.

Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Controlled Clin Trials 1995;16(1):62-73.

Mondrup K, Møller CE. Prophylactic treatment of migraine with clonidine: a controlled clinical trial. Acta Neurol Scand 1977;56(5):405-12.

Mongini F, Bona G, Garnero M, Gioria A. Efficacy of meclofenamate sodium versus placebo in headache and craniofacial pain. Headache 1993;33(1):22-8.

Monro J, Carini C, Brostoff J. Migraine is a food-allergic disease. Lancet 1984;2(8405):719-21.

Monro P, Swade C, Coppen A. Double-blind comparative study of mianserin vs. placebo in the prophylaxis of migraine. Clin Neuropharmacol 1984;7(Suppl 1):654-655.

Monro P, Swade C, Coppen A. Mianserin in the prophylaxis of migraine: a double-blind study. Acta Psychiatr Scand 1985;72(Suppl 320):98-103.

Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. Lancet 1988;2(8604):189-92.

Nanda RN, Arthur GP, Johnson RH, Lambie DG. Cimetidine in the prophylaxis of migraine. Acta Neurol Scand 1980;62(2):90-5.

Nanda RN, Johnson RH, Gray J, Keogh HJ, Melville ID. A double-blind trial of acebutolol for migraine prophylaxis. Headache 1978;18(1):20-2.

Nappi G, Sandrini G, Granella F, Ruiz L, Cerutti G, Facchinetti F, Blandini F, Manzoni GC. A new 5-HT_2 antagonist (ritanserin) in the treatment of chronic headache with depression: a double-blind study vs. amitriptyline. Headache 1990;30(7):439-44.

Nappi G, Sandrini G, Savoini G, Cavallini A, de Rysky C, Micieli G. Comparative efficacy of cyclandelate versus flunarizine in the prophylactic treatment of migraine. Drugs 1987;33(Suppl 2):103-98.

Nattero G, Biale L, Savi L. Lisuride and pizotifen in the treatment of migraine without aura. Cephalalgia 1991; p. 218-9.

Neuman M, Demarez JP, Harmey JL, Le Bastard B, Cauquil J. Prevention of migraine attacks through the use of dihydroergotamine. Int J Clin Pharmacol Res 1986;6(1):11-3.

Noone JF. Clomipramine in the prevention of migraine. J Int Med Res 1980;8(Suppl 3):49-52.

Olerud B, Gustavsson CL, Furberg B. Nadolol and propranolol in migraine management. Headache 1986;26(10):490-3.

Olsson JE, Behring HC, Forssman B, Hedman C, Hedman G, Johansson F, Kinnman J, Palhagen SE, Samuelsson M, Strandman E. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. Acta Neurol Scand 1984;70(3):160-8.

O'Neill BP, Mann JD. Aspirin prophylaxis in migraine. Lancet 1978;2(8101):1179-81.

Opavsky J. Magnesium and its combination with cinnarizine in the long-term treatment of headache. Acta Univ Palacki Olomuc Fac Med 1991;131:157-64.

Orholm M, Honoré PF, Zeeberg I. A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. Acta Neurol Scand 1986;74(3):235-9.

Orholm M, Le Fevre P. Prophylactic treatment of migraine with femoxetine: a randomized comparison with placebo. Cephalalgia 1985;5(Suppl 3):516-7.

Osterhaus JT, Gutterman DL, Plachetka JR. Healthcare resource and lost labour costs of migraine headache in the U.S. Pharmacoeconomics 1992;2(1):67-76.

Osterman PO. A comparison between placebo, pizotifen, and 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2.3.5.6-tetrahydroindol (Divascan) in migraine prophylaxis. Acta Neurol Scand 1977;56(1):17-28.

Palferman TG, Gibberd FB, Simmonds JP. Prophylactic propranolol in the treatment of headache. Br J Clin Pract 1983;37(1):28-9.

Pedersen E, Møller CE. Methysergide in migraine prophylaxis. Clin Pharmacol Ther 1966;7(4):520-6.

Penzien D, Johnson C, Carpenter D, Holroyd K. Drug vs. behavioral treatment of migraine: long-acting propranolol vs. home-based self-management training. Headache 1990;30(5):300.

Penzien D, Johnson C, Seville J, Rubman S, Boggess JT, Rains JC. Interrelationships among daily and global self-report measures of headache. Headache Quarterly 1994;5:8-14.

Pini LA, Ferrari A, Guidetti G, Galetti G, Sternieri E. Influence of flunarizine on the altered electronystagmographic (ENG) recordings in migraine. Cephalalgia 1985;5(Suppl 2):173-5.

Pita E, Higueras A, Bolaños J, Perez N, Mundo A. Propranolol and migraine: a clinical trial. Arch Farmacol Toxicol 1977;3(3):273-8.

Pradalier A, Serratrice G, Collard M, Hirsch E, Feve J, Masson M, Masson C, Dry J, Koulikovsky G, Nguyen G, et al. Double-blind placebo-controlled study of the use of long-acting propranolol in migraine prophylaxis. Cephalalgia 1989a;9(Suppl 10):367-8.

Pradalier A, Serratrice G, Collard M, Hirsch E, Feve J, Masson M, Masson C, Dry J, Koulikovsky G, Nguyen G, et al. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia 1989b;9(4):247-53.

Presthus J. BC 105 and methysergide (Deseril) in migraine prophylaxis. Acta Neurol Scand 1971;47(4):514-8.

Rascol A, Montastruc JL, Rascol O. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. Cephalalgia 1985;5(Suppl 3):542.

Rascol A, Montastruc JL, Rascol O. Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine. Headache 1986;26(2):83-5.

Rasmussen BK, Jensen R, Olesen J. Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 1992;46(4):443-6.

Rompel H, Bauermeister PW. Aetiology of migraine and prevention with carbamazepine (Tegretol): results of a double-blind, cross-over study. S Afr Med J 1970;44(4):75-80.

Ryan RE. Double-blind crossover comparison of BC-105, methysergide, and placebo in the prophylaxis of migraine headache. Headache 1968;8(3):118-26.

Ryan RE. BC-105, a new preparation for the interval treatment of migraine: a double blind evaluation compared with a placebo. Headache 1971;11(1):6-18.

Ryan RE. A controlled study of the effect of oral contraceptives on migraine. Headache 1978;17(6):250-2.

Ryan RE Sr. Comparative study of nadolol and propranolol in prophylactic treatment of migraine. Am Heart J 1984;108(4 Pt 2):1156-9.

Ryan RE Sr, Diamond S, Ryan RE Jr. Double-blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache 1975;15(3):202-10.

Ryan RE Sr, Ryan RE Jr. Clonidine--its use in migraine therapy. Headache 1975;14(4):190-2.

Ryan RE Sr, Ryan RE Jr. The effects of clonidine in the prophylactic treatment of migraine. Headache 1975;14(4):199-212.

Ryan RE Sr, Ryan RE Jr. Migraine prophylaxis: a new approach. Laryngoscope 1981;91(9 Pt 1):1501-6.

Ryan RE Sr, Ryan RE Jr, Sudilovsky A. Nadolol and placebo comparison study in the prophylactic treatment of migraine. Panminerva Med 1982;24(2):89-94.

Ryan RE Sr, Ryan RE Jr, Sudilovsky A. Nadolol: its use in the prophylactic treatment of migraine. Headache 1983;23(1):26-31.

Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. Headache 1990;30(11):705-9.

Sances G, Martignoni E, Rosettino G, Fioroni L, Montorsi S, Runge I, Nappi G. Lisuride in menstrual migraine prophylaxis. Cephalalgia 1989;9(Suppl 10):444-5.

Sandrini G, Savoini G, Cavallini A, Pacchetti C, Micieli G, Nappi G. Efficacy of cyclandelate in migraine prophylaxis. Cephalalgia 1987;7(Suppl 6):481-2.

Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 1994;34(9):497-502.

Sargent J, Solbach P, Damasio H, Baumel B, Corbett J, Eisner L, Jessen B, Kudrow L, Mathew N, Medina J. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. Headache 1985;25(6):320-4.

Scopa J, Jorgensen PB, Foster JB. Migraleve in the prophylaxis of migraine. Curr Ther Res Clin Exp 1974;16(12):1270-5.

Shafar J, Tallett ER, Knowlson PA. Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet 1972;1(747):403-7.

Shekelle RB, Ostfeld AM. Methysergide in the migraine syndrome. Clin Pharmacol Ther 1964;5:201-4.

Shimell CJ, Fritz VU, Levien SL. A comparative trial of flunarizine and propranolol in the prevention of migraine. S Afr Med J 1990;77(2):75-7.

Shukla R, Garg RK, Nag D, Ahuja RC. Nifedipine in migraine and tension headache: a randomised double-blind crossover study. J Assoc Physicians India 1995;43(11):770-2.

Sicuteri F. Prophylactic and therapeutic properties of 1-methyl-lysergic acid butanolamide in migraine. Int Arch Allergy Appl Immunol 1959;15:300-7.

Sicuteri F. The ingestion of serotonin precursors (L-5-hydroxytryptophan and L-tryptophan) improves migraine headache. Headache 1973;13(1):19-22.

Sjaastad O, Stensrud P. Appraisal of BC-105 in migraine prophylaxis. Acta Neurol Scand 1969;45(5):594-600.

Sjaastad O, Stensrud P. 2-(2.6-dichlorophenylamino)-2-imidazoline hydrochloride (ST 155 or Catapresan) as a prophylactic remedy against migraine. Acta Neurol Scand 1971;47(1):120-2.

Sjaastad O, Stensrud P. Clinical trial of a beta-receptor blocking agent (LB 46) in migraine prophylaxis. Acta Neurol Scand 1972;48(1):124-8.

Smits MG, van der Meer YG, Pfeil JP, Rijnierse JJ, Vos AJ. Perimenstrual migraine: effect of Estraderm TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. Headache 1994;34(2):103-6.

Solomon GD. Verapamil and propranolol in migraine prohylaxis: a double-blind crossover study. Headache 1986;26:325.

Solomon GD, Freitag FG, Mehta N, Diamond S. Fenoprofen calcium in migraine prophylaxis: a double-blind, placebo-controlled study. Cephalalgia 1987;7(Suppl 6):473-4.

Solomon GD, Kunkel RS. Flurbiprofen in the prophylaxis of migraine. Cephalalgia 1991;11(Suppl 11):161.

Solomon GD, Kunkel RS. Flurbiprofen in the prophylaxis of migraine. Cleve Clin J Med 1993;60(1):43-8.

Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine: a double-blind, placebo-controlled study. JAMA 1983;250(18):2500-2.

Somerville BW, Hermann WW. Migraine prophylaxis with lisuride: a double-blind study of lisuride versus placebo. Headache 1976;16:85-6.

Somerville BW, Herrmann WM. Migraine prophylaxis with lisuride hydrogen maleate: a double-blind study of lisuride versus placebo. Headache 1978;18(2):75-9.

Sørensen PS. Prophylactic effects of flunarizine versus metoprolol in migraine. Cephalalgia 1989;9(Suppl 10):355-6.

Sørensen PS, Hansen K, Olesen J. Flunarizine in common migraine prophylaxis: a double-blind cross-over study. Cephalalgia 1985;5(3):540-1.

Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia 1986;6(1):7-14.

Sørensen PS, Larsen BH, Rasmussen MJ, Kinge E, Iversen H, Alslev T, Nohr P, Pedersen KK, Schroder P, Lademann A, et al. Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. Headache 1991;31(10):650-7.

Sovak M, Kunzel M, Sternbach RA, Dalessio DJ. Mechanism of the biofeedback therapy of migraine: volitional manipulation of the psychophysiological background. Headache 1981;21(3):89-92.

Soyka D, Oestreich W. Therapeutic effectiveness of flunarizine and propranolol in the interval therapy of migraine. Cephalalgia 1987;7(Suppl 6):467-8.

Standnes B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. Cephalalgia 1982;2(3):165-70.

Steardo L, Bonuso S, Di Stasio E, Marano E. Selective and non-selective beta-blockers: are both effective in prophylaxis of migraine? A clinical trial versus methysergide. Acta Neurol (Napoli) 1982;4(3):196-204.

Steardo L, Marano E, Barone P, Denman DW, Monteleone P, Cardone G. Prophylaxis of migraine attacks with a calcium-channel blocker: flunarizine versus methysergide. J Clin Pharmacol 1986;26(7):524-8.

Steiner TJ, Cook GE, Joseph R, Clifford Rose F. Double-blind dose-ranging comparison of metoprolol with placebo in the prophylaxis of classical and common migraine. Cephalalgia 1985;5(Suppl 3):558-9.

Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. Headache 1988;28(1):15-23.

Stellar S, Ahrens SP, Meibohm AR, Reines SA. Migraine prevention with timolol: a double-blind crossover study. JAMA 1984;252(18):2576-80.

Stensrud P, Sjaastad O. Clinical trial of a new anti-bradykinin, anti-inflammatory drug, ketoprofen (19.583 r.p.) in migraine prophylaxis. Headache 1974;14(2):96-100.

Stensrud P, Sjaastad O. Clonidine (Catapresan)-double-blind study after long-term treatment with the drug in migraine. Acta Neurol Scand 1976a;53(3):233-6.

Stensrud P, Sjaastad O. Short-term clinical trial of propranolol in racemic form (Inderal), D-propranolol, and placebo in migraine. Acta Neurol Scand 1976b;53(3):229-32.

Stensrud P, Sjaastad O. Clonazepam (rivotril) in migraine prophylaxis. Headache 1979;19(6):333-4.

Stensrud P, Sjaastad O. Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine. Headache 1980a;20(4):204-7.

Stensrud P, Sjaastad O. Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine. Ups J Med Sci Suppl 1980b;31:37-40.

Stensrud P, Skaug OE, Sjaastad O. Clinical trial of MY-25 (1-methyl-ergotamine-bitartrate) in migraine prophylaxis. Headache 1971;11(3):128-31.

Sternieri E, Bussone G, Manzoni GC, Martucci N, Nappi G. Lornoxicam, a new non-steroidal anti-inflammatory drug, in migraine prophylaxis: a double-blind multicenter study. Cephalalgia 1991;11(Suppl 11):154-5.

Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence: a review of population-based studies. Neurology 1994;44(6 Suppl 4):S17-23.

Stieg RL. Double-blind study of belladonna-ergotamine-phenobarbital for interval treatment of recurrent throbbing headache. Headache 1977;17(3):120-4.

Sudilovsky A, Elkind AH, Ryan RE Sr, Saper JR, Stern MA, Meyer JH. Comparative efficacy of nadolol and propranolol in the management of migraine. Headache 1987;27(8):421-6.

Sudilovsky A, Stern M, Meyer JH. Comparative efficacy of nadolol and propranolol in the prophylaxis of migraine. Headache 1986a;26(6):311-2.

Sudilovsky A, Stern MA, Meyer JH. Nadolol: the benefits of an adequate trial duration in the prophylaxis of migraine. Headache 1986b;26:325.

Sulman FG, Pfeifer Y, Superstine E. Preventive treatment of serotonin-migraine with 1,3,4,14b-tetrahydro-2,7-dimethyl-2H-dibenzo(b,f)pyrazino-(1,2--d)-(,4)-oxazepine hydrogen maleate (Org GC 94): a double-blind study. Arzneimittelforschung 1981;31(1):109-12.

Szekely B, Merryman S, Croft H, Post G. Prophylactic effects of naproxen sodium on perimenstrual headache: a double-blind, placebo-controlled study. Cephalalgia 1989;9(Suppl 10):452-3.

Tfelt-Hansen P, Standnes B, Kangasniemi P, Hakkarainen H, Olesen J. Timolol vs. propranolol vs. placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand 1984;69(1):1-8.

Thomas M, Behari M, Ahuja GK. Flunarizine in migraine prophylaxis: an Indian trial. Headache 1991;31(9):613-5.

Titus F, Dávalos A, Alom J, Codina A. 5-Hydroxytryptophan versus methysergide in the prophylaxis of migraine: randomized clinical trial. Eur Neurol 1986;25(5):327-9.

Titus F, Dávalos A, Codina A. 5-hydroxytryptophan versus methysergide in the prophylaxis of migraine: a randomized clinical trial. Cephalalgia 1985;5(Suppl 3):518-9.

Vilming S, Standnes B, Hedman C. Metoprolol and pizotifen in the prophylactic treatment of classical and common migraine: a double-blind investigation. Cephalalgia 1985;5(1):17-23.

Viswanathan KN, Rajendiran C, Manohar DS, Balaraman VT. Cinnarizine-propranalol in migraine prophylaxis: a double-blind clinical study. Cephalalgia 1991;11(Suppl 11):166-7.

Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology 1972;22(4):366-9.

Welch KM. Naproxen sodium in the treatment of migraine. Cephalalgia 1986;6(Suppl 4):85-92.

Welch KM, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. Neurology 1985;35(9):1304-10.

Wessely P, Baumgartner C, Klingler D, Kreczi J, Meyerson N, Sailer L, Saltuari L, Schutt P. Preliminary results of a double-blind study with the new migraine prophylactic drug Gabapentin. Cephalalgia 1987;7(Suppl 6):477-8.

Widerøe TE, Vigander T. Propranolol in the treatment of migraine. Br Med J 1974;2(921):699-701.

Wilkinson M. Preliminary report on the use of clonidine (Boehringer Ingelheim) in the treatment of migraine. Res Clin Stud Headache 1970;3:315-20.

Wilkinson M, Agnoli A, Gerber WD, Grotemeyer KH, Langer H, Runge I. Multicentre migraine study. Cuvalitr (lisuride 0.025mg) vs. lisuride 0.05 mg tds. Cephalalgia 1989;9(Suppl 10):353-4.

Wörz R, Reinhardt-Benmalek B, Foeh M, Grotemeyer KH, Scharafinski HW. Migraine prophylaxis with bisoprolol. Headache Quarterly 1992;3(1):64-72.

Wörz R, Reinhardt-Benmalek B, Grotmeyer KH, Foh M. Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura: a randomized double-blind cross-over multicenter study. Cephalalgia 1991;11(Suppl 11):152-3.

Zeeberg I, Orholm M, Nielsen JD, Honoré PL, Larsen JJ. Femoxetine in the prophylaxis of migraine: a randomised comparison with placebo. Acta Neurol Scand 1981;64(6):452-9.

Ziegler DK, Ellis DJ. Naproxen in prophylaxis of migraine. Arch Neurol 1985;42(6):582-4.

Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis: a comparison of propranolol and amitriptyline. Arch Neurol 1987;44(5):486-9.

Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J. Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. Arch Neurol 1993;50(8):825-30.

Zuddas A. Usefulness of lisuride on menstrual migraine in a double-blind trial. Cephalalgia 1985;5(Suppl 3):514-5.

List of Evidence Tables

Table		*Pages*
1.	Study descriptions and results	125-244
2.	Efficacy of alpha-2 agonists	245-248
3.	Efficacy of anticonvulsants	249-251
4.	Efficacy of antidepressants	253-255
5.	Efficacy of beta-blockers	257-270
6.	Efficacy of calcium antagonists	271-277
7.	Efficacy of ergots	279-281
8.	Efficacy of methysergide	283-285
9.	Efficacy of NSAIDs	287-291
10.	Efficacy of other serotoninergic agents	293-299
11.	Efficacy of other treatments	301-302
12.	Adverse events	303-415

Evidence Table 1: Study Descriptions and Results[1, 2]

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Adam, Gore, and Price, 1978	CrOv QS: 3 (r, db, dd)	N = 96 Age: 38 (range: 11-67) 84% female Chron: N/S Migraine; ≥ 1 paroxys-mal HA/mo for ≥ 3 mos, including visual or gastro-intestinal problems Rec: GP clinic in Edinburgh, Scotland	***Placebo:*** n = 70* ***Clonidine (Dixarit®):*** 0.025 mg (1 tab), 3x/day; dose could be increased as soon as needed to a maximum of 0.050 mg, 3x/day; n = 70* No baseline period; two 6-mo treatment periods for 2 groups of pts (Grp 1 started with active drug, then switched to placebo after 6 mos; Grp 2 started with placebo, then switched to active drug after 6 mos); no washout; no follow-up Nothing on acute meds	***HA frequency:*** No. of HAs per assessment period; analyzed in 3-mo periods ***HA intensity:*** Obtained from pt's recordings of whether HAs required treatment or caused functional disability. Recorded on 4-point scale (always, usually, sometimes, never). HAs coded as less, equally, or more severe (-1, 0, 1) than baseline HAs	Between-group results were reported as the difference in ***HA frequency*** (response on clonidine minus response on placebo, measured at the end of each 6 mos). Both treatments reduced ***HA frequency*** equally well, as median ***frequency*** difference was 0 in each of Groups 1 and 2. The median ***HA frequency*** for all 70 pts diminished from 9 HAs/3mos at baseline to 3 HAs/3 mos at the end of both 6-mo periods.	Dropouts: 26 (27%), 3 due to AEs (2 clonidine, 1 placebo) Efficacy results based on frequency and intensity, obtained and *defined* by physician during assessment periods at 1, 2, 3, & 6 mos for both 6-mo periods. These findings were compared with baseline ratings (for 3 mos prior to treatment) gathered by physician at initial visit

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Adly, Straumanis, and Chesson, 1992	SPPG QS: 3 (r, db, dd)	N = 32 Age: N/S % female N/S Migraine (physician diagnosis and Ad Hoc); ≥ 1 severe, disabling attack/wk Chron: N/S Rec: News-paper ad	***Placebo:*** n = 9 ***Fluoxetine:*** 20 mg every other day for first 4 wks; at that point, dose increased to 20 mg/day for those patients who showed minimal or no improvement during first 4 wks; these patients assessed again 14 days later, and dose increased to 40 mg/day for patients still not improving (all increases in dosage subject to tolerance); n = 9 2-wk baseline period; 8-wk treatment period; no follow-up Use of acute meds permitted	***HA index:*** Calculated on basis of patient diary data on intensity (graded on scale of 1-10), duration, disability, accompanying symptoms, and amount of acute med taken; formula used not described; score calculated for each day, and daily scores then summed for each 2-wk period	***HA index:*** During wks 7-8 of treatment, median HA index scores in the fluoxetine group were significantly lower than they had been at baseline ($p<0.01$); median scores in the placebo group did not decrease significantly compared to baseline (no p-value reported). There was no significant difference in median baseline HA index scores between the two groups, but post-treatment (wks 7-8) median scores were significantly lower in the fluoxetine group than in the placebo group ($p<0.05$). The median baseline HA index score in the fluoxetine group was 32; during wks 7-8, it was 6. The corresponding scores in the placebo group were 35 and 24, respectively (ranges not reported).	Dropouts: 14 (44%), 1 due to AEs (associated with fluoxetine) High dropout rate 2 patients in the fluoxetine group and 1 in the placebo group had dis-continued migraine prophylactic med just 3 days before starting trial; rest drug-free
Agnoli, Bussone, Mailland, et al., 1991	SPPG QS: 3 (r, db, dd)	N = 102 Age: N/S 71% female Migraine w/o aura; 4-12 HA days/mo for past 3 mos Chron: N/S Rec: N/S	***Flunarizine:*** 5 mg, 1x/day; n = 41 ***Dihydroergokryptine (DEK):*** 10 mg, 2x/day; n = 42 1-mo baseline period (placebo); 6-mo treatment period; 51% of patients followed up 3 mos after end of treatment Acute meds permitted	***HA frequency:*** No. of HA days/mo ***Pain total index:*** Not defined	Baseline mean ***HA frequencies*** were comparable in the two groups (flunarizine, 6.4 ± 2.7; DEK, 6.4 ± 2.5). At 6 mos, HA frequency was significantly lower in the DEK group than in the flunarizine group ($p=0.025$) (post-treatment mean scores were reported only graphically and could not be reliably read off the graph). 3/42 patients in the DEK group (7%) and 4/41 in the flunarizine group (10%) experienced a 50% or more reduction in HA frequency vis-à-vis baseline. Mean HA frequency rose in both groups during the post-treatment follow-up period. ***Pain total index*** was significantly lower in the DEK group after 6 mos of treatment and at follow-up ($p=0.05$ for both timepoints). Mean scores could not be read off the graph on which they were reported.	Dropouts: 19 (19%), 4 due to AEs (all DEK) Abstract reporting limited results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ahuja and Verma, 1985	CrOv QS: 3 (r, db+, dnd)	N = 26 Age: N/S (range: 17-55) 46% female Migraine (Ad Hoc); hist. ≥ 2 HAs/mo in 3 mos prior to trial (described as "frequent") Chron: N/S (range: N/S) Rec: Neuro. clinic in India	***Placebo:*** n = 26* ***Propranolol:*** 40 mg, 3x/day; n = 26* No baseline period described; two 8-wk treatment periods; no washout; no follow-up Nothing on acute migraine meds	***HA index (intensity):*** Calculated as HA frequency multiplied by no. of HA intensity points (intensity rated on 3-point scale) ***HA frequency:*** Not defined, but reported as overall means per 8 wks ***HA index (duration):*** Calculated as HA frequency multiplied by duration score (duration rated on 5-point scale; score derived relative to pre-treatment duration)	Propranolol was significantly better than placebo at reducing ***HA index (intensity)*** ($p < 0.05$). Pre-treatment mean values were not provided. The post-treatment mean scores (and SDs) for HA index (intensity) were 20.69 (± 16.84) for propranolol and 38.00 (± 39.10) for placebo. Authors did not report whether they analyzed pre- to post-treatment results for statistical significance. Results were similar for ***HA index (duration).*** Results were similar for ***HA frequency***, except that propranolol reduced this outcome significantly from pre- to post-treatment (p-value not reported).	Dropouts: N/S Not clear how baseline or treatment data gathered; not clear if data obtained from pt's diaries or post hoc from interviews with physician
Albers, Simon, Hamik, et al., 1989	SPPG QS: 3 (r+, ndb, dd)	N = 40 Age: 35 89% female Common or classic migraine (Ad Hoc); ≥ 3 HAs/mo for last 3 mos; no previous migraine prophylactic treatment Chron: N/S Rec: N/S	***Propranolol:*** 40-60 mg, 3x/day (dosage adjusted according to patient's tolerance); n = 12 ***Nifedipine:*** 20-30 mg, 3x/day (dosage adjusted according to patient's tolerance); n = 7 No baseline period; 6-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of HAs/mo	Mean ***HA frequency*** (± SD) in the propranolol group was 6.1 (± 0.7) at the start of treatment and 2.2 (± 0.9) for months 4-6. In the nifedipine group, the corresponding figures were 3.6 (± 0.3) and 1.5 (± 0.7), respectively. The investigators did not report whether the difference between the two treatments was statistically significant.	Dropouts: 20 (50%), 18 due to AEs (5 propranolol, 13 nifedipine); in addition, 1 propranolol patient who completed the trial did not report adequate data to be included in the efficacy analysis Not double-blind High dropout rate Baseline frequency values established by history

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Al Deeb, Biary, Bahou, et al., 1992	SPPG QS: 2 (nr, db, dd)	N = 50 Age: 34 76% female Migraine w/ or w/o aura (IHS) Chron: 12 yrs Rec: Hospital outpatients	***Placebo:*** n = 21 ***Flunarizine:*** 10 mg, 1x/day; n = 21 6-mo baseline period; 3-mo treatment period; no follow-up Patients permitted to continue with their usual acute meds	***HA frequency:*** Mean number of attacks/3 mos ***HA severity:*** Mean severity/3 mos; severity of each attack graded on 4-pt scale (not described) ***HA duration:*** Mean duration/3 mos	There was no significant difference between the two groups for reduction in ***HA frequency*** from pre- to post-treatment (p=0.08). In the flunarizine group, the mean HA frequency (± SD) was reduced from 13.75 (± 7.7) pre-treatment to 9.9 (± 5.3) post-treatment. In the placebo group, the corresponding figures were 9.83 (± 5.0) and 7.86 (± 5.9), respectively. There was also no significant difference between the two treatments for ***HA severity*** (no p-value reported). Six of 21 patients (29%) in the flunarizine group and 5/21 (24%) in the placebo group reported a reduction in mean HA severity of ≥ 50% from pre- to post-treatment. Most patients (12/21 flunarizine, 11/21 placebo) experienced no reduction in mean ***HA duration***. However, 7 patients in each group showed dramatic reductions (85%-100%) in duration from pre- to post-treatment.	Dropouts: 8 (16%), 4 due to AEs Not randomized 7/21 patients in the flunarizine group had migraine with aura, compared with 1/21 in the placebo group
Al-Qassab and Findley, 1993	CrOv QS: 4 (r, db+, dd)	N = 45 Age: 36 (median) (range: 18-65) 80% female Common or classical migraine: ≥ 3 HAs/mo; described as "severe" Excl: Pts with contraindications for beta-blockers Chron: 9 (median) (range: 1-49) Rec: General neuro. clinic	***Placebo:*** n = 30* ***Propranolol (long-acting):*** 80 mg, 1x/day; n = 30* ***Propranolol (long-acting):*** 160 mg, 1x/day; n = 30* 4-wk run-in (placebo); two 2-mo treatment periods; 1-wk washout between treatment periods; no follow-up Patients' usual meds for acute migraine attacks permitted, except psychotropics or drugs known to interact with beta-blockers	***HA frequency:*** Not defined, but recorded daily by pts ***HA Intensity:*** Rated on 4-point scale and recorded daily by pts	No baseline scores were provided. Post-treatment *median* scores for ***HA frequency*** were 3.8, 3.8, and 3.2 for propranolol LA 160 mg/day, propranolol LA 80 mg/day, and placebo, respectively. There were no significant differences in HA frequency results between either of the active doses and placebo or between the two active doses. For propranolol LA 160 mg vs. placebo, the p-value was $p > 0.96$; for propranolol 80 mg vs. placebo, it was $p > 0.63$; and for propranolol LA 160 mg vs. propranolol LA 80 mg, it was $p > 0.75$. Results for ***HA intensity*** were similar.	Dropouts: 15 (33%), 1 due to AEs (treatment group N/S) Not clear if baseline data gathered

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Andersson, 1973	CrOv QS: 4 (r, db+, dd)	N = 73 Age: 38 84% female Classic or common migraine (Ad Hoc) Chron: N/S Rec: N/S	***Methysergide:*** 1 mg, 4x/day; n = 48* ***Pizotifen:*** 0.5 mg, 4x/day; n = 47* No baseline period described; two 3-mo treatment periods; no washout; data used from 3rd month of treatment only, presumably to minimize carry-over effects; no follow-up No acute meds permitted, except in exceptionally severe cases, when ergot preparations or morphine administered	***HA index:*** Frequency times severity; severity of each attack graded on scale of 1-3 (slight, moderate, severe) ***HA frequency:*** No. of attacks per month; number of patients reporting > 50% reduction in HA frequency	Mean ***HA index*** scores were 16.6 pre-treatment, 9.5 with methysergide, and 7.5 with pizotifen (no variance data reported). There was no significant difference between the two treatments for this outcome ($p<0.05$). Mean ***HA frequency*** (± SD) was reduced from 5.9 (± 2) pre-treatment (n = 49) to 4.1 (± 4) with methysergide (n = 48) and 3.5 (± 3) with pizotifen (n = 47). The investigator found no significant difference between the two treatments for this outcome ($0.40<p<0.50$). 15/48 patients (31%) reported a > 50% reduction in ***HA frequency*** with methysergide, as did 18/47 patients (38%) with pizotifen.	Dropouts: 24 (33%), 13 due to AEs (9 pizotifen, 4 methysergide) Not clear how baseline values established
Andersson, Dahl, Hansen, et al., 1983	SPPG QS: 3 (r, db, dd)	N = 71 Age: 40 (range: 17-57) 85% female Classical or nonclassical migraine; hist. ≥ 2 yrs; ≥ 3 HAs/mo in mo prior to trial Excl: Other vascular HAs; chronic, daily HAs nonseparable from migraine; contraindi-cation for beta-blockers Chron: 18.4 (range: N/S) Rec: 3 neuro. clinics in Denmark	***Placebo:*** n = 35 ***Metoprolol (Durules®):*** 200 mg (in controlled release formulation), 1x/day; n = 30 4-wk baseline period; one 8-wk treatment period; no follow-up Acute migraine meds permitted (ergotamine and analgesics)	***HA index:*** Calculated as sum of intensity score (no. of migraine days multiplied by HA intensity rating) ***HA frequency:*** Defined as "number of migraine days" and recorded daily by pt ***HA intensity:*** Recorded daily by pt on 3-point scale	Metoprolol was significantly better than placebo at reducing ***HA index*** mean values ($p \leq 0.05$). In the metoprolol group, HA index was reduced from 17.63 (S.D. = 8.51) at baseline to 11.95 (S.D. = 7.69) after treatment. The reduction was statistically significant ($p \leq 0.001$). In the placebo group, HA index *increased* from 16.33 (S.D. = 7.48) at baseline to 16.51 (S.D. = 7.97) after treatment. The pre- to post-treatment difference was not significant ($p > 0.05$). Similar results were reported for ***HA frequency***. Ten of 30 (33%) and 4/35 (11%) of patients treated with metoprolol and placebo, respectively, improved (achieved ≥ 50% reduction in ***HA index*** from pre- to post-treatment). The difference between the two results was statistically significant ($p \leq 0.001$).	Dropouts: 6 pts (8%), 2 from AEs (metoprolol 1, placebo 1); 3 additional pts dropped out but were not included in the efficacy analyses for which we reported results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Andersson and Petersen, 1981	CrOv QS: 3 (r, db, dd)	N = 49 Age: 38 (range: 22-68) 69% female Classical or common migraine; ≥ 3 attacks/mo in last 2 mos Chron: 18 yrs (range: 2-40) Rec: N/S	***Propranolol:*** 80 mg, 2x/day; dose reduced by half during first week; n = 37* (completed trial); n = 28* (completed trial and recorded HA data during baseline period) ***Femoxetine:*** 200 mg, 2x/day; dose reduced by half during first week; n = 37* (completed trial); n = 28* (completed trial and recorded HA data during baseline period) 1-mo baseline period; two 3-mo treatment periods; no washout, but first month of each treatment period dropped from analysis to minimize carry-over effects No information on acute meds	***HA index:*** Mean number of HA days/30 days multiplied by severity ***HA frequency:*** Mean number of attacks/30 days (attacks must be separated by a HA-free day) ***HA severity:*** Mean severity/30 days, where each HA scored on scale of 1-3	We analyzed results from the 28 patients who recorded HA data during the baseline period. Both drugs reduced ***HA index*** significantly compared to pre-treatment values ($p<0.001$ for both comparisons). There was no significant difference between the two interventions (no p-value reported). The mean HA index (± SEM) pre-treatment was 24.5 (± 1.8); after treatment with propranolol, it was 16.0 (± 2.2); after treatment with femoxetine, it was 17.9 (± 1.9). The authors also reported the number of patients with a > 50% reduction in HA index compared with pre-treatment values for each intervention. 10/28 patients (36%) achieved this level of improvement with propranolol, as did 6 of the same 28 patients (21%) with femoxetine. The difference between the two treatments was not significant (no p-value reported). Very similar continuous and categorical results were reported for ***HA frequency*** and ***HA severity***. No order effect was detected.	Dropouts: 12 (24%), 4 due to AEs (2 with each treatment)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ansell, Fazzone, Festenstein, et al., 1988	SPPG QS: 3 (r, db, dd)	N = 68 Age: N/S (range: 18-60) 74% female Common or classical migraine (World Fed of Neurology); patients with non-migrainous HAs excluded; patients with < 2 HAs/mo during base-line period excluded Chron: N/S Rec: Migraine clinic	***Placebo:*** n = 27 ***Nimodipine:*** 40 mg, 3x/day; n = 30 2-mo baseline period (placebo); 4-mo treatment period; no follow-up Acute meds permitted	Patients made clinic visits at approx 4-wk intervals; following outcomes calculated for each visit period: ***HA index:*** For each HA, peak HA severity times HA duration was added to peak nausea/vomiting severity times nausea/ vomiting duration; these individual HA scores were summed for all attacks during the visit period, and the resulting number was divided by the no. of days in the visit period HA duration was measured in terms of no. of migraine days per attack; severity of HA and of nausea/vomiting were measured on scale of 0-3 (none, mild, severe, incapacitating) ***HA frequency:*** No. of attacks per visit period	Significant improvement in median ***HA index*** scores was reported in both treatment groups, but there was no statistically significant difference between the nimodipine and placebo groups (no p-values reported; median values for each month reported graphically and could not be reliably read off graph). There was no significant difference between the two groups for median ***HA frequency*** at baseline. Neither group improved significantly during treatment, and the changes in the two groups were not significantly different from each other at any timepoint (no data or p-values reported).	Dropouts: 11 (16%), none due to AEs
Anthony and Lance, 1968	SPPG QS: 4 (r, db+, dd)	N = 38 Age: N/S (range: 19-61) 76% female Migraine Chron: N/S (range: 8 mos - 40 yrs) Rec: Neuro clinic	***Placebo:*** n = 19 ***Indomethacin:*** 25 mg, 3x/day; n = 19 1-mo baseline period; 1-mo treatment period; at conclusion of this controlled trial, all patients took indomethacin for an additional 1-mo treatment period; patients who had responded to indomethacin continued to take it and were followed up through 9 mos We analyzed data from controlled portion of trial only Nothing on acute meds	***HA frequency:*** No. of attacks ***HA severity:*** Not defined	Investigators analyzed the number of patients who were HA-free, who had a > 50% improvement in ***HA frequency or severity*** compared with baseline values, and who were "unimproved" (≤ 50% improvement in frequency or severity). There was no significant difference between indomethacin and placebo for this outcome (no p-value reported). Among patients taking indomethacin, 1/19 (5%) was HA-free; 6/19 (32%) were > 50% improved, and 12/19 (63%) were unimproved. Among patients taking placebo, 2/19 (11%) were HA-free, 5/19 (26%) > 50% improved, and 12/19 (63%) unimproved.	Dropouts: None during controlled portion of trial

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Anthony, Lance, and Somerville, 1972	CrOv (analyzed as SPPG) QS: 1 (nr, ndb, dd)	N = 153 Age: N/S (range: 17-65) 79% female Migraine; ≥ 2 attacks/mo Chron: N/S (range: 1-47 yrs) Rec: Neuro clinic	***Prindolol:*** 2.5 mg, 4x/day (dose reduced by half for first 3 days); n = 79* (total); n = 33 (first treatment period) ***Clonidine:*** 75 μg, 3x/day (dose reduced by half for first 3 days); n = 73* (total); n = 30 (first treatment period) ***Carbamazepine:*** 200 mg, 3x/day (dose reduced by half for first 3 days); n = 51* (total); n = 30 (first treatment period) No baseline period described; initial treatment period of 1 mo; at end of this period, patients with > 50% reduction in HA frequency continue on same med, rest switched to one of the other drugs; patients followed up for varying lengths of time (1-20 mos) Nothing on acute meds	***HA frequency:*** Patients recorded number of HAs; at monthly assessments, classified as either HA-free, > 50% improved, or unimproved	Because of the unusual study design (see under "Interventions," at left), we analyzed the results from the first month of treatment as if this were a parallel group trial. Among patients taking prindolol during the first month, 21/33 (64%) had a > 50% reduction in ***HA frequency*** compared with pre-trial values, as did 16/30 patients (53%) in the clonidine group, and 10/30 (33%) in the carbamazepine group. Prindolol was significantly better than carbamazepine for this outcome ($0.01<p<0.025$). There was no significant difference between clonidine and carbamazepine ($0.1<p<0.2$). Investigators did not directly compare prindolol and clonidine.	Dropouts: 12 (8%) during initial month of treatment, all due to AEs (3 prindolol, 3 clonidine, 6 carbamazepine); for entire trial, 28 patients (18%) dropped out due to AEs (8 prindolol, 8 clonidine, 12 carbamazepine) Not clear how pre-treatment frequency established (no baseline period described)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Arthur and Horna-brook, 1971	CrOv QS: 4 (r, db+, dd)	N = 63 Age: N/S (range: ≤ 10 - >70) 73% female Common or classical migraine; migrainous neuralgia (5 pts); ≥ 2 severe attacks of migraine or migrainous neuralgia/mo Chron: N/S Rec: 23 pts referred by MDs to neuro. dept. for lack of improvement; 9 pts, both improved & unimproved, were from previous trial of pts with severe HAs	***Placebo:*** n = 52* ***Pizotifen (BC 105):*** 3 mg (6 tabs)/day; n = 52* 1-mo baseline period; two 1-mo treatment periods; no washout; no follow-up Ergotamine and analgesic meds permitted during trial, but not acute meds that might obscure efficacy of pizotifen (pheno-barbitone, prochlorperazine, et al.); 5 pts took tranquilizers during baseline, but not during treatment with active drug; 2 pts were gradually withdrawn from methysergide during baseline	***HA frequency:*** Definition N/S, but recorded daily by pt as "presence/absence of HAs/day" ***HA intensity:*** Recorded daily by pts on 3-point scale	Twenty-one of 52 pts (40%) treated with pizotifen and 6/52 (12%) treated with placebo improved (obtained > 50% reduction in ***HA frequency*** from baseline to post-treatment). Pizotifen was significantly better than placebo at reducing ***HA frequency*** ($p < 0.005$). The overall number of HAs decreased from 423 at baseline to 330 in pts taking pizotifen but *increased* to 457 in patients taking placebo. There were significantly fewer HAs during the pizotifen period than during either the baseline or the placebo periods ($p \leq 0.01$, each comparison).	Dropouts: 11 (17%) withdrew and were not included in efficacy analyses; an additional 3 pts, included in efficacy analyses, withdrew due to AEs (pizotifen)
Autret and de Chast-eigner, 1987	SPPG QS: 3 (r, db, dd)	N = 115 Age: 36 % female N/S Common migraine; 3-10 migraine days in previous month; no daily HAs Chron: N/S Rec: N/S	***Placebo:*** n = 57 ***DHE (timed-release):*** 5 mg, 2x/day; n = 58 4-wk baseline period (placebo); 8-wk treatment period; no follow-up Acute meds permitted	***HA index:*** Sum of intensity times duration for all attacks ***HA frequency:*** No. of attacks; number of days with HA	DHE was significantly better than placebo at reducing ***HA index*** compared with baseline values ($p \leq 0.0017$). Mean within-patient differences (± SD) from baseline to post-treatment were 1.98 (± 3.54) in the DHE group and 0.058 (± 2.80) in the placebo group. There were no significant differences between the two groups for ***HA frequency***, considered either as number of attacks or number of days with HA (no data and no p-values reported).	Dropouts: 0 Abstract reporting limited results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Baldrati, Cortelli, Procacci-anti, et al., 1983	CrOv QS: 3 (r, db, dd)	N = 18 Age: N/S (range: 18-49) 89% female Common migraine (Ad Hoc); ≥ 2 attacks/mo Chron: 13 yrs (range: 3-38) Rec: N/S	***Propranolol:*** Mean daily dose approx 120 mg, taken in three doses; dose increased gradually over 20 days; n = 12* ***Aspirin:*** Mean daily dose approx 975 mg, taken in three doses; dose increased gradually over 20 days; n = 12* 1-mo baseline period; two 3-mo treatment periods; 2-wk washout; only last month of each treatment period analyzed; no follow-up Nothing on acute meds	***HA index:*** Defined as $1(F_1xD_1) + 2(F_2xD_2) + 3(F_3xD_3)$, where 1-3 refers to severity score, F=mean number of attacks/mo, D=mean duration in hrs ***HA frequency:*** No. of attacks/mo; no of migraine days/mo ***HA severity:*** Mean attack severity; each attack graded on scale of 1-3 (not described) ***HA duration:*** Mean attack duration (hrs)	There was no significant difference between the two treatments for reduction in ***HA index*** (no p-values reported). The mean percentage reduction in HA index from baseline to the third month of treatment was 64.8% with aspirin and 65.2% with propranolol (no variance data reported). Over the same period of time, 9/12 patients (75%) reported a greater than 50% reduction in HA index with aspirin; the same number of patients (9/12) reported a greater than 50% reduction with propranolol. Investigators reported finding no significant differences between the two treatments for ***HA frequency*** (both number of attacks/mo and number of HA days/mo), ***severity***, or ***duration*** (no data and no p-values reported).	Dropouts: 6 (33%), 5 due to AEs (3 aspirin, 2 propranolol) High dropout rate (33%)
Bánk, 1994	SPPG QS: 3 (r, db, dd)	N = 70 Age: 34 (range: 20-62) 73% female Migraine w/ or w/o aura (IHS); history > 1 yr; ≥ 3 attacks/mo Chron: N/S Rec: N/S	***Fluvoxamine:*** 50 mg, single dose at bedtime; n = 24 ***Amitriptyline:*** 25 mg , single dose at bedtime; n = 20 4-wk baseline period (placebo); 12-wk treatment period Patients permitted to use their usual acute meds (ergotamine compounds, NSAIDs, benzodiazepines)	Patients made clinic visits at approx 4-wk intervals. The following three outcomes were analyzed: ***HA index:*** No. of HAs times severity (scale of 1-3) divided by no. of days in visit period ***HA frequency:*** No. of HAs divided by no. of days in visit period ***Corrected HA unit index:*** Severity of attacks (scale of 1-3) times duration of attacks (scale of 1-3) divided by no. of days in visit period	Both drugs reduced ***HA index*** significantly compared with pre-treatment levels. With fluvoxamine, the median pre-treatment HA index was 0.43; after treatment, it was 0.18 ($p<0.0003$). With amitriptyline, the corresponding figures were 0.41 and 0.24 ($p<0.001$). The two treatments were not directly compared by investigators. Results were very similar for ***HA frequency*** and ***corrected HA unit index***.	Dropouts: 21 (30%), 10 due to AEs (7 amitriptyline, 3 fluvoxamine); in addition, 5 patients (3 amitriptyline, 2 fluvoxamine) did not experience any HAs during the 12-wk treatment period and were excluded from the efficacy analysis by the investigators

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Barrie, Fox, Weatherall, et al., 1968	CrOv (ortho-gonally balanced) QS: 3 (nr, db+, dd)	N = 105 Age: N/S (range: 17-68) % female N/S Common, classic, or hemiplegic migraine, or migraine + muscle-contraction HA; ≥ 1-yr history; ≥ 1 HA/mo Chron: N/S Rec: HA clinics	***Methysergide:*** 1 mg, 3x/day; n = 16 ***Methysergide:*** 2 mg, 3x/day; n = 11 ***Ergotamine:*** 0.17 mg, 3x/day; n = 17 ***Ergotamine:*** 0.33 mg, 3x/day; n = 15 ***Ergometrine maleate:*** 0.33 mg, 3x/day; n = 3 ***Ergometrine maleate:*** 0.67 mg, 3x/day; n = 3 No baseline period described; four 4-wk treatment periods; after third period, patients chose which of first three drugs to use for remainder of trial; no washout; no follow-up Aspirin or prochlorperazine used for acute attacks	***HA severity:*** Patients graded each attack on scale of 0, 50, and 100 (mild, moderate, severe); investigators reported the number of patients in each group and in each period who had decreased HA severity (no threshhold specified) compared with the previous period	Results from the second, third, and fourth periods were compromised for the following reasons: (1) in periods 2, 3, and 4 each patient was evaluated vis-á-vis the immediately preceding period; however, it was not possible to trace the sequence of interventions used in particular cases from the data reported; (2) at one of the two sites, patients were permitted to choose which drug to use for acute attacks during the third and fourth periods (aspirin was assigned for one of the first two periods, prochlorperazine for the other, then patients chose which one to use for third and fourth); (3) at both sites, patients were allowed to choose one of the preventive agents used in periods 1-3 to use in period 4. For all these reasons, we were only able to consider the data from the first period of the trial (month 1). Also, period one results from the two ergometrine treatment arms are not considered here, since there were fewer than 5 patients in each group. ***HA severity:*** During the first month of treatment, the numbers of patients reporting decreased HA severity vis-á-vis baseline values were: methysergide 3 mg/day, 9/16 (56%); methysergide 6 mg/day, 5/11 (45%); ergotamine 0.5 mg/day, 8/17 (47%); ergotamine 1 mg/day, 7/15 (47%). Investigators did not analyze these results.	Dropouts: 40 patients (38%) were excluded from the efficacy analysis of period 1 data because they did not provide complete enough reports or a sufficient number of reports (4 attacks or more) Baseline data gathered by history and was "not always available"

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Bassi, Brunati, Rapuzzi, et al., 1992	SPPG QS: 2 (r, ndb, dd)	N = 40 Age: 30 (range: 18-50) 83% female Migraine w/ or w/o aura (IHS); history of ≥ 2 yrs; ≥ 2 HAs/mo; no prophylactic meds in previous 3 mos Chron: 140 mos (range: 2-35 yrs) Rec: Hospital HA dispensary	***Flunarizine:*** 10 mg, 1x/day for one wk, then 3 mg, 1x/day; n = 14 ***Flunarizine:*** 10 mg, 1x/day; n = 15 1-mo baseline period (no prophylactic med); 4-mo treatment period; no follow-up Acute meds permitted	***HA index:*** No. of hrs of HA/mo times HA severity; severity of each HA graded on scale of 0-3 (pain absent; slight pain, but no need for analgesics; medium intensity pain, improving with analgesics; strong pain with partial incapacity even after taking analgesics)	Both doses of flunarizine significantly reduced ***HA index*** in comparison with baseline values from the second treatment month on ($p<0.01$ for both groups during the final month of treatment); the lower dose also produced a significant improvement already in the first month ($p<0.01$). The 3-mg dose outperformed the 10-mg dose during the first month ($p<0.05$); otherwise, there were no significant differences between the two doses at any timepoint (p-values not reported). Some data were reported (what appear to be median HA index scores and median reductions in HA index scores), but could not be interpretd with confidence.	Dropouts: 11 (28%), 2 due to AEs (1 in each group) Low quality score (2); not double-blind
Behan, 1985	SPPG QS: 2 (r, ndb, dd)	N = 60 Age: 30 (average) % female N/S Chron: N/S Common or classical Ms; > 2 Ms/mo Rec: Migraine clinic	***Pizotifen (Sanomigran®):*** 1.5 mg, 1x/night for 1 mo; dose could be increased to 3.0 mg, 1x/night, if HAs unimproved after 1 mo; n = 18 ***Clonidine (Dixarit®):*** 50 µg, 2x/day for 1 mo; dose could be increased to 75 µg, 2x/day, if HAs unimproved after 1 mo; n = 26 No baseline period; 2-mo treatment period; no washout; no follow-up Nothing on acute meds	***HA frequency:*** See below ***HA intensity:*** See below No definitions given for either of above outcomes, but data obtained from pts' diaries. No baseline data gathered. Pts assessed monthly by physician	***HA frequency*** and ***intensity*** results were reported as the "reduction" in those outcomes over each month for individual pts. (No information on baseline data was provided, so it is not clear how reductions were determined.) At the end of each month, fewer and less severe HAs were reported from pts taking pizotifen than from those taking clonidine (authors reported that differences between treatments were not analyzed for statistical significance). During the first month, 12/18 pts (67%) and 3/25 pts (12%) in the pizotifen and clonidine groups, respectively, reduced ***HA frequency***. During the second month, 11/13 pts (85%) and 4/19 pts (21%) in the pizotifen and clonidine groups, respectively, reduced ***frequency***. During the first month, 14/18 pts (22%) and 3/22 pts (14%) in the pizotifen and clonidine groups, respectively, reduced ***HA intensity***. During the second month, 11/12 pts (92%) and 1/17 pts (6%) in the pizotifen and clonidine groups, respectively, reduced ***intensity***.	Dropouts: 16 (27%), 1 due to AEs (pizotifen) Information obtained from abstract Definition of "improvement" does not meet our criterion of ≥ 50% reduction from baseline to post-treatment Unclear how assessment of outcomes was determined from daily HA recordings

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Behan and Reid, 1980	CrOv QS: 2 (nr, db, dd)	N = 56 Age: N/S (range: 18-56) 66% female Classical or common migraine; ≥ 2 severe HAs/mo Chron: N/S (range: 6 mos-33 yrs) Rec: N/S	***Methysergide:*** 1 mg, 3x/day; n = 38* (36 patients completed both treatment periods, but 38 appear to have been included in the methysergide vs. baseline comparisons) ***Propranolol:*** 40 mg, 3x/day; n = 36* No baseline period described; two 3-mo treatment periods; 1-mo washout (acute analgesics only); no follow-up No drugs other than study meds allowed during treatment periods	***HA frequency:*** Not defined; investigators reported and analyzed the no. of patients reporting no change in HA frequency, < 50% reduction, 50-75% reduction, 75-99% reduction, and complete relief ***HA severity:*** Severity data recorded by patients not described; effect of treatment on severity was graded on scale of 0-3 (no effect, mild relief, moderate relief, complete relief)	Both propranolol ($p<0.0001$) and methysergide ($p<0.01$) signficantly reduced ***HA frequency*** compared with baseline values. There was no significant difference between the two drugs for this outcome ($p>0.05$). 19/36 patients (53%) reported a reduction in HA frequency of 50% or more with propranolol, as did 15/38 patients (39%) with methysergide. There was no significant difference between the two drugs for ***HA severity*** ($p=0.168$).	Dropouts: 20 (36%), 3 due to AEs (all methy-sergide) No indication of how baseline values established (no baseline period described) High dropout rate (36%) Low quality score (2); not randomized

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Bellavance and Meloche, 1990	SPPG QS: 3 (r, db, dd)	N = 176 Age: 33 (range: 18-45) 79% female Classical or common migraine (Ad Hoc); ≥ 1-yr history; 4-8 attacks during baseline period, severe enough to cause a reduction in activity or capacity for work; no other types of HA Chron: 12 yrs (range: 1-31) Rec: N/S ("outpatients")	***Placebo:*** n = 52 ***Pizotyline:*** 0.5 mg, 3x/day (gradual escalation to full dose over first 7 days); n = 58 ***Naproxen sodium:*** 550 mg, 2x/day; n = 56 2-mo baseline period (placebo); 3-mo treatment period; no follow-up Acute meds permitted	***HA index:*** Severity times duration for each episode, summed for all episodes and divided by the no. of days in the treatment period ***HA frequency index:*** No. of migraine attacks divided by the no. of days in the treatment period ***HA severity:*** Each attack graded on scale of 1-3 (slight, moderate, severe) ***HA duration:*** Each attack graded on scale of 1-3 (< 8 hrs, 8-16 hrs, > 16 hrs)	Naproxen sodium was significantly better than placebo at reducing mean ***HA index*** scores during all three treatment months; pizotyline was significantly better than placebo during the second treatment month only. There were no significant differences between naproxen sodium and pizotyline during any of the three months for this outcome (no p-values reported). Mean HA index scores were not reported for each month, but only for the baseline (2 mos) and treatment (3 mos) periods as wholes. In the naproxen sodium group, mean HA index scores were reduced from 5.32 at baseline to 2.85 during treatment; in the pizotyline group, the corresponding scores were 5.77 and 3.27; and in the placebo group, they were 5.56 and 5.08 (no variance data reported). Naproxen sodium was significantly better than placebo for this outcome ($p<0.0166$, Kruskal-Wallis with Bonferroni correction); otherwise, there were no significant differences among the treatments (no other p-values reported). Both naproxen sodium and pizotyline were significantly better than placebo at reducing mean ***HA frequency index*** scores ($p<0.0166$ for both comparisons); there was no significant difference between the two active treatments (no p-value reported). Naproxen sodium was significantly better than placebo and than pizotyline at reducing ***HA duration*** during the first month of treatment. Otherwise, there were no significant differences among the treatments for this outcome.	Dropouts: 25 (14%), 7 due to AEs (3 naproxen sodium, 2 pizotyline, 2 placebo); 15 of these 25 patients were included in the efficacy analysis; 21/25 were included in the AE analysis

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Boisen, Deth, Hübbe, et al., 1978	CrOv QS: 2 (r, db, dd)	N = 71 Age: N/S (range: N/S) % female N/S Chron: N/S Migraine (paroxysmal HAs with discomfort + 1 or more of: nausea, vomiting, visual disturbances, paraesthesia); ≥ 4 days of Ms/mo in 2 mos before trial Excl: Treatment with MAOIs; previous treatment with clonidine Rec: Neurology departments of 4 hospitals in Denmark	***Placebo:*** n = 49* ***Clonidine:*** 0.05 mg (in 2 tabs), 2x/day; n = 49* No baseline period; two 8-wk treatment periods; no washout, but first wk of each treatment period excluded from analysis to reduce crossover effects; no follow-up It appears that pts permitted to take other meds during trial	***HA frequency:*** Definition N/S, but derived from pts' daily recordings of time of onset & cessation of HAs	For ***HA frequency***, during the first treatment period 28 pts taking clonidine reported 407 HAs, whereas 21 pts taking placebo reported 278 HAs. During the second treatment period, 21 pts taking clonidine reported 235 HAs and 28 pts taking placebo reported 372. Thus, a total of 49 pts reported 642 and 650 HAs during 14 wks after taking clonidine and placebo, respectively. The difference between the two treatments for reducing ***HA frequency*** was not statistically significant, according to investigators. No within-group results were provided for comparisons of ***HA frequency*** before and after treatment with each intervention.	Dropouts: 22 (31%), 2 due to AEs (clonidine) Not clear if baseline information gathered. Pts' diaries reviewed by physician every 4 wks In the first trial period, the no. of HAs was 685, and in the second, 607. There was a significant difference between the no. of HAs depending on the order in which treatment was received ($p<0.05$)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Bono, Criscuoli, Martignoni, et al., 1982	SPPG QS: 3 (r, db, dd)	N = 80 Age: 37 (range: N/S) 82% female Common or classical migraine; hist. ≥ 3 yrs + treatment-free for ≥ 3 mos or never treated Excl: Age > 58 or < 18; HI < 6 (not defined) Chron: N/S (range: N/S) Rec: N/S	***Oxitriptan (L-5-HTP):*** 400 mg/day; n = 33 ***Pizotifen:*** 1.40 mg/day; n = 34 1-mo baseline with placebo treatment, followed by 2-mo treatment period with active drug Analgesics permitted, but pts asked to avoid foods containing large amounts of amines and amino acids	***HA index:*** Definition N/S ***HA frequency:*** Recorded daily ("hour by hour") by pt and reported as "no. of HAs/mo" ***HA intensity:*** Recorded daily by pt on 4-point scale; termed "pain total index"	Investigators reported results only as p-values; no mean scores were provided. Pizotifen was significantly better than oxitriptan at reducing ***HA index*** after both the first month ($p < 0.01$) and the second month ($p < 0.02$). Although placebo was not used as a treatment, investigators compared each active drug with baseline placebo. Oxitriptan decreased ***HA index*** significantly from baseline to post-treatment after the second month ($p < 0.02$), but not after the first month (n.s., no p-value given). No pre- to post-treatment results were provided for changes in ***HA index*** resulting from pizotifen.	Dropouts: 13 (16%), 5 due to AEs (oxitriptan)
Bonuso, Di Stasio, Barone, et al., 1983	SPPG QS: 2 (r, ndb, dd)	N = 41 Age: N/S (range: 18-55) 68% female Mixed HA (Ad Hoc) Chron: N/S Rec: N/S	***Amitriptyline:*** 75 mg/day (schedule not described); n = 15 ***DHE (timed-release):*** 5 mg, 2x/day; n = 15 1-mo baseline period; 2-mo treatment period; no follow-up Acute meds permitted	***HA severity:*** Mean monthly HA severity; no indication of precisely how this was calculated; patients graded HA pain every hr during day on scale of 0-4 (none, mild, moderate, severe, extremely severe); investigators considered it likely that "severe" and "extremely severe" attacks were of the migraine type, whereas "mild" and "moderate" attacks were tension-type; all HAs were included in the analysis ***HA duration:*** Mean % decrease (vis-á-vis baseline) in no. of HA hours/month, stratified by HA severity	Mean monthly ***HA severity*** scores (± SEM) for the group taking amitriptyline were 17.0 (± 1.6) during the baseline period and 5.4 (± 0.7) during treatment month 2. Corresponding scores in the DHE-treated group were 18.7 (± 1.3) and 10.7 (± 0.9). Investigators did not state whether they found the difference between the two treatments in this respect to be statistically significant. Analysis of the data on ***HA duration***, stratified by severity, showed that DHE was significantly better than amitriptyline at reducing the number of hours of extremely severe (65.1% vs. 48.7% reduction) and severe (71.6% vs. 53.4%), migraine-type pain; amitriptyline was significantly better than DHE at reducing the number of hours of moderate (74.4% vs. 26.0%) and mild (77.1% vs. 22.3%), tension-type HA-like pain ($p<0.01$ for all four comparisons).	Dropouts: 11 (27%), 5 due to AEs (DHE 2, amitriptyline 3) Low quality score (2); not double-blind

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Børgesen, Nielsen, and Møller, 1974	CrOv QS: 4 (r, db+, dd)	N = 45 Age: 38 (range: 18-59) 83% female Common or classical migraine (Ad Hoc); ≥ 1 HA/wk; all pts had failed to respond to known prophylactics; HAs described as "intractable" Chron: 21 (range: 1-50) Rec: Neuro. dept. of hospital in Denmark	***Placebo:*** n = 30* ***Propranolol (Inderal®):*** 40 mg, 3x/day (given in doses increasing during first 10 days of each period); n = 30* 4-wk baseline (no prophylactics); two 12-wk treatment periods; no washout, but first 4 wks of each period excluded from analysis to avoid carry-over effect from previous treatment; no follow-up Acute meds permitted (salicylates, ergotamines, narcotics), but not prophylactic meds	***HA frequency:*** Not defined, but reported as "mean attack frequency" ***HA severity:*** Recorded by pts on 3-point scale	Propranolol reduced ***HA frequency*** significantly better than did placebo (over the 8 wks analyzed of each relevant treatment period) (Wilcoxon's test; p-value not reported). The mean baseline HA frequency score was reduced from 1.77 to 1.03 after treatment with propranolol and to 1.33 after treatment with placebo. Investigators did not report whether they analyzed the pre- to post-treatment reductions for statistical significance. From data provided, we calculated that 15/30 patients (50%) treated with propranolol and 9/30 patients (30%) treated with placebo improved on ***HA frequency*** (achieved ≥ 50% reduction from pre- to post-treatment). Investigators did not report whether they analyzed these results for statistical significance.	Dropouts: 15 (33%), 2 due to AEs (placebo)
Bousser, Chick, Fuseau, et al., 1988	CrOv QS: 4 (r, db+, dd)	N = 45 Age: 40 (range: 18-66) 68% female Common or classical migraine (Ad Hoc); history > 2 yrs; 3-15 attacks/mo for past 2 mos; not taking migraine prophylactic medication Chron: N/S Rec: N/S	***Placebo:*** n = 38* ***DHE + aspirin (timed-release):*** 5 mg + 40 mg, 2x/day; n = 38* No baseline period described; two 8-wk treatment periods; 1-wk washout; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks per 8-wk treatment period ***HA severity:*** Mean per attack; severity of each attack graded on scale of 1-4 (mild-severe) ***HA duration:*** Mean per attack (in hrs)	DHE + aspirin was significantly better than placebo at reducing ***HA frequency*** (p=0.003). Mean HA frequency (± SD) was 11.5 (± 6.2) with DHE + aspirin and 16.6 (± 9.9) with placebo. There were no significant differences between the two treatments for ***HA severity*** or ***duration***.	Dropouts: 7 (16%), none due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Bradley, Hudgson, Foster, et al., 1968	CrOv QS: 5 (r+, db+, dd)	N = 48 Age: N/S 64% female "Typical" migraine; > 1 attack/ mo Chron: N/S Rec: N/S	***Placebo:*** n = 39* (14 men, 18 women with history of more frequent HAs around time of menstruation, 7 women with no such history) ***Flumedroxone (Demigran®):*** 10 mg, 3x/day; n = 39* (14 men, 18 women with history of more frequent HAs around time of menstruation, 7 women with no such history) No baseline period described; two 3-mo treatment periods; 1-mo washout (no specific therapy); no follow-up Nothing on acute meds	***HA index:*** Sum of HA severity scores per 3-mo treatment period; each attack graded on scale of 1-3 (mild, moderate, severe) ***HA frequency:*** No. of HAs per 3-mo treatment period ***HA duration:*** Total HA duration (in hrs) per 3-mo treatment period	Results were reported and analyzed separately for men, women with a history of more frequent HAs around the time of menstruation, and women with no such history. An analysis of within-patient differences found that flumedroxone was significantly better than placebo for ***HA index*** among those women patients with a history of more frequent HAs around the time of menstruation ($p<0.05$). There was no significant difference between the two treatments in the other two patient groups (no p-values reported). No individual patient data or mean within-patient differences were reported. Group mean ***HA index*** scores (with ranges) among women with a history of more frequent HAs around the time of menstruation were 31 (8-101) with flumedroxone and 37 (2-116) with placebo. Among men, the corresponding figures were 21.5 (2-169) and 24.5 (1-154), respectively. No group mean scores were reported for women with no history of more frequent HAs around the time of menstruation. Similar results were reported for ***HA frequency.*** None of the three patient groups experienced a significant reduction in ***HA duration*** with flumedroxone.	Dropouts: 9 (19%), 2 due to AEs (both flume-droxone)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Bredfeldt, Sutherland, and Kruse, 1989	CrOv QS: 3 (r-, db+, dd)	N = 43 Age: N/S (range: 20-57) 80% female Chron: N/S Migraine (Ad Hoc); hist. of recurrent Ms for ≥ 6 mos; ≥ 1 M in mo before trial; onset of HAs prior to age 40 Excl: Use of prophylactic meds for any reason Rec: Family practice outpatient clinics; physician referral	***Placebo:*** n = 30* ***Clonidine (Dixarit® via Catapres TTS-2® patches):*** ≈ 0.2 mg/day via 1 transdermal patch/wk; n = 30* No baseline period; two 6-wk treatment periods; no washout, but first wk of each treatment period excluded from analysis to reduce crossover effects; no follow-up Pts permitted to use OTC meds with acetaminophen or narcotic preparations prescribed by physicians	***HA frequency:*** No. of HAs per day ***HA intensity:*** Rated by pt on 5-pt scale (1=very mild and 5=very severe)	Results were reported only as averages per pt of ***HA frequency*** or ***intensity*** over the two 5 wks analyzed. Pts taking clonidine reported a slight decrease in each outcome compared with placebo, but the differences for both between-group comparisons were not statistically significant. For ***HA frequency***, pts taking clonidine had an average of 10 HAs during the 10 wks analyzed, whereas pts treated with placebo reported an average of 11.2 (p=0.24). For ***HA Intensity***, pts taking clonidine reported an average intensity of 2.4 during the 10 wks analyzed, whereas pts treated with placebo reported an average of 2.5 (p=0.27). No within-group results were provided for comparisons of ***HA frequency*** or ***intensity*** before and after treatment with each intervention.	Dropouts: 13 (30%), 3 due to AE (clonidine) Not clear if baseline information gathered. Pts' diaries reviewed by physician at 6 and 12 wks

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Briggs and Millac, 1979	CrOv QS: 3 (r, db, dd)	N = 14 Age: N/S (range: N/S) 71% female Common or classical migraine (Ad Hoc); ≥ 2 HAs/mo; all had failed to benefit from previous prophylactic treatment; "frequent" HAs Chron: N/S (range: N/S) Rec: Referrals to neuro. clinic	***Placebo:*** n = 13* ***Timolol:*** 10 mg, 2x/day; n = 13* 4-wk baseline (no prophylactics); four 6-wk treatment periods (double crossover); no washout; no follow-up Simple analgesics and ergotamine derivatives permitted for acute migraine attacks (pts asked to use same agent consistently throughout treatment period)	***HA frequency:*** Recorded daily by pt and reported as "number of migraines in each 6-wk period"	At the end of the double crossover trial, the ***HA frequency*** mean scores (average of both 6-wk periods) were 4.4 and 6.8 after treatment with timolol or placebo, respectively. Investigators did not report having analyzed these results for statistical significance.	Dropouts: 1 (7%), due to AEs (placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Buscaino, Sorge, Bussone, et al., 1991	SPPG QS: 4 (r, db+, dd)	N = 90 Age: 37 (range: 18-53) 70% female Common migraine (Ad Hoc); history ≥ 5 yrs; 2-8 HAs/mo in previous 3 mos; no migraine prophylactic med in previous 3 mos; no daily HA Chron: 16 yrs (range: 3-41) Rec: N/S	***DHE (timed-release), 5 mg, 2x/day:*** n = 45 ***DHE (timed-release), 10 mg, 1x/day:*** n = 45 1-mo baseline period (no meds); 2-mo treatment period; no follow-up Acute meds permitted	***HA index:*** Not described, but combined HA severity and frequency; severity of each attack graded on scale of 1-3 (does not restrict normal activity; restricts normal activities; bedridden) ***HA frequency:*** No. of days with migraine per month	Both dosing regimens significantly reduced ***HA index*** scores in comparison with baseline values ($p<0.01$ for both comparisons); there was no significant difference between the two interventions for this outcome (no p-value reported). At the end of the second month of treatment, HA index had been reduced by 39% in the twice-daily group, and by 55% in the once-daily group. Mean HA index scores were reported only in graphic form and could not be reliably read off the graph. Similar results were reported for ***HA frequency***.	Dropouts: 4 patients (4%) discontinued treatment due to AEs (3 in 2x/day group, 1 in 1x/day group); it appears that these 4 patients were included in the efficacy analysis, though this is not certain 36/90 patients had tried some form of preventive therapy before with results ranging from none to excellent
Bussone, Baldini, D'Andrea, et al., 1987	SPPG QS: 4 (r, db+, dd)	N = 30 Age: 36 83% female Common migraine (Ad Hoc); ≥ 2 HAs/mo for past 2 yrs Chron: 13 yrs Rec: N/S	***Flunarizine:*** 10 mg, 1x/day (bedtime); n = 13 ***Nimodipine:*** 40 mg, 3x/day; n = 12 4-wk baseline period (placebo); 12-wk treatment period; no follow-up Acute meds permitted	***HA index:*** Hours with HA times HA severity; severity graded daily on scale of 0-4 (no pain, mild, moderate, severe, excruciating)	Both flunarizine and nimodipine significantly reduced ***HA index*** in comparison with baseline values, nimodipine from one month on, and flunarizine from two months on. In the flunarizine group, the baseline mean HA index score (± SD) was 286.6 ± 352.1; after 3 mos, it was 200.4 (± 301.8) ($p<0.002$). In the nimodipine group, the corresponding figures were 258.4 (± 211.3) and 116.9 (± 105.0), respectively ($p<0.001$). There were no significant differences, at any time point, between flunarizine and nimodipine (no p-values reported). 6/14 patients treated with nimodipine (43%) and 6/16 treated with flunarizine (38%) reported a 50% or greater reduction in HA index from baseline to end of treatment. There was no significant difference between the two treatments for this outcome (no p-value reported).	Dropouts: 5 (17%), 3 due to AEs (2 flunarizine, 1 nimodipine)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Cangi, Boccuni, Zanotti, et al., 1989	SPPG QS: 3 (r, db+, dnd)	N = 22 Age: N/S % female N/S Migraine w/o aura (IHS); history ≥ 2 yrs; ≥ 2-3 HAs/mo; no spontaneous remission lasting > 15 days Chron: N/S Rec: N/S	***Methysergide:*** 1 mg, 2x/day; n = 11 ***Dihydroergokryptine (DEK):*** 10 mg, 2x/day; n = 11 1-mo baseline period (placebo), followed by 2-mo treatment period; no follow-up Acute meds permitted	***HA index:*** Not defined ***HA frequency:*** No. of HA days per month	We analyzed the results for ***HA frequency***, since the HA index used was not described. In the DEK group, the mean number of HA days/mo (± SD) was reduced from 9.8 (± 2.6) during the baseline period to 6.8 (± 2.7) during the second month of treatment; in the methysergide group, the corresponding figures were 8.6 (± 1.7) and 6.0 (± 2.8). The authors did not report whether they found the difference between the two groups to be statistically significant. Mean ***HA index*** scores (± SD) in the DEK group were reduced from 103.8 (± 25.48) during the baseline period to 87.17 (± 25.02) during the second month of treatment; the corresponding figures in the methysergide group were 84.4 (± 28.5) and 67.6 (± 31.24). The authors did not report whether they found the difference between the two groups to be statistically significant.	Dropouts: Not described Abstract reporting parallel-group interim results from longer-term crossover trial
Canonico, Scapagnini, Genazzani, et al., 1989	CrOv QS: 2 (r, db, dnd)	N = 102 Age: N/S (range: 13-58) 72% female Common migraine; 3-10 HA days/mo Chron: N/S Rec: N/S	***Placebo:*** n = 102* ***Dihydroergokryptine (DEK):*** 10 mg, 2x/day (half dose for first 5 days); n = 102* 1-mo baseline period (placebo); two 2-mo treatment periods; no washout; no follow-up Acute meds permitted	***HA index:*** Not defined	Both treatments produced a significant reduction in monthly ***HA index*** scores during the first treatment period of the trial (55% reduction for DEK; 18% for placebo; $p<0.001$ vs. baseline for each treatment). During the second treatment period, those patients taking placebo deteriorated, while those taking DEK registered a further significant improvement of 54% ($p<0.001$ compared with period 1 scores). No overall comparison of the two treatments was reported.	Dropouts: Not described Abstract reporting limited results Low quality score (2); dropouts not described

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Carrieri, Orefice, and Sorge, 1988	SPPG QS: 4 (r, db+, dd)	N = 40 Age: 36 (range: 19-53) 64% female Classical or common migraine (Ad Hoc); history ≥ 2 yrs; ≥ 4 HAs/mo for last 3 mos; avg duration 2 hrs to 4 days Chron: 15 yrs (range: 3-38) Rec: N/S	***Placebo:*** n = 17 ***Indobufen:*** 200 mg, 2x/day; n = 18 4-wk baseline period (HA recording and no prophylactic treatment); 3-mo treatment period; no follow-up Patients asked not to take anything except analgesic or ergotamine products for acute attacks for at least 10 days before or during treatment period; in particular, not allowed to take aspirin, dipyridamole, beta blockers, steroids, NSAIDs, antidepressants, or hypnotics	***HA index:*** Frequency times severity; severity of each attack graded on scale of 1-3 ***HA frequency:*** No. of attacks/mo	Indobufen, but not placebo, significantly reduced ***HA index*** from baseline to month 3. Mean HA index scores (± SD) in the indobufen group were 10.4 (± 3.8) at baseline and 6.1 (± 3.7) after 3 mos ($p<0.001$, Wilcoxon); corresponding scores in the placebo group were 10.6 (± 4.2) and 10.4 (± 6.4), respectively. The difference between indobufen and placebo for this outcome was statistically signficant ($p<0.01$, Mann-Whitney U). Similar results were reported for ***HA frequency***.	Dropouts: 5 (13%), none due to AEs
Carroll and Maclay, 1975	CrOv QS: 4 (r, db+, dd)	N = 27 Age: N/S (range: N/S) % female N/S Common or classical migraine (Ad Hoc); ≥ 3 migraines/mo in 6 mos preceding trial Excl: Pts with any disease that might interfere with absorption, metabolism, or excretion of pizotifen Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 14* ***Pizotifen (Sanomigran®):*** 0.5 mg, 1x/evening on Days 1 & 2; 0.5 mg, 2x/day on Days 3 & 4; 0.5 mg, 3x/day on Day 5; 0.5 mg, 3x/day for 2 wks or until end of trial -- if relief insufficient, dose could be increased to 1 mg, 3x/day; n = 14* 1-mo baseline period with pizotifen; two 2-mo treatment periods; 2-wk washout between treatment periods Nothing on acute migraine meds	***HA index:*** Calculated by multiplying no. of HA attacks by intensity rating ***HA frequency:*** Definition N/S, but recorded daily by pt ***HA intensity:*** Recorded daily by pt on 3-point scale	We could not analyze the data because of the manner in which they were reported. Results were reported as "improved," "worse," or "unchanged" when the patient's condition at the end of the trial was compared with his/her condition at the end of baseline. The criterion for determining "improvement" was not specified.	Dropouts: 13 (48%), 1 due to AEs (pizotifen) 3 mg was the most commonly used dose

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Carroll, Reidy, Savundra, et al., 1990	CrOv QS: 3 (r, db, dd)	N = 51 Age: 39 (range: 17-62) 69% female Common or classical migraine (Ad Hoc); median frequency of ≥ 8 HAs/mo Chron: 14 (median) (range: 2-50) (median) Rec: N/S	***Propranolol (long-acting):*** 80 mg/day; n = 37* ***Propranolol (long-acting):*** 160 mg/day; n = 37* 4-wk run-in (placebo); two 12-wk treatment periods; 2-wk washout (placebo) between treatment periods; no follow-up Meds for acute migraine attacks permitted	***HA frequency:*** Not defined, but recorded daily by pts ***HA intensity:*** Rated on 4-point scale and reported daily by pts	***HA frequency*** was reduced from a *median* score of 6.10 at baseline to median scores of 3.40 and 3.70 after treatment with propranolol LA 160 mg and propranolol LA 80 mg, respectively. HA frequency was reduced significantly better after treatment with each propranolol dosage than after the baseline run-in period ($p < 0.01$, each case). The higher dose of propranolol was significantly better at reducing this outcome than was the lower dose ($p = 0.03$).	Dropouts: 14 pts (27%) withdrew and were not included in efficacy analyses, 5 for AEs (3 propranolol 160 mg; 1 propranolol 80 mg; 1 placebo washout) Not clear if baseline data gathered
Cerbo, Casacchia, Formisano, et al., 1986	CrOv QS: 1 (nr, db-, dd)	N = 27 Age: N/S % female N/S Common or classical migraine (Ad Hoc); 4-14 attacks/mo; history ≥ 2 yrs Chron: N/S Rec: N/S	***Pizotifen:*** 1.5 mg, 1x/day (at night); n = 21* (18 of whom completed both periods) ***Flunarizine:*** 15 mg, 1x/day (at night); n = 21* (18 of whom completed both periods) 1-mo baseline period (no HA-specific drugs); two 2-mo treatment periods; 15-day washout (drug-free); no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo ***Total pain index:*** Duration times severity, divided by duration; severity graded on scale of 1-4 (mild, moderate, intense, severe) ***HA duration:*** No. of hrs of pain/mo	An ANOVA analysis performed by the investigators found that both treatments significantly reduced ***HA frequency*** compared to baseline values ($p<0.01$ for flunarizine; $p<0.05$ for pizotifen). Only flunarizine significantly reduced the ***total pain index*** ($p<0.05$). Both drugs significantly reduced ***HA duration*** compared to baseline values ($p<0.01$ for flunarizine; $p<0.05$ for pizotifen). There were no significant differences between the two treatments for any of the above outcomes (no p-values reported). Analysis of the data using Student's t test and the Wilcoxon matched-pairs test confirmed the above results, except in the case of HA duration, for which flunarizine was found to be more effective than pizotifen. No baseline data were reported, and post-treatment data were reported only in graphic form; mean values could not be reliably read off the graphs.	Dropouts: 9 patients (33%) did not complete the trial, 4 due to AEs; 6 of these 9 (including all 4 who withdrew due to AEs) completed at least one treatment phase and were included in the efficacy analysis Not randomized; double-blinding not adequate

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Couch, Bearss, and Verhulst, 1987	SPPG QS: 1 (r, ndb, dnd)	N = 73 Age: N/S % female N/S Migraine Chron: N/S Rec: N/S	***Placebo:*** n = 26 ***Fenoprofen 200 mg:*** 3x/day; n = 23 ***Fenoprofen 600 mg:*** 3x/day; n = 24 4-wk baseline period (placebo); 12-wk treatment period; no follow-up Nothing on acute meds	***HA Index:*** Calculated as follows: $3(F_{DA} \times D_{DA}) + 2(F_S \times D_S) + 1(F_{MOD} \times D_{MOD})$, where F = frequency, D = duration, DA = disabling, S = severe, MOD = moderate/mild	Fenoprofen was no more effective than placebo at reducing HA index from week 0 (start of treatment) to week 12 (no p-values reported). Mean week 0 and 12 migraine scores were 216 and 161 in the 600-mg group (25% reduction), 140 and 95 in the 200-mg group (32% reduction), and 222 and 168 in the placebo group (24% reduction) (no variance data reported).	Dropouts: Not described Abstract reporting very limited information Low quality score (1); not double-blind; dropouts not described

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Couch and Hassanein, 1979 *and* Couch and Hassanein, 1976 (12-mo interim report)	SPPG QS: 4 (r, db+, dd)	N = 162 Age: N/S 84% female Migraine; ≥ 2 disabling or severe HAs in mo prior to study Chron: N/S Rec: HA clinic	***Placebo:*** n = 53 (final report); n = 36 (interim report) ***Amitriptyline:*** 50 mg/day for first wk; 75 mg/day for second wk; 100 mg/day for wks 3-4; patients instructed to contact investigator if AEs experienced; n = 47 (final report); n = 37 (interim report) 4-wk baseline period (placebo); 4-wk treatment period; at end of 4-wk treatment period, patients given option of continuing on same med for another 4 wks or taking amitriptyline as an open trial for 4 wks Use of acute meds permitted	Patients graded each HA as "disabling" (must go to bed), "severe" (>50% limitation of activity), "moderate" (10-50% limitation of activity), or "mild" (<10% of activity); most "disabling" and "severe" HAs were migrainous, while "moderate" and "mild" HAs were frequently tension-type or nonspecific in type Both interim and final publications reported results for ***weighted migraine index (M):*** $M = 2(FxD)_{disabling} + 1(FxD)_{severe}$, where F = frequency (no. of HAs/mo) and D = mean duration (hrs) Interim publication also reported results for ***weighted total HA index (TH):*** $TH = 4(FxD)_{disabling} + 3(FxD)_{severe} + 2(FxD)_{moderate} + 1(FxD)_{mild}$, where F = frequency and D = duration	***Mean weighted migraine index scores (continuous data)*** for wks 1-4 (pre-treatment) and 5-8 (post-treatment) were not reported in the final publication, but investigators stated that when the pre- to post-treatment differences were compared, amitriptyline was significantly better than placebo ($p<0.01$). The interim report provided mean scores for 73 of the 100 patients who were eventually included in the efficacy analysis. For the amitriptyline group, the mean weighted migraine index score was 112.1 pre-treatment and 68.5 post-treatment, a difference of -43.7 (no variance data reported). For the placebo group, the corresponding mean scores were 67.7 and 104.1, a difference of +36.3 (no variance data reported). When the pre- to post-treatment differences were compared, amitriptyline was significantly better than placebo ($p<0.01$). Very similar continuous results were reported in the interim report for the ***mean weighted total HA index scores*** ($p<0.02$ in favor of amitriptyline). ***Mean weighted migraine index scores (dichotomous data):*** The final publication reported that an improvement of 50% or more in the mean migraine index score was achieved by 26/47 (55%) patients in the amitriptyline group, and by 18/53 (34%) in the placebo group ($p<0.05$). Among those patients who had achieved 50% or more improvement by the end of the active treatment period and who chose to continue in the double-blind trial for another 4 wks (amitriptyline, n = 23; placebo, n = 13), patients in the amitriptyline group maintained their improvement significantly better than did patients in the placebo group ($p<0.05$).	Dropouts: 62 (38%), 7 due to AEs (5 amitriptyline, 2 placebo); 46/62 dropouts withdrew before the end of the baseline period

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Dahlöf, 1987	CrOv QS: 4 (r, db+, dd)	N = 28 Age: N/S (range: 18-60) 93% female Common or classical migraine; hist. ≥ 2 yrs; ≥ 2-8 well-defined migraines/mo, plus fulfillment of ≥ 4 of 7 criteria, including photo- or phonophobia, auras, etc. Excl: Previous treatment with beta-blockers Chron: N/S (range: N/S) Rec: N/S, but "outpatients"	***Placebo:*** n = 28* ***Propranolol (Inderal®):*** 40 mg, 3x/day; n = 28* 4-wk run-in; two 1-mo treatment periods, each followed by a 5-mo assessment period; no follow-up (other than the two assessment periods) Patients permitted to use their usual meds for acute migraine attacks	***HA frequency:*** Not defined, but recorded daily by pts ***Integrated HA:*** Not defined	Propranolol reduced ***HA frequency*** (number of HAs/4 wks) from 4.3 (± 0.4) (SEM) to 3.2 (± 0.4) compared with placebo. Investigators reported that propranolol was significantly better than placebo at reducing this outcome ($p < 0.01$). No results were provided for pre- to post-treatment results.	Dropouts: 0 Information obtained from abstract

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Das, Ahuja, and Naraina-swamy, 1979	CrOv QS: 2 (nr, db+, dnd)	N = 20 Age: N/S (range: 20-48) 70% female Chron: N/S Migraine (Ad Hoc); hist. of Ms ≥ 1 yr; ≥ 2 Ms/mo in 3 mos before trial Rec: N/S	***Placebo:*** n = 20* ***Clonidine:*** 25 µg, 2x/day; n = 20* Baseline data obtained before each of two 6-wk treatment periods; no washout; no follow-up Nothing on acute meds	***HA frequency:*** Definition N/S ***HA intensity:*** Reported as a "severity index" from intensity ratings gathered on 3-point scale (1=mild; 2=moderate, inconvenient; 3=severe, incapacitating). Severity index calculated by multiplying no. of HAs/6 wks by intensity ratings	Results were reported only as group mean scores, and investigators did not clarify whether these scores were derived from one or both treatment periods. For ***HA frequency***, the mean scores were 8.2 and 8.0 for pts taking clonidine or placebo, respectively. For ***HA intensity*** (severity index), the mean scores were 21.4 and 21.9 for pts taking clonidine or placebo, respectively. Investigators found no statistically significant difference between the two treatments for either ***HA frequency*** or ***intensity*** ($p>0.05$ for each outcome measure). Investigators did not provide results for the efficacy of each intervention before and after treatment. They did report, however, that "[a] statistically significant difference was found when the pre-treatment period was compared to the treatment period (clonidine and placebo) indicating that placebo or clonidine were almost equally effective in the prophylaxis of migraine."	Dropouts: N/S Not clear how baseline data obtained or how results determined from that data Not clear whether data obtained from pts' diaries or by other means
De Benedittis and Massei, 1986	CrOv QS: 4 (r, db+, dd)	N = 40 Age: 41 (range: 18-59) 65% female Migraine (Ad Hoc); hist. ≥ 10 HAs/mo for ≥ 1 yr Excl: < 18 or > 60 yrs + HI < 10 (see "Outcomes" for definition) Chron: N/S (range: N/S) Rec: Pain research & treatment unit of university	***Placebo:*** n = 31* ***Oxitriptan (L-5-HTP)***: 400 mg/day orally; n = 31* 1-mo washout period; two 2-mo treatment periods; no washout between treatment periods; no follow-up Patients asked to discontinue or minimize use of analgesics and to avoid foods containing monoamines; no other acute meds mentioned	***HA index:*** Termed "headache density" and calculated by multiplying ***HA frequency*** by ***HA intensity*** score ***HA frequency:*** Defined as "number of HA days" and termed "headache index" ***HA intensity:*** Rated *by patient* on 11-point scale; *investigator* grouped pt's "1-3" ratings as "1," the "4-6" ratings as "2," and the "≥ 6" ratings as "3"	The between-group results were provided only on a figure from which it is difficult to determine precise results. However, investigators reported that there was no significant difference between the active drug and placebo for reducing ***HA index*** (no p-value given). For ***HA index***, the overall mean score (SEM in parentheses) decreased from 43.8 (± 2.7) at baseline to 26.0 (± 2.9) after the first month and to 25.1 (± 3.2) after the second month following treatment with the active drug. The difference between the pre- and post-treatment mean scores was statistically significant for both reductions ($p < 0.0001$ for each comparison). Also for ***HA index***, the overall mean score decreased from 43.8 (± 2.7) at baseline to 26.5 (± 2.9) after the first month and to 26.5 (± 3.3) after the second month following treatment with placebo. The difference between the pre- and post-treatment mean scores was statistically significant for both reductions ($p < 0.0001$ for each comparison).	Dropouts: 9, (23%), 1 due to AEs (placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Dennerstein, Morse, Burrows, et al., 1988	CrOv QS: 3 (r, db, dd)	N = 22 Age: 40 100% female Migraine; regularly occurring attacks during the 7 days encompassing menstruation; typically of severe intensity and not relieved by minor analgesics Chron: N/S Rec: Referrals to menstrual disorders clinic	***Placebo:*** n = 19* ***Estradiol (percutaneous gel, Oestrogel®):*** 1.5 mg estradiol in 2.5 g gel per application; applied to upper arms and body using a special graduated applicator; applied for 7 days per cycle, beginning at least 2 days before expected migraine; n = 19* Baseline period lasting 2 menstrual cycles; two 2-cycle treatment periods; no washout; 1-cycle follow-up (no treatment) Acute meds permitted	***HA frequency:*** No. of days with migraine of moderate to severe intensity during 7 days encompassing menstruation	Estradiol was significantly better than placebo at reducing ***HA frequency*** during the 7 days encompassing menstruation ($p<0.05$). A total of 47 days with migraine were reported with estradiol, compared with 86 with placebo.	Dropouts: 3 (14%), 1 due to AEs (estradiol); one other patient withdrew due to AEs after 2 mos of treatment with placebo and one mo with estradiol, but was included in the efficacy analysis Most patients also reported migraines at other times of the month "Nearly all" had tried preventive med before, but found it ineffective for their hormonally-triggered HAs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Diamond and Freitag, 1993 *and* Freitag, Diamond, and Diamond, 1991	SPPG QS: 4 (r, db+, dd)	N = 143 Age: 35 74% female Migraine w/ or w/o aura; ≥ 2-yr history; 2-8 attacks/ mo in last 3 mos (and during baseline period); no migraine prophylactic meds in last 3 mos; patients with combination HA (migraine and TTH) excluded Chron: 17 yrs Rec: HA clinic outpatients	***Placebo:*** n = 51 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 50 4-wk baseline period (placebo); 20-wk treatment phase; no follow-up Use of acute meds permitted	Patients evaluated at approximately 1-mo intervals; following measures calculated and analyzed: ***HA index:*** Severity index times the duration index ***HA frequency:*** No. of attacks/mo ***Frequency index:*** No. of attacks divided by no. of days in evaluation period ***Severity index:*** Sum of severity of attacks divided by no. of days in evaluation period; severity of each attack rated on scale of 1-3 (mild-severe) ***Duration index:*** Sum of duration of attacks divided by no. of days in evaluation period	There was no significant difference between the two treatments for reduction in ***HA index*** from baseline to last visit (p=0.063). Mean change from baseline (± SD) was -2.083 (± 3.816) in the flunarizine group and -0.640 (± 3.900) in the placebo group. Flunarizine was significantly better than placebo at reducing ***HA frequency*** (p<0.05). In the flunarizine group, mean HA frequency was 4.2 at baseline and was reduced by an average of 2.3 attacks per month after five months of treatment; corresponding values in placebo group were 4.4 and 1.7 (no variance data reported). 20/50 patients in the flunarizine group (40%) reported a 50% or greater reduction in ***HA frequency or severity*** from baseline to final visit, compared to 17/51 patients in the placebo group (33%); the difference between the two treatments was not statistically significant (p=0.54).	Dropouts: 42 patients (29%) dropped out before completing 1 mo of active treatment and were thus excluded from the efficacy analysis; 5 patients treated with flunarizine and 3 treated with placebo withdrew due to AEs, but it is not clear whether they were among the 42 who failed to complete 1 mo of treatment None of the study participants had a history of drug treatment failure for migraine

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Diamond and Medina, 1976	CrOv QS: 3 (r, db, dd)	N = 83 Age: 38 (average) (range: 21-62) 81% female Common or classical migraine; frequency N/S Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 62* ***Propranolol:*** 80 mg (or up to 160 mg/day -- see below); n = 62* No baseline period described; two treatment periods at least 4 wks long -- at the end of the first 4 wks of each period, pt could choose to stop the drug or continue for up to 6 or 8 wks; at the end of the second, fourth, or sixth wks of each period, pt could choose to double the amount of medication or placebo or to remain on the same dosage; no washout; no follow-up Analgesics, narcotics, or ergotamines permitted for acute migraine attacks, but not prophylactics	***HA index:*** Defined as "total of HA units divided by number of days observed" ***HA frequency:*** Termed "HA units," but not defined	Results were reported as "patients' preference" for one intervention over the other one, and we could not analyze the results.	Dropouts: 21 (25%), 7 due to AEs (propranolol 6, placebo 1) Not clear how data gathered
Diamond, Solomon, Freitag, et al., 1987	SPPG QS: 4 (r, db+, dd)	N = 118 Age: N/S (range: 19-62) 81% female Classic and/or common migraine (Ad Hoc); history ≥ 2 yrs; ≥ 3 mod-severe HAs/mo; no daily HA or chronic cephalgia other than migraine Chron: N/S Rec: N/S	***Placebo:*** n = 35 ***Fenoprofen 200 mg:*** 3x/day; n = 34 ***Fenoprofen 600 mg:*** 3x/day; n = 27 2-wk washout period for patients using prophylactic med; 4-wk baseline period (placebo); 12-wk treatment period; no follow-up Use of meds for acute attacks permitted, though not aspirin or other NSAIDs	***HA index:*** (Sum of HA severity x duration for all HAs) ÷ no. of days in treatment period ***HA frequency:*** No. of HAs divided by no. of days in treatment period	For both HA index and HA frequency, investigators analyzed the number of patients with no improvement, <50% improvement, and >50% improvement compared with baseline values. For ***HA index***, fenoprofen 600 mg, but not 200 mg, was significantly better than placebo ($p<0.001$, 600 vs. placebo; no p-value reported for 200 vs. placebo); there was no significant difference between the two doses of fenoprofen (no p-value reported). 16/27 patients (59%) taking fenoprofen 600 mg reported a > 50% improvement, as did 11/34 patients (32%) taking fenoprofen 200 mg and 11/35 patients (31%) taking placebo. Both doses of fenoprofen were significantly better than placebo for ***HA frequency*** ($p<0.05$ for 200 mg; $p<0.005$ for 600 mg); there was no significant difference between the two doses (no p-value reported).	Dropouts: 16 (14%), 11 due to AEs (4 600 mg, 3 200 mg, 4 placebo); another 6 patients (5%) were excluded from the analysis of the data on HA index due to inadequate reporting

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ekbom, 1975	CrOv QS: 3 (r, db, dd)	N = 33 Age: 41 (range: 17-58) 82% female Common or classical migraine; hist. ≥ 3 HAs/mo (most had more frequent HAs) Chron: N/S (range: N/S) Rec: N/S, but treated at neuro. clinic in Sweden	***Placebo:*** n = 28* ***Alprenolol:*** 200 mg, 2x/day; n = 28* No baseline described; two 6-wk treatment periods; 1-wk washout between treatment periods (no meds); no follow-up Patients permitted to take their usual meds (all contained ergotamine) for acute migraine attacks	***HA index:*** Calculated as the sum of HA frequency and intensity for each 3-wk period ***HA frequency:*** Not defined, but recorded daily by pts ***HA intensity:*** Rated on 3-point scale and recorded daily by pts	The average ***HA index*** per patient per wk was 4.0 (± 0.7) (SEM) after treatment with alprenolol and was 3.8 (± 0.7) after treatment with placebo. There were no significant differences between the active drug and placebo for reducing HA index (no p-value reported). No baseline scores were provided. Investigators did not report having analyzed the pre- to post-treatment results for statistical significance.	Dropouts: 5 (15%), 1 due to AEs (alprenolol) Investigators provided an overall assessment of HA frequency based on number of HAs per patient
Ekbom and Lundberg, 1972	SPPG QS: 3 (r, db, dd)	N = 30 Age: 34 (range: 19-56) 87% female Classic or common migraine (Ad Hoc); ≥ 4 attacks/mo Chron: N/S Rec: N/S	***Placebo:*** n = 10 ***Pindolol 5 mg:*** 3x/day; n = 9 ***Pindolol 2.5 mg:*** 3x/day; n = 7 1-mo baseline period; 1-mo treatment period; no follow-up Patients permitted to use ergotamine compounds to treat acute attacks	***HA index:*** Sum of severity scores; severity of each attack graded on scale of 1-3 ***HA frequency:*** No. of attacks/mo ***HA duration:*** Per attack, in hrs	Neither dose of pindolol significantly reduced ***HA index*** scores compared with baseline values (no p-values reported). In the placebo group, mean HA index scores were 18 during the baseline period and 14 during treatment; in the low-dose pindolol group, the corresponding figures were 21 and 21, respectively; and in the high-dose group, 20 and 16, respectively (no variance data reported). The authors speculated that the doses used may have been too small to have an effect. Similar results were reported for ***HA frequency*** and ***duration***.	Dropouts: 4 (13%), all due to AEs (pindolol, dose N/S)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ekbom and Zetterman, 1977	CrOv QS: 2 (nr, db, dd)	N = 34 Age: 42 (range: 18-55) 77% female Classical or common migraine (Ad Hoc); ≥ 3 attacks/mo Chron: N/S Rec: Neuro dept	***Placebo:*** n = 30* ***Oxprenolol:*** 80 mg, 3x/day; n = 30* No baseline period described; two 8-wk treatment periods; 1-wk washout (no medication); no follow-up Patients permitted to take their usual meds for acute attacks	***HA index:*** No. of HA days times severity of attacks; severity of each attack graded on scale of 1-3 (mild, moderate, severe) ***HA frequency:*** No. of attacks	There was no significant difference between the two treatments for ***HA index***. Mean HA index (± SEM) was 30.9 (± 3.7) during treatment with oxprenolol and 33.9 (± 3.8) during treatment with placebo. Similar results were reported for ***HA frequency***.	Dropouts: 4 (12%), none due to AEs Low quality score (2); not randomized
Elkind, Webster, Herbertson, et al., 1989a	SPPG QS: 2 (nr, db, dd)	N = 37 Age: N/S (range: N/S) 84% female Chron: N/S Common or classical migraine; ≥ 3 days of Ms/mo when not taking prophylactic meds Rec: N/S	***Placebo***: n = 12 ***Guanfacine:*** 0.5 mg/day; n = 13 ***Guanfacine:*** 1.0 mg/day; n = 12 2-wk washout prior to 4-wk baseline; 12-wk treatment period followed by 2 wks of tapering; follow-up (length N/S) Nothing on acute meds	***HA frequency:*** No. of migraine days/mo ***Frequency of HAs with nausea/vomiting:*** Defined as "migraines/mo with nausea/vomiting"	Results were reported only as one-sided p-values for comparisons of each active treatment with placebo. For ***HA frequency***, guanfacine 1.0 mg was significantly better than placebo (p=0.005), whereas guanfacine 0.5 mg was not significantly different from placebo (p=0.62). For ***frequency of HAs with nausea/vomiting***, guanfacine 1.0 mg was again significantly better than placebo (p=0.01), whereas guanfacine 0.5 mg was not significantly different from placebo (p=0.64). No within-group results were provided for comparisons of ***HA frequency*** or ***frequency of HAs with nausea/vomiting*** before and after treatment with each intervention.	Dropouts: 3 (8%), all due to AEs (treatment group N/S); data from these pts were included in efficacy analyses Results are from 1 site of 2-site study

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ferrari, Wilkinson, Hirt, et al., 1991	SPPG QS: 4 (r, db+, dd)	**Both studies** N = 204 Common or classical migraine (Ad Hoc); hist. of migraine ≥ 1 yr; 2-10 HAs/mo in 2 mos prior to & during baseline Excl: Use of migraine prophylactic meds in 2 wks prior to baseline; complicated or ophthalmoplegic migraine; concurrent use of "drugs potentially influencing migraine" or "prophylactic non-drug treatments" Rec: N/S **Study 1** N = 146 Age: 42 (range: 18-70) 75% female Chron: N/S (range: N/S) **Study 2** N = 58 Age: 41 (range: 18-	**Study 1** ***Placebo:*** n = 47 ***Tropisetron HCl (ICS 205-930)***: 25 mg/day; n = 43 ***Tropisetron HCl (ICS 205-930)***: 50 mg/day; n = 45 2-wk washout period from previous prophylactic migraine treatment; 1-mo baseline period of placebo treatment and observation; 3-mo treatment period; no follow-up Analgesic meds permitted; no mention of other acute migraine meds **Study 2** ***Placebo:*** n = 17 ***Tropisetron HCl (ICS 205-930)***: 15 mg/day; n = 30 Same washout, baseline, and treatment periods as in Study 1 Analgesic meds permitted; no mention of other acute migraine meds	***HA frequency:*** Defined as "no. of HAs/mo"; considered the "primary efficacy variable" by investigators ***HA index:*** Calculated as no. of HAs multiplied by ***HA intensity*** grade ***HA intensity:*** Rated daily on 3-point scale by pt	**Study 1** Results were reported on graphs from which it was difficult to obtain precise numbers. Investigators reported that neither dose of tropisetron was significantly better than placebo at reducing ***HA frequency*** ($p > 0.05$, both cases). Investigators did not report having compared the two doses of tropisetron. From baseline to 3 mos, there was "virtually no change" in the mean proportional change in ***HA frequency*** for the group receiving tropisetron 50 mg. Over the same period, both the placebo and the tropisetron 25 mg groups reduced ***HA frequency***, though not at a statistically significant level ($p > 0.05$, both cases). Investigators also reported results for "responders" and "partial responders" to treatment. Responders were pts who had achieved ≥ 50% reduction in *both* ***HA index*** and ***HA frequency*** from pre- to post-treatment. In Study 1, 20% (9/45), 35% (15/43), and 21% (10/47) of pts were responders to tropisetron 50 mg, Tropisetron 25 mg, and placebo, respectively. There were no significant differences between either active dose and placebo ($p > 0.05$, both cases). Partial responders were pts who had achieved ≥ 50% reduction in *either* ***HA index*** or ***HA frequency***. Thirteen of 45 (29%), 16/43 (37%), and 19/47 (40%) of pts were partial responders to tropisetron 50 mg, 25 mg, and placebo, respectively. Investigators did not report having compared these results for statistical significance. **Study 2** Results were reported on graphs from which it was difficult to obtain precise numbers. Investigators reported that 15 mg/day of tropisetron was not significantly better than placebo at reducing ***HA frequency*** ($p > 0.05$). After 3 mos, the tropisetron 15 mg group reduced ***HA frequency*** significantly ($p < 0.05$). Over the same period, the placebo group had reduced ***HA frequency***, but not at a statistically significant level ($p > 0.05$). (cont'd)	Dropouts: **Study 1** -- 11 (8%), 7 due to AEs (4, 50 mg tropisetron; 2, 25 mg tropisetron; 1, placebo) **Study 2** -- 11 (19%), 3 due to AEs (all from 15 mg tropisetron) Data are from 2 trials of a multicenter study, 1 in Belgium, France, and The Netherlands (Study 1), and 1 in the U.K. (Study 2) In 13 patients from Study 1, constipation led to reduction of dose by 0.5 -1 capsule every other day; dose not reduced in Study 2

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ferrari, Wilkinson, Hirt, et al., 1991 (cont'd from previous page)					Investigators also reported results for "responders" and "partial responders" to treatment. Responders were pts who had achieved ≥ 50% reduction in *both* ***HA index*** and ***HA frequency*** from pre- to post-treatment. In Study 2, 43% (13/30) and 23% (4/17) of pts were responders to tropisetron 15 mg and placebo, respectively. There was no significant difference between the active dose and placebo ($p > 0.05$). Partial responders were pts who had achieved ≥ 50% reduction in *either* ***HA index*** or ***HA frequency***. Seventeen of 30 (57%) and 6/17 (35%) of pts were partial responders to tropisetron 15 mg and placebo, respectively. Investigators did not report having compared these results for statistical significance.	
Fiorini, Sances, Martignoni, et al., 1991	CrOv (analyzed as SPPG) QS: 3 (r, db, dd)	N = 20 Age: 33 100% female Perimenstrual migraine (not defined); normal menstrual cycles Chron: N/S (range: 2-15 yrs) Rec: N/S	***Placebo:*** n = 19* ***Dihydroergokryptine (DEK):*** 10 mg, 2x/day (half dose administered in first week); n = 19* 2-mo baseline period; 2-menstrual-cycle treatment period; no washout; no follow-up Nothing on acute meds	***HA index:*** Not defined	Mean ***HA index*** scores were reported separately for the two treatment sequence groups. We analyzed the data from the first treatment period as if the trial were parallel-group. Among patients taking placebo during the first treatment period (n = 9), mean ***HA index*** scores (± SD) were reduced from 93.2 (± 31.1) at baseline to 60.8 (± 33.5). Among those taking DEK first (n = 10), scores were reduced from 84.4 (± ?) at baseline to 32.9 (± 26.7). Both reductions were statistically significant ($p<0.01$). We calculated an effect size based on post-treatment means only, since an anomalous SD (2.8) was reported for the pre-treatment mean in the DEK-first group.	Dropouts: 1 (5%), not due to AEs Abstract reporting limited results
Formisano, Falaschi, Cerbo, et al., 1991	SPPG QS: 2 (r, ndb, dd)	N = 22 Age: 39 53% female Migraine w/ or w/o aura (IHS); no prophylactic med in past 3 mos Chron: 20 yrs Rec: N/S	***Propranolol:*** 40 mg, 3x/day; n = 8 ***Nimodipine:*** 40 mg, 3x/day; n = 11 1-mo baseline period (placebo); 4-mo treatment period; 1-mo washout period Acute meds permitted	***HA frequency:*** No. of attacks/mo	Both treatments significantly reduced ***HA frequency*** from basal levels (at time of admission to trial) to the end of the 4th treatment month ($p<0.05$ for both drugs). Mean basal frequencies (± SD) were 4.0 (± 1.2) in the nimodipine group and 5.0 (± 2.0) in the propranolol group. During the fourth month of treatment, these mean frequencies were reduced to 2.9 (± 1.7) in the nimodipine group and 2.6 (± 1.5) in the propranolol group. There was no significant difference between the two treatments for this outcome (p-value not reported).	Dropouts: 3 (14%), all due to AEs (2 pro-pranolol, 1 nimodipine) Not clear how "basal" frequency established

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Forssman, Henriksson, Johannsson, et al., 1976	CrOv QS: 4 (r, db+, dd)	N = 40 Age: 37 (range: 17-51) 88% female Common or classical migraine; ≥ 3 HAs/mo; "serious and prolonged HAs" Excl: Hist. of earlier treatment with prophylactics Chron: 19 (range: 2-40) Rec: N/S	***Placebo:*** n = 32* ***Propranolol:*** 20 mg (½ tab), 3x/day for 7 days; then 40 mg, 3x/day for 7 days; then 80 mg, 3x/day; n = 32* 10-wk baseline (no active drug or placebo); two 12-wk treatment periods; no washout, but first 2 wks of each treatment period excluded from analysis; no follow-up Acute migraine meds permitted (analgesics and ergotamines), but not prophylactics	***HA index:*** Calculated from HA intensity (rated on 3-point scale) and duration ***HA frequency:*** Not defined, but recorded daily by pts	***HA index*** was reduced from a mean score (and SD) of 5.14 (± 2.98) at baseline to 4.77 (± 3.45) and 3.00 (± 2.81) after treatment with placebo or propranolol, respectively. Propranolol was significantly better than placebo at reducing this outcome ($p < 0.01$). Investigators did not report pre- to post-treatment results.	Dropouts: 8 (20%), 4 due to AEs (propranolol, 2; (placebo, 2)
Forssman, Henriksson, and Kihlstrand, 1972	CrOv QS: 4 (r, db+, dd)	N = 22 Age: 40 (range: 16-56) 53% female Classic or common migraine (Ad Hoc); ≥ 2-3 HAs/mo; one patient had cluster HA Chron: N/S Rec: N/S	***Methysergide:*** 4-6 mg/day (dose adjusted over first 10 days of treatment period); n = 17* ***Pizotifen:*** 2-3 mg/day (dose adjusted over first 10 days of treatment period); n = 17* 6-wk baseline period (no prophylactic med); two 10-wk treatment periods; no washout, but only last 6 wks of each treatment period analyzed; no follow-up Acute meds permitted	***HA index:*** Mean HA index per week, where HA index = frequency times severity ***HA frequency:*** Mean no. of attacks per week ***HA severity:*** Mean severity per attack per week; each attack graded on scale of 1-3 (slight, moderate, severe) ***HA duration:*** Mean duration per attack (hrs)	Both pizotifen and methysergide significantly reduced ***HA index*** scores in comparison with the baseline period ($p<0.01$ for both comparisons); there was no significant difference between the two treatments for this outcome (no p-value reported). Mean HA index scores were 3.5 during the baseline period, 2.1 with pizotifen, and 1.8 with methysergide (no variance data reported). Similar results were reported for ***HA frequency***. Neither treatment significantly reduced ***HA severity*** or ***duration*** compared with baseline.	Dropouts: 5 (23%), 1 due to AEs (experienced with both drugs) One patient included in the efficacy analysis had cluster HA, not migraine

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Forssman, Lindblad, and Zbornikova, 1983	CrOv QS: 4 (r, db+, dd)	N = 24 Age: 40 (range: 17-55) 80% female Migraine (Ad Hoc); frequency N/S Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 20* ***Atenolol:*** 100 mg, 1x/day; n = 20* 2-mo baseline period; two 3-mo treatment periods; 2-wk washout period between treatment periods; no follow-up period Analgesics and ergotamines, but not prophylactics, permitted for acute migraine attacks	***HA index:*** Calculated as a ratio of "integrated HA" (which combined HA intensity & duration) over HA frequency ***HA frequency:*** Defined as "number of HA attacks" and recorded by pts on forms ***HA intensity***: Rated by pt on 3-point scale and recorded on forms	***HA frequency*** was reduced to mean values per day of 0.17 and 0.23 after treatment with atenolol or placebo, respectively. No baseline mean scores were reported. Investigators did not report having analyzed the results for statistical significance.	Dropouts: 4 pts (17%) withdrew, 1 due to AEs (Atenolol), but were included in efficacy analyses
Frediani, Grazzi, Zanotti, et al., 1991	CrOv (analyzed as SPPG) QS: 4 (r, db+, dd)	N = 30 Age: 34 (range: 20-47) 77% female Migraine w/o aura (IHS) Chron: N/S Rec: N/S	***DHE (timed-release):*** 5 mg, 2x/day; n = 27* (completed both periods); n = N/S (took DHE during first period) ***Dihydroergokryptine (DEK):*** 10 mg, 2x/day (half dose administered for first 15 days); n = 27* (completed both periods); n = N/S (took DEK during first period) 1-mo baseline period (non-ergot analgesics only); two 4-mo treatment periods; 2-mo washout (non-ergot analgesics only); no follow-up Acute meds permitted	***HA index:*** $1D_1 + 2D_2 + 3D_3$, where D_1 = total no. of hrs/mo with HA of intensity 1, etc. ***HA frequency:*** No. of HA days/mo	Investigators found a significant carry-over effect ($p<0.05$) and so analyzed the first-period data only. DEK significantly reduced ***HA index*** (by 35%) in comparison with baseline values ($p<0.05$); the reduction produced by DHE (27%) was not statistically significant (no p-value reported). The two treatments were not directly compared for this outcome. DEK reduced ***HA frequency*** by 31% compared to baseline, DHE by 23% (no p-values or other measures of statistical significance reported).	Dropouts: , 4 due to AEs (3 DHE, 1 DEK)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Freitag and Diamond, 1984	SPPG QS: 4 (r, db+, dd)	N = 32 Age: 36 (range: 23-57) 81% female Common or classical migraine (Ad Hoc); frequency N/S Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 8 ***Nadolol:*** Nadolol treatment group comprised pts from 3 groups who had taken 80, 160, and 240 mg of nadolol; had achieved similar results; and had been combined into one group; n = 24 2-mo baseline (placebo); one 3-mo treatment period; no follow-up Patients permitted to take usual acute migraine meds as long as dosages remained constant; no prophylactics; no nonpharmacological treatments (e.g., biofeedback)	***HA index:*** Termed "intensity index" and defined as "sum of intensity units, divided by number of days observed"; "intensity units" derived from HA intensity score (rated on 4-point scale) multiplied by number of HAs with relevant intensity score ***HA frequency:*** Termed "frequency index" and defined as "number of distinct HAs (bracketed by 24-hr HA-free periods), divided by the number of days in observation period"	Seven of 22 patients (32%) treated with nadolol improved (achieved ≥ 50% reduction in ***HA index*** from pre- to post-treatment), but none of 8 patients improved after treatment with placebo. The difference between the two treatments was not significant (p = 0.073). Authors did not report having analyzed the pre- to post-treatment differences for statistical significance.	Dropouts: 1 pt (3%) was withdrawn due to AEs (nadolol) but was included in efficacy analyses
Frenken and Nuijten, 1984	SPPG QS: 4 (r, db+, dd)	N = 35 Age: N/S (range: 20-51) 83% female Common or classic migraine (Ad Hoc); HAs throbbing or pulsating in character and severe or unbearable in intensity; ≥ 1 attack/mo; no cluster HA Chron: 14 yrs (median) (range: 1-35) Rec: Family practice(s?)	***Placebo:*** n = 18 ***Flunarizine:*** 10 mg, 1x/day; n = 17 All anti-migraine medication withdrawn prior to treatment period (no clear baseline period described); 12-wk treatment period; no follow-up Patients permitted to take their usual acute meds	***HA frequency:*** Mean no. of attacks/mo; % reduction in mean no. of attacks/mo from baseline	After the first month of treatment, the percentage reduction in ***HA frequency*** (vis-à-vis baseline) was significantly higher in the flunarizine group than in the placebo group (p=0.029). Mean monthly HA frequency in the flunarizine group was 3.3 at baseline, 2.1 during treatment month 1, 1.5 during treatment month 2, and 0.8 during treatment month 3 (no variance data reported). Corresponding figures for the placebo group were 3.8, 3.4, 3.4, and 2.6, respectively (no variance data reported).	Dropouts: 0 15/35 patients had been treated prophylactically before, 10 of them un-successfully Not clear how baseline frequency established (baseline period not clearly described)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Gawel, 1987	CrOv QS: 3 (r, db, dd)	N = 60 Age: N/S % female N/S Classical and common migraine Chron: N/S Rec: N/S	***Pizotifen:*** 3 mg, 1x/day (bedtime); n = 54* (crossover); n = 29 (first period, parallel-group) ***Nimodipine:*** 40 mg, 3x/day; n = 54* (crossover); n = 25 (first period, parallel-group) 1-mo baseline period; two 3-mo treatment periods; 1-mo washout; no follow-up Nothing on acute meds	***HA frequency:*** No. of attacks/mo	Investigators observed a dramatic rebound in ***HA frequency*** during the washout period among those patients treated first with pizotifen. This rebound effect made it difficult to interpret the crossover results, so we analyzed the first period data as if it were from a parallel-group trial (as did the investigators). Mean HA frequency (± SD) in the pizotifen group went from 7.55 (± 5.94) at baseline to 6.65 (± 6.34) after the first treatment period ($p<0.05$); the corresponding numbers in the nimodipine group were 7.56 (± 5.79) and 6.04 (± 4.68), respectively ($p>0.05$). The investigators' analysis found no significant difference between the two treatments for this outcome (no p-value reported).	Dropouts: 6 (10%); unclear how many (if any) of these were due to AEs Abstract reporting limited results
Gawel, Kreeft, Nelson, et al., 1992	SPPG QS: 4 (r, db+, dd)	N = 89 Age: 36 90% female Migraine w/ or w/o aura (World Fed of Neurology); 2-8 attacks/ mo; no prophylactic med in wk preceding trial; no propranolol in previous 6 mos Chron: > 16 yrs Rec: N/S	***Propranolol:*** Dose titrated over 8 days to max of 80 mg, 2x/day; n = 45 ***Flunarizine:*** 10 mg, 1x/day (dose reduced by half for first six days); n = 44 1-mo baseline period (placebo); 4-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of days with migraine; no. of attacks ***HA severity:*** Each attack graded on scale of 1-10 (mild-excruciating) ***HA duration:*** In hrs	Both treatments significantly reduced the mean ***no. of days with migraine*** per month compared with baseline ($p<0.001$ for both interventions). The percentage reduction at the end of treatment was greater with flunarizine (45%) than with propranolol (29%), but the difference between the two groups did not reach statistical significance (no p-value reported). Both treatments also significantly reduced the mean ***no. of migraine attacks*** per month ($p<0.0001$). Flunarizine was significantly better than propranolol during months 1 and 4 ($p<0.01$ for both timepoints). Percentage reduction in attack frequency at the end of treatment was 49% for flunarizine and 25% for propranolol. Mean values for these two HA frequency outcomes were reported in graphic form only and could not be reliably read off the graphs. Neither treatment significantly affected ***HA severity.*** Mean difference scores (baseline to last evaluable) (± SD) for HA severity were -0.02 (± 2.68) in the flunarizine group and -0.20 (± 2.95) in the propranolol group (no p-values reported). Neither treatment significantly affected ***HA duration.***	Dropouts: 13 patients (15%) withdrew before completing trial, 8 due to AEs (5 propranolol, 3 flunarizine); all 13 completed at least 1 mo of treatment and were included in the efficacy analysis Patients who had been unresponsive to more than two prophylactic meds were excluded

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Gelmers, 1983	SPPG QS: 4 (r, db+, dd)	N = 60 Age: 30 62% female Classic or common migraine (Ad Hoc); ≥ 2-3 HAs/mo Chron: 10 yrs Rec: Out-patients at neuro clinic	***Placebo:*** n = 22 ***Nimodipine:*** 40 mg, 3x/day; n = 28 2-wk baseline period (no prophylactic meds); 3-mo treatment period; no follow-up Acute meds permitted	Patients graded each HA as "disabling" (requiring bed rest), "severe" (≥50% limitation of activity), or "moderate to mild" (<50% limitation of activity); following index calculated using only attacks of severe or disabling intensity: ***Weighted migraine index (M):*** $M = 2(FxD)_{disabling} + 1(FxD)_{severe}$, where F = frequency (no. of HAs/mo) and D = mean duration (hrs)	In the nimodipine group, the ***mean weighted migraine index*** (± SD) was reduced from 56 (± 25) pre-treatment to19 (± 28) after 3 mos; the corresponding scores in the placebo group were 72 (± 39) and 53 (± 32), respectively. This represents a significantly greater percentage reduction in the nimodipine group (66%) than in the placebo group (26%) ($p<0.01$).	Dropouts: 10 (17%), all due to lack of therapeutic effect (2 nimodipine, 8 placebo)
Gerber, Diener, Scholz, et al., 1991	SPPG QS: 3 (r, db, dd)	N = 58 Age: 42 (range: 18-65) 81% female Migraine w/ or w/o aura (IHS); ≥ 2 attacks/mo in previous mo Chron: 21 yrs (range: 1-55) Rec: N/S	***Propranolol:*** 80 mg/day (low dose); 160 mg/day (high dose); 120, 80, and 40 mg/day (reduced dosages); n = 19 (randomized; unclear how many patients included in the efficacy analysis) ***Metoprolol:*** 100 mg/day (low dose); 200 mg/day (high dose); 150, 100, and 50 mg/day (reduced dosages); n = 22 (randomized; unclear how many patients included in the efficacy analysis) ***Nifedipine:*** 20 mg/day (low dose); 40 mg/day (high dose); 30, 20, and 10 mg/day (reduced dosages); n = 17 (randomized; unclear how many patients included in the efficacy analysis) 2-mo baseline period; 6-mo treatment period, divided as follows: 1 mo at low dose, 2 mos at high dose, 3 mos of successive reductions in dose; 2-mo follow-up after end of treatment Patients permitted to use their usual acute meds	***HA frequency:*** No. of days with migraine ***HA severity:*** Graded 3x/day on a visual analog scale (not described) ***HA duration:*** Measured for each attack (in hrs)	A time-series analysis (ARIMA) performed by the investigators found that, during the high-dose phase of the trial (treatment mos 4-6), a statistically significant ($z \leq -1.96$) reduction in ***HA frequency***, vis-à-vis baseline, was achieved by 32.0% of patients taking propranolol, 54.4% taking metoprolol, and 7.7% taking nifedipine (number of patients analyzed in each group could not be established). Conventional ANOVA analysis showed significant differences among the three treatments at the 5% level for ***HA frequency***. The Scheffé test revealed significant differences between metoprolol and nifedipine, but not between metoprolol and propranolol or between propranolol and nifedipine. The same combination of ANOVA and Scheffé analyses showed that metoprolol was significantly ($p<0.05$) better than nifedipine and propranolol for ***HA severity***; there was no significant difference between propranolol and nifedipine for this outcome.	Dropouts: 20 patients (34%) did not complete entire treatment period; 7 withdrew after baseline period; 1 during high-dose period; 12 after high-dose period; not clear which of these patients (if any) were included in the efficacy analysis; not clear how many withdrew due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Gerber, Schellenberg, Thom, et al., 1995	SPPG QS: 3 (r, db, dd)	N = 84 Age: 41 90% female Migraine w/ or w/o aura (IHS); ≥ 2-yr history; ≥ 2 attacks/mo for past 3 mos Chron: 20 yrs Rec: N/S	***Propranolol:*** 120 mg/day for 8wks; then 160 mg/day for 8 wks; n = 34 ***Cyclandelate:*** 1200 mg/day for 8 wks, then 1600 mg/day for 8 wks; n = 28 4-wk baseline period (HA recording); followed by 4-wk placebo period; followed by two 8-wk treatment periods, one low-dose, one high-dose Patients permitted to use their usual acute meds	***HA frequency:*** No. of days per month with reduced working ability due to migraine ***HA severity:*** Mean monthly severity score; severity of HA graded 3x/day using a visual analog scale (not described) ***HA duration:*** Migraine duration/mo	A time-series (ARIMA) analysis showed that, during the last 4 wks of the high-dose period, 12/28 patients taking cyclandelate (43%) had a statistically significant reduction of ***HA frequency*** vis-à-vis baseline, as did 11/34 patients taking propranolol (32%). There was no significant difference between the two treatments for this outcome (no p-value reported). More conventional analysis showed that, during the last 4 wks of the high-dose period, 20/28 (71%) patients taking cyclandelate and 18/34 (53%) patients taking propranolol reported a 50% or greater reduction in ***HA frequency*** from baseline. There was no significant difference between the two groups (no p-value reported). Both treatments significantly reduced mean ***HA frequency*** during the last 4 wks of the high-dose period compared to baseline values ($p<0.001$ for both treatments). In the cyclandelate group, mean HA frequency was reduced over this period of time from 6.3 to 2.7; the corresponding figures in the propranolol group were 5.7 and 3.1 (no variance data reported for either group). There was no significant difference between the two groups (no p-value reported). Similar results were reported for ***HA severity*** and ***HA duration***.	Dropouts: 22 (26%), "most" due to AEs or lack of motivation None of the patients had used prophylactic meds before

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Gomersall and Stuart, 1973	CrOv QS: 3 (r, db, dd)	N = 26 Age: N/S 75% female Classical, common, or hemiplegic migraine (Ad Hoc); > 2 attacks/mo; 50% of attacks of ≥ moderate severity Chron: N/S Rec: Volun-teers recruited through British Migraine Assoc and press ads	***Placebo:*** n = 20* ***Amitriptyline:*** 30 mg/day for two wks (preferably at night); increased to 60 mg/day if no therapeutic effect observed after two wks; if AEs occurred, dose could be reduced; n = 20* 26-wk baseline period; two 27-wk treatment periods; no washout, but data from first wk of each treatment period excluded to minimize carry-over effects Patients allowed to take their usual acute meds, but asked not to change these during trial	***HA frequency:*** No. of attacks in each trial period; no. of patients improving by 50% or more on amitriptyline vs. placebo	***HA frequency:*** The total number of attacks experienced in 26 wks on amitriptyline (207) was significantly lower than the total number experienced on placebo (356) ($p<0.001$). Nine of 20 patients (45%) reported a 50% or more reduction in the number of HAs on amitriptyline, compared with placebo. Four of the same 20 patients (20%) had more frequent attacks on amitriptyline than on placebo, but the degree of their improvement on placebo was not quantified.	Droupouts: 6 (23%), 1 due to AEs (placebo)
Grotemey-er, Schara-finski, Schlake, et al., 1990	CrOv QS: 3 (nr, db+, dd)	N = 28 Age: 31 82% female Common migraine (Ad Hoc); history > 3 yrs; 4-8 attacks/mo; no attacks lasting > 24 hrs Chron: 10 yrs Rec: N/S	***Metoprolol:*** 200 mg, 1x/day; n = 21* ***Aspirin:*** 500 mg, 3x/day; n = 21* 2-mo baseline period (no prophylactic treatment); two 3-mo treatment periods; no washout, but first month of each treatment period excluded from the analysis to reduce crossover effects Acetaminophen 500 mg + metoclopramide 10 mg allowed for acute attacks	***HA frequency:*** Mean percentage reduction from baseline to months 2-3; number of patients reporting a < 25%, 25%-50%, and >50% reduc-tion in frequency from baseline to months 2-3 ***HA intensity:*** Mean HA intensity; each attack graded on scale of 1-3 (HA alone; HA with reduced activities; no activity possible/bed rest required)	Both treatments significantly reduced ***HA frequency*** compared with the run-in period. Mean % reduction (± SD) with aspirin was 26% ± 22% ($p<0.001$); with metoprolol, it was 50% ± 18% ($p<0.00005$). When the two treatments were directly compared for this outcome, metoprolol was significantly better than aspirin ($p<0.01$). 3/21 patients (14%) on aspirin, and 14/21 patients (67%) on metoprolol reported a greater than ***50% reduction in HA frequency*** during the treatment period compared with baseline. Investigators did not analyze this result. Mean ***HA intensity*** (± SD) was 2 ± 0.5 during the baseline period; 1.4 ± 0.5 during treatment with aspirin, and 1.6 ± 0.7 during treatment with metoprolol. Study investigators did not analyze this result.	Dropouts: 7 (25%), all due to AEs (2 metopro-lol, 5 aspirin) Not randomized

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Grotemeyer, Schlake, and Husstedt, 1989	SPPG QS: 3 (r, db, dd)	N = 34 Age: 33 56% female Migraine w/o aura; low blood pressure (avg systolic 106) Chron: N/S Rec: N/S	***Flunarizine:*** 5 mg, 1x/day; n = ? ***Etilefrine pivalate:*** 20 mg, 1x/day; n = ? 2-mo baseline period; 2 mos of treatment with DHE (5 mg/day); then treatment period of 3 mos comparing above two interventions; no follow-up Nothing on acute meds	***HA frequency:*** Not defined	Both interventions significantly reduced ***HA frequency*** in comparison to baseline values. The average percentage reduction in the flunarizine group was 42% (± 22%) ($p<0.008$); in the etilefrine pivalate group, it was 56% (± 23%) ($p<0.0002$). The two treatments were not directly compared.	Dropouts: 5 (15%), 1 due to AEs (flunarizine) Abstract reporting limited results Population restricted to patients with low blood pressure
Grotemeyer, Schlake, Husstedt, et al., 1987	CrOv QS: 3 (r, db, dd)	N = 28 Age: 39 79% female Classic or common migraine; vomiting at the beginning of attacks Chron: N/S Rec: N/S	***Metoprolol:*** 200 mg/day (dosing schedule not described); n = 24* ***Flunarizine:*** 10 mg/day (dosing schedule not described); n = 24* 2-mo baseline period (no prophylactic med); two 3-mo treatment periods; no washout; no follow-up Nothing on acute meds	***HA frequency:*** Not defined	The mean percentage reduction in ***HA frequency*** vis-à-vis baseline was 53% with metoprolol and 56% with flunarizine. Frequency was reduced by 50% or more in 50% of patients on metoprolol (12/24) and 29% of patients on flunarizine (7/24). No mean frequency scores and no p-values were reported.	Dropouts: 4 (14%), 2 due to AEs (both metoprolol) Abstract reporting limited results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b	CrOv QS: 3 (r, db, dd)	N = 33 Age: 33 (range: 19-48) 85% female Common or classic migraine (Ad Hoc); ≥ 2 HAs/mo during baseline period; no prophylactic med during baseline period Chron: 14 yrs (range: 1-36) Rec: Patients referred to neuro dept	***Placebo:*** n = 29* ***Nimodipine:*** 30 mg, 4x/day; n = 29* 4-mo baseline period to establish eligibility (no baseline data used to evaluate efficacy); two 8-wk treatment periods; no washout, but investigators found no carry-over effect; no follow-up Patients permitted to continue taking their usual acute meds	***HA index:*** Sum of severity scores for all HAs experienced during treatment period; severity of each attack graded on scale of 1-3 (light, severe, very severe) ***HA frequency:*** No. of attacks per treatment period ***HA duration:*** Mean HA duration (min)	***HA index*** was significantly lower with nimodipine than with placebo (p=0.003). Mean HA index scores were 10.3 (range 1-34) with nimodipine and 13.7 (range 4-39) with placebo. Similar results were reported for ***HA frequency***. Nimodipine did not significantly reduce ***HA duration*** in comparison with placebo (p=0.127).	Dropouts: 4 (12%), none due to AEs 20 patients had had prophylactic therapy before
Havanka-Kanniainen, Hokkanen, and Myllylä, 1987	CrOv QS: 4 (r, db+, dd)	N = 50 Age: 38 (range: 16-64) 79% female Common or classic migraine (Ad Hoc) Chron: 18 yrs (range: 0.33-54) Rec: Outpatient neuro dept	***Pizotifen:*** 0.5 mg, 3x/day; n = 43* ***Nimodipine:*** 40 mg, 3x/day; n = 43* 1-mo baseline period (placebo); two 3-mo treatment periods; 1-mo washout (placebo); no follow-up Patients allowed to take their usual acute meds	***HA frequency:*** No. of attacks/mo; no. of days with HA/mo ***HA intensity:*** Each attack graded on scale of 1-3 (mild, moderate, severe); outcome measure analyzed not described ***HA duration:*** Duration of attack (in hrs)	Both treatments significantly reduced ***HA frequency*** in comparison with baseline values. The ***mean number of attacks per month*** (± SD) was 6.2 (± 3.3) at baseline; during the third month of treatment with nimodipine, this number was reduced to 2.3 (± 2.9); with pizotifen, it was reduced to 2.6 (± 2.4) ($p<0.001$ for both comparisons with baseline). There was no significant difference between the two treatments for this outcome (no p-value reported). Very similar results were reported for the ***mean number of days with HA per month***. There was no significant difference between the two drugs for ***HA intensity*** (no results and no p-value reported). ***HA duration*** was reduced to a small degree by both drugs. There was no significant difference between them in this respect (no p-value reported).	Dropouts: 7 (14%), none due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Havanka-Kanniainen, Hokkanen, and Myllylä, 1988	CrOv (analyzed as SPPG) QS: 2 (nr, db, dd)	N = 48 Age: 37 (range: 18-54) 81% female Classic or common migraine (Ad Hoc); patients with other types of HA excluded Chron: 19 Rec: N/S	***Propranolol (long-acting), 160 mg/day:*** Taken as a single dose; n = 21 ***Propranolol (long-acting), 80 mg/day:*** Taken as a single dose; n = 21 4-wk baseline period (placebo); two 12-wk treatment periods; 4-wk washout (placebo); no follow-up Patients permitted to take their usual meds for acute attacks	***HA frequency:*** No. of attacks; no. of HA days	Because ***HA frequency*** (both no. of attacks and no. of HA days) was significantly lower ($p<0.001$ for both outcomes) during the washout period than during the baseline period, investigators analyzed the results from the first period as if the trial were parallel-group. We followed the same procedure. The mean ***number of HA days*** (± SD) was reduced in the 160-mg group from 5.4 (± 2.9) during the baseline period to 4.4 (± 4.4) during the first treatment period; the corresponding numbers in the 80-mg group were 6.2 (± 2.7) and 5.2 (± 4.2), respectively. There was no significant difference between the two doses for this outcome (no p-value reported). A reduction of 50% or more in the ***number of HA attacks*** was reported by 17/21 patients (81%) in the 160-mg group and by 18/21 (86%) in the 80-mg group.	Dropouts: 6 (13%), 1 due to AEs (dose N/S) Low quality score (2); not randomized
Hering and Kuritzky, 1992	CrOv QS: 4 (r, db+, dd)	N = 32 Age: 34 (range: 18-54) 79% female Classical or common migraine (Ad Hoc); history ≥ 2 yrs; ≥ 4 attacks/mo Chron: 14 yrs Rec: HA clinic	***Placebo:*** n = 29* ***Sodium valproate:*** 400 mg, 2x/day; n = 29* 2-wk baseline period (no prophylactic med); two 8-wk treatment periods; no washout; no follow-up Patients permitted to take their usual meds for acute attacks	***HA frequency:*** No. of attacks per 8-wk treatment period ***HA severity:*** Each HA graded on scale of 1-3 (mild, moderate, severe); an "overall severity index" was calculated, but this index was not defined ***HA duration:*** Total duration of attacks (hrs) per treatment period	Sodium valproate was significantly better than placebo at reducing ***HA frequency*** ($p<0.001$). Mean HA frequency (± SD) per 8 wks was 8.826 (± 6.066) with sodium valproate and 15.586 (± 8.330) with placebo. Sodium valproate was also significantly better than placebo for ***HA severity*** ($p<0.005$) and ***duration*** ($p=0.002$).	Dropouts: 3 (9%), all due to AEs (1 sodium valproate, 2 placebo) Nothing on carry-over effect

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Herrmann, Horowski, Dannehl, et al., 1977	SPPG QS: 4 (r, db+, dd)	N = 253 Age: N/S 73% female Migraine; ≥ 2 severe attacks/mo Chron: N/S Rec: N/S	***Methysergide:*** 2 mg, 3x/day (gradual increase to full dose over first 4 days); n = 53 ***Lisuride:*** 25 mcg, 3x/day (gradual increase to full dose over first 4 days); n = 72 No baseline period described; single 3-mo treatment period; no follow-up Individually preferred meds permitted for acute attacks	***HA frequency:*** No. of attacks/mo; percentage of patients with < 2, 3-6, 7-10, and > 10 attacks/mo; no. of patients with ≥ 50% reduction in no. of attacks/mo ***HA severity:*** Percentage of attacks graded as "severe" (scale used not described) ***HA duration:*** Percentage of attacks lasting more than 3 hrs	***HA frequency:*** 53% of patients in the lisuride group (38/72) experienced a reduction of 50% or more in the number of attacks/mo, as did 51% of patients (27/53) in the methysergide group. Investigators did not analyze this outcome. There were no significant differences between lisuride and methysergide for ***HA severity*** or ***duration.***	Dropouts: 128 (51%), 70 due to AEs (22 lisuride, 48 methysergide) High dropout rate (51%) Not clear how baseline values established
Herrmann, Krištof, and Sastre y Hernandez, 1978	SPPG QS: 3 (r, db, dd)	N = 240 Age: N/S (range: N/S) % female N/S Migraine; > 2 HAs/mo Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 111 ***Lisuride:*** Dose gradually increased during first wk of trial until it was 0.075 mg/day; n = 103 No baseline period described; one 6-mo treatment period; no follow-up Analgesics permitted during trial	***HA frequency:*** Defined as "no. of HAs/mo"; recorded daily by pts and also assessed by physician supervising trial ***HA intensity:*** Definition N/S, but recorded daily by pt	"Success" was defined as a reduction to ≤ 2 HAs/mo and also as a decrease in ***HA frequency/mo*** of > 50% compared with baseline frequency. Based on the *patients'* recordings, ***HA frequency*** was reduced to ≤ 2 HAs/mo after 1 month of treatment with lisuride in 12.1% of patients (12/103) and in 3.6% of patients (4/111) treated with placebo. After 6 months, 37.4% of patients (38/103) treated with lisuride and 25.5% of patients (28/111) treated with placebo reduced ***HA frequency*** to ≤ 2 HAs/mo. Investigators reported that lisuride was significantly better than placebo at reducing ***HA frequency*** (p = 0.05).	Dropouts: 26 (11%) 2 due to AEs (lisuride) Some pts withdrawn from trial because of "insufficient efficacy" Trial was multicenter study Baseline data estimated post hoc by patients

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Hesse, Møgelvang, and Simonsen, 1994	SPPG QS: 2 (r, ndb, dd)	N = 85 Age: 45 (range: 25-70) 84% female Migraine w/ or w/o aura (IHS); history ≥ 2 yrs; 2-6 attacks/mo; able to distinguish migraine from TTH Chron: 23.4 yrs (range: 2-55) Rec: Newspaper ads or referred by GP; Denmark	***Metoprolol + sham acupuncture*** (metoprolol 100 mg/day + superficial touching of myofascial trigger points in neck region with broad end of needle); n = 39 ***Placebo tablets + acupuncture*** (dry needling of myofascial trigger points in neck region; number of trigger points needled per treatment, interval between treatments, and total number of treatments determined individually by therapist): n = 38 4-wk baseline period, followed by 17-wk treatment period; no follow-up Nontrial preventive med and nontrial physical treatments not permitted; symptomatic med OK	***HA frequency*** (medians compared) ***Global rating of attack*** (scored for each HA on scale of 1-3: mild, moderate, severe; took into account severity, duration, and associated symptoms; medians compared) ***HA duration*** (medians compared)	Both treatment groups exhibited significant reductions in median ***HA frequency*** over the course of the trial ($p<0.01$). There was no significant difference between the two treatments ($p>0.20$). Metoprolol was significantly better than acupuncture for median ***global rating of attack*** ($p<0.05$). There was no significant difference between the two treatments for median ***HA duration*** ($p>0.10$). ***Adverse events (AEs):*** 14/39 patients (36%) taking metoprolol reported AEs on open questioning, compared to 3/38 (8%) receiving acupuncture.	Dropouts: 8 (9%) Nonparametric statistical analysis performed by investigators
Holroyd, France, Cordingley, et al., 1995	Matched pairs QS: 2 (r, ndb, dd)	N = 33 Age: 31.7 (range: 16-52) 79% female Diagnosis of migraine (IHS) from 3 sources; ≥ 1 attack/mo; history ≥ 1 yr; no prophylactic meds for ≥ 6 mo bef. treatment Chron: 15.2 (range: 1-47) Rec: Univ. research clinic; U.S.	***Relax. + thermal BF:*** n = 14; two sessions (time N/S) 4 wks apart, followed by a third session + two telephone consultations (tot.: 12 wks) ***Relax. + thermal BF + propranolol HCl:*** n = 13; same treatment design/schedule as for above therapy, plus 60, 120, or 180 mg of propranolol HCl daily (dose increased as tolerated); at 1 mo, max. tolerated dose was determined, then continued for 2 mo Home practice: Both groups, with tapes, manuals, & equipment (time N/S)	***HA index:*** Av. daily HA activity, comprising HA intensity, duration, & frequency. Calculated as sum of four daily recordings averaged over ea. wk (range: 0-40) HA intensity recorded 4 x /day on 11-point scale Both groups monitored HAs daily by diary for 4 & 12 wks for pretreat. & treatment, respectively; the percentage change in ***HA index*** was assessed by physician at end of treatment.	Authors reported that pts who received relax. + thermal BF + propranolol decreased ***HA index*** significantly better than did pts who received relax. + thermal BF alone ($p < 0.05$). The relax. + thermal BF + propranolol group reduced ***HA index*** significantly from pre- to posttreat. ($p < 0.05$); the relax. + thermal BF also reduced ***HA index*** levels over this period, but not at a statistically significant level ($p < 0.10$). At posttreat., 92% of pts (12/13) who received the combined treatment and 57% of pts (8/14) who received relax. + thermal BF alone showed at least a 50% reduction in ***HA index***. There was a statistically significant difference between the two proportions ($p < 0.05$).	Dropouts: 6 Dropouts were replaced in this matched-pair study.

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Hübbe, 1973	CrOv QS: 4 (r, db+, dd)	N = 43 Age: 35 (range: 18-60) 70% female Migraine; attacks on ≥ 4 days in previous 2 mos Chron: 18 yrs (range: 1-50) Rec: Out-patient neuro clinic	***Prochlorperazine:*** 5 mg, 3x/day; n = 40* ***Pizotifen:*** 1 mg, 3x/day; n = 40* No baseline period described; two 8-wk treatment periods; no washout (though first week of each treatment period omitted from efficacy analysis to minimize carry-over effect); no follow-up Acute meds permitted	***HA frequency:*** Total no. of attacks; total no. of attacks during which patient unable to work ***HA duration:*** Not defined; measured only for attacks lasting > 12 hrs	***HA frequency:*** The total number of attacks in the last 7 wks of the treatment period was lower with pizotifen than with prochlorperazine (322 vs. 355), but the difference between the two treatments was not significant (no p-value reported). There was also no significant difference between the two treatments in the number of attacks during which patients were unable to work (pizotifen, 191; prochlorperazine, 192; no p-value reported). There was no significant difference between the two treatments for ***HA duration.***	Dropouts: 3 (7%), none due to AEs
Hudgson, Foster, and Newell, 1967	CrOv QS: 3 (r+, db-, dd)	N = 53 Age: N/S % female N/S "Typical" migraine (not defined); frequent severe attacks, requiring prophylactic treatment at some time in the past Chron: N/S Rec: N/S	***Methysergide:*** 1 mg, 3x/day; n = 35* ***Flumedroxone (Demigran®):*** 5 mg, 3x/day; n = 35* No baseline period described; two 4-mo treatment periods; 1-mo washout ("without specific treatment"); no follow-up Nothing on acute meds	***HA frequency:*** No. of HAs per month	***HA frequency:*** 17/35 patients had 50% or fewer HAs per month with methysergide than with Demigran®; no corresponding figures were reported for cases in which Demigran® was superior. Excluding two patients who had almost daily HAs throughout the trial, the average number of HAs per month on Demigran® was 4.3, compared with 2.8 on methysergide (no variance data and no p-value reported).	Dropouts: 18 (34%), 5 due to AEs (4 Demigran®, 1 methysergide) High dropout rate (34%)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Hughes and Foster, 1971	CrOv QS: 5 (r+, db+, dd)	N = 26 Age: N/S (range: 23-63) 81% female Classical migraine (25 pts); 1 with migrainous neuralgia; ≥ 2-33 migraines/mo -- "frequent & severe" HAs Chron: N/S (range: 3-50) Rec: N/S, but many pts had participated in previous trials of prophylactic drugs for migraine	***Placebo (lactose):*** n = 26* ***Pizotifen (BC105):*** 0.5 mg, 1x/day for 2 days; then 0.5 mg, 2x/day for 2 days; then 0.5 mg, 3x/day for 10 days; then 1 mg, 3x/day for 6 wks; n = 26* No baseline period described; two 2-mo treatment periods; no washout; no follow-up Other acute migraine meds permitted during trial	***HA frequency:*** Defined as "no. of HAs/mo" ***HA intensity:*** Definition N/S, but recorded daily by pt	The mean number of HAs for baseline (***HA frequency***) was calculated for the 2 mos prior to treatment (derived from patients' estimates for the preceding 12 mos). ***HA frequency*** was increased from 18.1 at baseline to 18.5 and 20.3 following treatment with pizotifen and placebo, respectively. Investigators reported that there were no significant differences between the two treatments for reducing ***HA frequency*** (no p-value given). Nine of 26 patients (35%) had a better response (≥ 50% fewer HAs) after taking pizotifen than after taking placebo. Investigators did not report how many patients responded better on placebo than on pizotifen.	Dropouts: 0 Information obtained from preliminary report No baseline data gathered on ***HA frequency***; such data estimated post hoc by pts for 12 mos preceding trial. Pts assessed by investigators at 2, 4, and 8 wks of each half of trial
Jacobs, 1972	SPPG QS: 4 (r, db+, dd)	N = 47 Age: 42 (range: 23-67) 78% female Migraine Chron: N/S Rec: Referrals from GPs and others	***Placebo:*** n = 13 (completed pre-treatment and first 6-wk treatment period); n = 12 (completed pre-treatment and both treatment periods) ***Opipramol:*** 50 mg, 3x/day; n = 14 (completed pre-treatment and first 6-wk treatment period); n = 13 (completed pre-treatment and both treatment periods) 6-wk baseline period, during which patients instructed to "avoid all drugs for migraine as far as humanely and reasonably practicable"; two 6-wk treatment periods Nothing on acute meds	***HA frequency:*** Total no. of attacks in each period; mean no. of attacks per patient in each treatment period; mean reduction in number of attacks per patient in each treatment period (vis-á-vis baseline)	The data summarized here are from those patients who completed the baseline period and both 6-wk treatment periods. ***HA frequency:*** Among patients taking opipramol, the mean number of attacks per patient in the baseline period was 5.6; for weeks 7-12 of treatment, it was 2.9. In the placebo group, the corresponding figures were 4.2 and 4.2 (no variance data reported for either group). The mean reduction in number of attacks per patient was 2.8 in the opipramol group and -0.1 in the placebo group; the difference between the two treatments for this outcome was statistically significant in favor of opipramol (0.05>p>0.02). Opipramol was *not* significantly better than placebo at reducing the frequency of severe attacks, considered on their own (0.3>p>0.2).	Dropouts: 20 (43%), none known to be due to AEs; 2 more patients completed the first 6-wk treatment period, but not the second (see left) High dropout rate

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Jensen, Brinck, and Olesen, 1994	CrOv QS: 4 (r, db+, dd)	N = 43 Age: 46 (range: 27-62) 84% female Migraine w/o aura (IHS); history ≥ 1 yr; 2-10 migraine days/mo Chron: N/S Rec: HA clinic	***Placebo:*** n = 34* ***Sodium valproate (slow-release):*** 1000-1500 mg/day (to attain serum level > 50 mg/L), administered in 3 doses/day; n = 34* 4-wk baseline period (medication-free); two 12-wk treatment periods; 4-wk washout; no follow-up Patients permitted to take usual analgesics for acute attacks	***HA frequency:*** No. of days with migraine per 4-wk period; number of patients reporting ≥ 50% reduction in no. of migraine days per 4-wk treatment period (vs. baseline) ***HA severity:*** Measured for each HA on scale of 0-3 (none; no influence on daily activities; inhibits, but does not prohibit, daily activites; prohibits daily activities) ***HA duration:*** Recorded for each HA (hrs)	***HA frequency (continuous data):*** The mean number of days with migraine per 4-wk period was significantly lower during treatment with sodium valproate than during the baseline period (p=0.0003) and during treatment with placebo (p=0.0018). The mean number of migraine days per 4-wk period was 6.1 (range 2-10) during the baseline period, 3.5 (CI 2.7 to 4.3) with sodium valproate, and 6.1 (CI 4.8 to 7.4) with placebo. ***HA frequency (categorical data):*** During treatment with sodium valproate, 17/34 patients (50%) showed a reduction of ≥ 50% in migraine days per 4-wk period (compared to baseline); 13/34 (38%) showed a reduction of 0-50%, and 4/34 (12%) had more migraine days. During treatment with placebo, the corresponding figures were 6/34 (18%), 14/34 (41%), and 14/34 (41%), respectively. The effect of sodium valproate increased over time. During the last 4 wks of treatment, 22/34 patients (65%) reported a reduction of ≥ 50% in migraine days per 4-wk period with sodium valproate, compared to 7/34 (21%) with placebo. There was no significant difference between sodium valproate and placebo for ***HA severity*** (p=0.45) or ***HA duration*** (p=0.9).	Dropouts: 9 (21%), 6 due to AEs (4 sodium valproate, 2 placebo) Investigators found no significant carry-over effect (p=0.55)
Johannsson, Nilsson, Widelius, et al., 1987	CrOv QS: 4 (r, db+, dd)	N = 72 Age: 43 (range: 27-63) 70% female Classical or common migraine (Ad Hoc); ≥ 2 HAs/mo Chron: 26 yrs Rec: N/S	***Placebo:*** n = 63* ***Atenolol:*** 100 mg, 1x/day; n = 63* 2-mo baseline period (no prophylactic med); two 3-mo treatment periods; 2-wk washout; no follow-up Acute meds permitted	***HA index:*** Not described, but incorporated intensity and duration ***HA frequency:*** No. of days with HA	***HA index*** was significantly reduced (not defined) in 70% of patients (44/63) during treatment with atenolol compared with placebo (p=0.004). The reduction was more than 50% in 33% of patients (21/63). Atenolol was also significantly better than placebo for ***HA frequency*** (p=0.010).	Dropouts: 9 (13%), 3 due to AEs (placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Johnson, Hornabrook, and Lambie, 1986	CrOv QS: 4 (r, db+, dd)	N = 29 Age: 42 (range: 22-67) 76% female Classical or common migraine; ≥ 1 HA in previous mo Chron: 20 yrs (range: 4-50) Rec: N/S	***Placebo:*** n = 17* ***Propranolol:*** 80 mg, 3x/day; n = 17* ***Mefenamic acid:*** 500 mg, 3x/day; n = 17* Baseline period ≥ 1 mo; three 3-mo treatment periods; no washout; no follow-up Acute meds permitted	***HA frequency:*** Mean no. of attacks per 3-mo treatment phase; number of patients reporting a 50% or greater reduction in frequency vs. placebo ***HA duration:*** Mean attack duration (hrs); sum of duration for all attacks per 3-mo treatment phase ***HA severity:*** Mean attack severity; each attack graded on scale of 1-10 (not described)	Mefenamic acid and propranolol were both significantly better than placebo for mean ***HA frequency*** ($p<0.05$ and $p<0.01$, respectively); there was no significant difference between the two active treatments ($p = 0.65$). The mean number of attacks per 3-mo treatment period (± SD) was 20.1 ± 18.0 with placebo, 12.9 ± 10.8 with mefenamic acid, and 13.8 ± 12.0 with propranolol. Compared to the placebo phase, 9/17 patients (53%) showed a ≥ 50% reduction in frequency with mefenamic acid, as did 6 of the same 17 patients (35%) with propranolol (no measure of statistical significance reported). Both mefenamic acid and propranolol were significantly better than placebo for ***total duration of attacks*** ($p<0.05$ and $p<0.01$, respectively); there was no significant difference between the two active treatments (no p-value reported). Neither mefenamic acid nor propranolol significantly reduced ***mean attack duration*** or ***severity.***	Dropouts: 12 (41%), 3 due to AEs (1 with each intervention) High dropout rate (41%)
Johnson, Kadam, Hylands, et al., 1985	SPPG QS: 4 (r, db+, dd)	N = 17 Age: 48 % female N/S Common or classical migraine; history ≥ 2 yrs; ≤ 8 HAs/ mo at time of admission; all patients had been self-administering fresh feverfew leaves daily for ≥ 3 mos Chron: N/S Rec: Migraine clinic	***Withdrawal of feverfew (placebo):*** n = 7 ***Continuation of feverfew:*** 50 mg, 1x/day of pulverized, freeze-dried leaves in capsules; n = 8 No baseline period described; 6-mo treatment period; no follow-up Analgesics and patients' usual drugs permitted for acute migraine attacks Prophylactic meds also permitted	Patients (and diary card entries) were assessed at 1- to 2-mo intervals throughout trial for the following outcomes: ***HA frequency:*** HAs recorded at onset by patient and reported as "no. of HAs/mo" ***HA intensity:*** Recorded by patients on 4-point scale (0=no pain; 1=mild, unpleasant but not affecting work or recreational activities; 2=severe, reducing ability to work or carry out recreational activities; 3=incapacitating, unable to work or carry out recreational activities)	For ***HA frequency***, the post-treatment mean score (± SEM) was 1.50 (± 0.62) for patients continuing treatment with feverfew. (We reported the average of mean scores for the last 3 mos of treatment as the post-treatment score, rather than the average over all 6 mos, to exclude carryover effects from patients' previous use of feverfew.) Investigators reported that there was no change in HA frequency for patients taking active treatment, but did not report having analyzed the pre- to post-treatment results for statistical significance. In the group receiving placebo, HA frequency *increased* to a mean score of 3.43 (± 1.02) after treatment. Investigators reported that the difference between these pre- and post-treatment scores was statistically significant ($p < 0.02$). (Pre-treatment values for both groups were estimated and reported by patients retrospectively.) No results were provided for between-group comparisons.	Dropouts: 2 patients (12%), withdrew and were not included in efficacy analyses, 1 due to AEs (placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kallanranta, Hakkarainen, Hokkanen, et al., 1977	**Study 1** CrOv QS: 0 (nr, ndb, dnd)	**Study 1** N = 50 Age: 32 (range: 20-49) 72% female Chron: N/S Common or classical migraine; ≥ 1 M in month before trial	**Study 1** ***Placebo:*** n = 50* ***Clonidine:*** 25 µg, 3x/day; n = 50* No baseline period; two 4-wk treatment periods; one 1-wk crossover period between treatments (not clear whether washout or not); no follow-up Acute migraine meds permitted during trial	***HA frequency:*** Recorded by pt as "time of attack"	For **Study 1**, treatment with 75 µg/day of clonidine for 4 wks reduced the mean no. of HAs/mo (± S.D.) from 3.94 (± 2.19) before treatment to 2.26 (± 1.57) after treatment, whereas the no. decreased to 2.98 (± 1.63) following treatment with placebo. Clonidine was significantly better than placebo at reducing ***HA frequency*** ($p<0.05$). For **Study 2**, treatment with 150 µg/day of clonidine for 8 wks reduced the mean no. of HAs/mo (± S.D.) before treatment from 4.0 (± 2.20) to 1.88 (± 2.79) after treatment. Treatment with 150 mg/day of practolol for 8 wks reduced the mean no. of HAs/mo to 2.49 (± 3.13). Clonidine was significantly better than practolol at reducing ***HA frequency*** ($p<0.05$).	Dropouts: N/S Trial consisted of 2 parts, 1½ yrs apart Every other pt received first clonidine and then placebo, and every other pt received the treatments in reversed order Not clear how baseline data gathered or how results determined from that data
	Study 2 CrOv QS: 0 (nr, ndb, dnd)	**Study 2** N = 50 Age: 36 (range: 22-55) 64% female Chron: N/S Common or classical migraine; ≥ 4 Ms in month before trial Rec: Neurology depts of 2 hospitals in Finland	**Study 2** ***Practolol:*** 150 mg, 3x/day; n = 50* ***Clonidine:*** 50 µg, 3x/day; n = 50* No baseline period; two 8-wk treatment periods; one 1-wk crossover period between treatments (not clear whether washout or not); no follow-up Acute migraine meds permitted during trial			

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kallos and Kallos-Deffner, 1971	CrOv QS: 1 (r, ndb, dnd)	N = 20 Age: N/S (range: 20-45) 100% female Migraine attacks occurring in connection with the menstrual period Chron: N/S Rec: N/S	***Placebo:*** n = 20* ***Cafergot comp.® (1 cap = ergotamine 1 mg + caffeine 100 mg + butalbital 50 mg + belladonna alkaloids 0.125 mg):*** 1 cap, 2x/day for 3 days before, during, and two days after menstrual period; n = 20* No baseline period described; 3 treatment periods lasting 2 menstrual cycles each; no washout; no follow-up Nothing on acute meds	***HA frequency:*** No. of attacks during two menstrual cycles	***HA frequency:*** Investigators reported only the total number of attacks reported over two menstrual cycles with each intervention. With placebo, 31 attacks were reported (mean of 1.55 per patient); with Cafergot comp.®, 7 (mean of 0.35 per patient) (no p-values or other measures of statistical significance reported).	Dropouts: Not described All 20 patients had used Cafergot comp.® prophylactically in the past, with good results Low quality score (1); not double-blind; dropouts not described Trial also included an investigational drug (LCC 115 = ergostine + caffeine + pimethixene) that was never brought to market

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kangas-niemi, 1979	CrOv QS: 4 (r, db+, dd)	N = 50 Age: 36 (range: 19-58) 80% female Common or classical migraine (Ad Hoc); ≥ 2-4 HAs/mo for 1-3 mos preceding trial; pts had "severe & chronic migraines" Chron: N/S (range: N/S) Rec: Physi-cian referrals to neuro. clinic of hospital	***Pizotifen (Sandomigrin®):*** 0.5 mg, 1x/day on Days 1 & 2; 0.5 mg, 2x/day on Days 3 & 4; 0.5 mg, 3x/day on Day 5 and until end of trial; n = 34* ***Iprazochrome (Divascan® or Migrenon®):*** 5 mg, 1x/day on Days 1 & 2; 5 mg, 2x/day on Days 3 & 4; 5 mg, 3x/day on Day 5 and until end of trial; n = 34* No baseline period described; two 3-mo (or two 14-wk) treatment periods (length of treatment period is unclear); 1 mo washout period using placebo between treatment periods; no follow-up Previous long-term migraine meds discontinued 1-3 mos prior to start of trial; ergotomine permitted during trial	***HA index:*** Not defined, but derived from pt's recordings on "weekly card" ***HA frequency:*** Not defined, but recorded by pt on weekly card ***HA intensity:*** Rated on 3-point scale by pt	The mean weekly ***HA index*** scores after treatment with Migrenon® and pizotifen were 3.2 (± 2.0) (SD) and 2.7 (± 1.9). Pizotifen was slightly more effective than Migrenon®, but not at a statistically significant level ($p > 0.05$). Investigators also reported that 11/34 pts (32%) decreased weekly ***HA index*** > 50% better on pizotifen than on the placebo given during the washout period (not a "true" placebo treatment). Four of 34 pts (12%) decreased weekly ***HA index*** > 50% better on Migrenon® than on placebo. Authors did not report whether the difference between these results was statistically significant. No pre- to post-treatment results were provided.	Dropouts: 16 (32%), 3 due to AEs (2 pizotifen, 1 Migrenon®) Not clear whether or not baseline data gathered

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kangas-niemi, Andersen, Andersson, et al., 1987	CrOv QS: 4 (r, db+, dd)	N = 77 Age: 38 (16-65) 80% female Classical migraine (Ad Hoc); 2-8 HAs/mo, of which ≥ 50% accompanied by focal auras; "frequent" HAs Excl: High daily or monthly use of analgesics or ergota-mines; use of narcotic analgesics, chronic treatment with calcium antagonists, clonidine, other beta-blockers, or NSAIDs; contraindica-tions for beta-blockers Chron: 17 (range: 2-51) Rec: 8 neuro. centers in Scandinavia	***Placebo:*** n = 73* ***Metoprolol (Durules®):*** 200 mg (slow-release tabs), 1x/day; n = 73* 4-wk run-in (baseline), with no prophylactics; two 8-wk treatment periods; 4-wk washout between treatment periods; no follow-up described Patients permitted to take, but not to change, their usual acute migraine meds	***HA frequency:*** Recorded daily by pts and reported as "total number of migraine attacks/mo" ***HA intensity:*** Recorded daily by pts and rated on 3-point scale	Metoprolol was significantly better than placebo at reducing ***HA frequency*** (p = 0.004). HA frequency was reduced from a median score of 3.8 at baseline to 1.8 and 2.5 after treatment with metoprolol or placebo, respectively. Investigators did not report having analyzed the pre- to post-treatment differences for statistical significance. Similar results were found for ***HA intensity***.	Dropouts: 4 pts (5%) withdrew, none due to AEs Trial was a multi-center study

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kangas-niemi, Falck, Långvik, et al., 1978	CrOv QS: 2 (nr, db, dd)	N = 8 Age: 34 (range: 24-49) 75% female Migraine; all pts "rather resistant" to treatment Chron: > 10 (range: N/S) Rec: N/S	***Placebo (levoleucine)***: 320 mg, 4x/day; n = 8* ***Oxitriptan (Levotryptophan):*** 500 mg, 4x/day; n = 8* No baseline period described; two 3-mo treatment periods; no washout, but data from first mo of each treatment period excluded from analysis; no follow-up Nothing on acute migraine meds	***HA index:*** Calculated by multiplying no. of HAs per month by ***HA intensity*** score (see below) ***HA frequency:*** Defined as "no. of attacks/mo" (see below) ***HA intensity:*** Rated on 3-point scale (see below) Not clear how treatment period data obtained; ***frequency*** and ***intensity*** data determined by "subjective estimate," but not clear whether estimate provided by pt or physician	The post-treatment mean ***HA index*** score was 16.0 (± 16.4) (SD) for pts treated with levotryptophan (for the 2 mos analyzed) and 23.8 (± 18.2) for pts treated with placebo. Investigators reported that although the ***HA index*** score was lower for pts taking oxitriptan than for those taking placebo, the difference was not statistically significant (no p-value given). No results were provided for pre- to post-treatment comparisons. Investigators reported that 4/8 pts (50%) had "markedly lower" ***HA index*** scores after treatment with the active drug than after treatment with placebo, but did not provide further details.	Dropouts: 0 Results described as "preliminary" Not clear how baseline data gathered ***HA index*** estimated at monthly intervals when pt examined by physician
Kangas-niemi and Hedman, 1984	CrOv QS: 4 (r, db+, dd)	N = 36 Age: 34 (range: 18-51) 89% female Classical or common migraine (World Fed of Neurology); ≥ 3-yr history; avg duration ≥ 1 hr; 3-10 attacks/mo; patients with other types of vascular HA or with chronic daily HA excluded Chron: 16 yrs Rec: Neuro dept	***Propranolol:*** 80 mg, 2x/day; n = 33* ***Metoprolol (controlled-release):*** 200 mg, 1x/day; n = 34* 4-wk baseline period (placebo); two 8-wk treatment periods; 4-wk washout (placebo); ten patients followed up for six months after end of trial Acute meds permitted	***HA index:*** Severity times no. of migraine days; severity of each attack graded on scale of 1-3 (light, moderate, severe) ***HA frequency:*** No. of attacks per 4 wks; no. of migraine days per 4 wks	There were no statistically significant differences between metoprolol and propranolol for any of the outcomes measured (p-values not reported). Both drugs significantly reduced ***HA index*** in comparison with baseline values ($p \leq 0.001$ for both comparisons). Mean HA index scores (± SD) were 9.7 (± 4.9) during the baseline period (n = 35), 5.4 (± 3.5) during treatment with propranolol (n = 33), and 4.9 (± 3.2) during treatment with metoprolol (n = 34). 15/33 patients (45%) reported a 50% or greater reduction in ***HA index*** scores with propranolol in comparison with baseline values, as did 17/34 (50%) with metoprolol.	Dropouts: 3 (8%), 2 due to AEs (both propranolol); 2 of the 3 dropouts provided enough data to be included in the efficacy analysis for some outcome variables 28% of patients had tried preventive treatment before

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kangas-niemi, Nyrke, Lang, et al., 1983	CrOv QS: 3 (r, db, dd)	N = 29 Age: 37 (range: 24-47) 86% female Classical or common migraine; no prophylactic meds in previous 2 mos Chron: 17 yrs (range: 4-40) Rec: Neurologist's private practice	***Propranolol:*** 80 mg, 2x/day; dose reduced by half during first week; n = 24* ***Femoxetine:*** 200 mg, 2x/day; dose reduced by half during first week; n = 24* 1-mo baseline period; two 3-mo treatment periods; no washout, but first month of each active treatment period dropped from analysis to minimize carry-over effects; 1-mo placebo treatment period at end of study Patients allowed to take their usual meds for acute attacks (generally tolfenamic acid or ergotamine)	***HA index:*** No. of HA days multiplied by severity (severity of each attack graded on scale of 1-3) ***HA frequency:*** No. of attacks per month	Propranolol significantly decreased ***HA index*** compared with pre-treatment values ($p<0.01$); no significant change was seen with femoxetine (no p-value reported). When the two treatments were directly compared for this outcome, propranolol was significantly better than femoxetine ($p<0.05$). During the pre-treatment period, the mean HA index (± SEM) was 10.30 (± 1.42); after treatment with propranolol, it was 7.07 (± 1.04); and after treatment with femoxetine, 9.68 (± 1.98). Very similar results were reported for ***HA frequency***.	Dropouts: 5 (17%), 3 due to AEs associated with propranolol
Kåss and Nestvold, 1980	CrOv QS: 3 (r, db, dd)	N = 23 Age: 40 (range: 22-62) 70% female Chron: N/S Common or classical migraine Excl: Previous use of study meds; combination of M + TTHs "avoided" Rec: N/S	***Propranolol (Inderal®):*** 80 mg, 2x/day; n = 21* ***Clonidine (Catapresan®):*** 50 µg, 2x/day; n = 21* 4-wk washout prior to treatment; one 4-wk baseline period prior to each of two 16-wk treatment periods; first 4 wks of each treatment period excluded from analysis to reduce crossover effects; no follow-up Acute migraine meds permitted during trial	***HA frequency:*** Defined as no. of days with HAs ***HA intensity:*** Rated by pts on 4-pt scale (N/S)	For ***HA frequency***, results were reported as the total of HA days reported by each pt for each treatment type. Investigators reported that 10/21 pts (48%) and 9/21 pts (43%) had fewer HA days after treatment with propranolol and clonidine, respectively, whereas 2/21 pts (10%) had no changes in ***HA frequency***, regardless of the treatment taken. Investigators reported that neither treatment was significantly better than the other (no p-value given). A comparison of the last 4 wks of treatment data with that from the 4-wk baseline revealed that 13/21 pts (62%) improved (had > 50% reduction in ***HA frequency*** from pre- to post-treatment) after being treated with propranolol, whereas 8/21 pts (38%) improved after taking clonidine. Investigators did not report whether or not there was a statistically significant difference between these results.	Dropouts: 2 (9%), none due to AEs Pts were initially hospitalized for 2 days, then treated as outpatients

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994	CrOv (analyzed as SPPG for some outcomes) QS: 4 (r, db+, dd)	N = 76 Age: 43 (median) (range: 19-65) 79% female Migraine w/ or w/o aura (IHS); history ≥ 1 yr; 2-8 HAs/mo over last 3 mos Chron: 20 yrs (median) (range: 1-40) Rec: Referrals to neuro depts	***Propranolol:*** 40 mg, 3x/day; n = 56* (total completing trial); n = 29 (took propranolol in *first* treatment period and completed trial) ***Tolfenamic acid:*** 100 mg, 3x/day; n = 56* (total completing trial); n = 27 (took tolfenamic acid in *first* treatment period and completed trial) 1-mo baseline period (no prophylactic med); two 3-mo treatment periods; 1-mo washout (placebo); no follow-up Patients allowed to take meds for acute attacks	***HA index:*** No. of migraine hrs per month ***HA frequency:*** No. of migraine days per month ***HA severity:*** Mean HA severity; each attack graded on scale of 1-3 (able to work; unable to work, but not in bed; in bed)	Investigators analyzed several outcomes for the first treatment period (vs. baseline) only. ***HA index:*** Both treatments significantly reduced the average number of migraine hours per month during the first treatment period compared with baseline (no p-value reported). Among patients taking tolfenamic acid in the first period (n = 27), the mean reduction in HA index score (± 2 SDs) was 6.9 (-55.7 to +41.9); among patients taking propranolol (n = 29), it was 15.7 (-106.6 to +75.1). Over the course of the entire trial, there was no significant difference between the two treatments for HA index (no p-value reported). The mean difference (± 2 SDs) between scores with tolfenamic acid and with propranolol was 2.9 (-47.9 to + 53.7) (n = 56 patients completing treatment with both drugs). There were no significant differences between the two treatments for ***HA frequency*** or ***HA severity.***	Dropouts: 20 (26%), 14 due to AEs (9 propranolol, 5 tolfenamic acid) Investigators tested for carry-over and period effects for all the main efficacy parameters and found none
Klapper, 1994	CrOv QS: 2 (r, ndb, dd)	N=24 Age: N/S % female N/S Migraine w/ or w/o aura (IHS); ≥ 2 HAs/mo; no previous experience with study drugs Chron: N/S Rec: N/S	***Propranolol:*** Dose titrated to highest level tolerated; avg dose 140 mg/day, range 80-240 mg/day; n = 12* ***Divalproex sodium:*** Dose titrated to highest level tolerated; avg dose 1100 mg/day, range 750-1500 mg/day; n = 12* 2-wk+ lead-in period of dosage adjustment; followed by 2-mo treatment period; then 2-wk+ washout and dosage adjustment period; followed by second 2-mo treatment period; no follow-up Nothing on acute meds	***HA frequency:*** Mean no. of HAs per 2-mo treatment period	***HA frequency:*** The mean number of HAs per 2 mos was 10.9 with divalproex sodium and 20.4 with propranolol (no variance data and no p-value reported). Investigators did not state whether they found the difference between the two treatments to be significant for this outcome.	Dropouts: 12 (50%), all due to AEs (9 divalproex sodium, 3 propranolol) Abstract reporting limited results Open-label trial High dropout rate (50%)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Klapper, 1996	SPPG QS: 4 (r, db+, dd)	N = 176 Age: 41 (range: 17-76) 89% female Migraine w/ or w/o aura (IHS); history ≥ 6 mos; ≥ 2 attacks in previous 3 mos; patients with chronic daily HA or TTH on ≥ 15 days/mo excluded Chron: 22 yrs Rec: HA clinic	***Placebo:*** n = 42 ***Divalproex sodium, 500 mg/day:*** Given in two doses; n = 45 ***Divalproex sodium, 1000 mg/day:*** Given in two doses; n = 40 ***Divalproex sodium, 1500 mg/day:*** Given in two doses; n = 44 4-wk baseline phase (placebo); 12-wk treatment phase (4 wks dose escalation + 8 wks maintenance at randomized dose); no follow-up Patients permitted to use symptomatic meds to treat acute attacks, but use of such meds must average < 3 days/wk	***HA frequency:*** Mean 4-wk attack frequency; percentage reduction in mean 4-wk attacks frequency; percentage of patients reporting a > 50% reduction in frequency ***HA severity:*** Peak severity per attack (scale used not described) ***HA duration:*** Per attack, in hrs	The mean reductions in ***HA frequency*** from baseline to post-treatment, adjusted for differences in baseline frequency, were 0.5 attacks per 4 wks in the placebo group, and 1.7, 2.0, and 1.7 attacks per 4 wks in the 500-mg, 1000-mg, and 1500-mg divalproex sodium groups, respectively. Each of the divalproex sodium doses was significantly better than placebo for this outcome ($p \leq 0.05$). Investigators did not directly compare the three doses of active medication for this outcome. The proportions of patients reporting a 50% or greater reduction in mean 4-wk attack frequency were 21% in the placebo group (9/42), 44% in the 500-mg group (20/45), 43% in the 1000-mg group (17/40), and 45% in the 1500-mg group (20/44). Each of the divalproex sodium doses was significantly better than placebo for this outcome ($p \leq 0.05$). Investigators did not directly compare the three doses of active medication for this outcome. No significant differences were observed among the four treatments for ***HA severity*** or ***duration***.	Dropouts: 5/176 patients (3%) did not provide any HA data and were excluded from the efficacy analysis; 39 patients (22%) discontinued treatment before the end of the 12-wk treatment period, but provided some data for the efficacy analysis; 27 of these 39 patients withdrew due to AEs (12, 1500 mg; 6, 1000 mg; 7, 500 mg; 2, placebo) Only patients who were previously untreated or had failed ≤ 2 trials of prophylactic med were included

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Krakowski and Engisch, 1973	SPPG QS: 4 (r, db+, dd)	N = 29 Age: 38 (range: N/S) 82% female Common or classical migraine; ≥ 6 HAs in 4 wks prior to trial Chron: 24 (range: N/S) Rec: N/S, but pts "ambulatory"	***Placebo:*** n = 9 ***Pizotifen:*** 2 mg, 3x/day; n = 13 4-wk baseline period with placebo; 12-wk treatment period; no washout, but data from first mo of each treatment period excluded from analysis; 4-wk "post-treatment" period with placebo; no other follow-up described Nothing on acute migraine meds	***HA index:*** Calculated as the sum of severe HAs times 3, moderate HAs times 2, and mild HAs times 1 ***HA frequency:*** Defined as "total no. of HAs" and reported as no. of HAs/mo ***HA intensity:*** Rated on 3-point scale	Results for ***HA index*** were reported as the difference of mean changes at the end of the trial compared with baseline. Pizotifen was significantly better than placebo at reducing ***HA index*** from pre- to post-treatment ($p < 0.05$). Investigators reported a mean ***HA index*** score for each 4-wk period. From baseline (average of 4 wks) to 16 wks (the average of last 4 wks of 12-wk treatment period), pizotifen reduced mean ***HA index*** from 31.8 to 16.8, a reduction that was statistically significant ($p < 0.001$). Placebo reduced that outcome over the same period from 36.2 to 32.8, a reduction that was not significant ($p > 0.05$).	Dropouts: 7 (24%), not clear if any due to AEs on placebo; none due to AEs on pizotifen Not clear how data gathered; no mention of pt diaries. Data appear to have been obtained post hoc by physician at weeks 0, 4, 6, 8, 12, and 20
Kuritzky and Hering, 1987	CrOv QS: 3 (r, db, dd)	N = 38 Age: N/S (range: 17-53) % female N/S Classical or common migraine; ≥ 2-yr history; ≥ 3 attacks/mo Chron: 14 yrs Rec: N/S	***Placebo:*** n = 31* ***Propranolol (long-acting):*** 160 mg, 1x/day; n = 31* 4-wk baseline period; two 4-wk treatment periods; no washout; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo ***HA severity:*** Each attack graded on scale of 1-3; outcome measure not described ***HA duration:*** Not described	Propranolol was significantly better than placebo for ***HA frequency*** (p=0.014). Mean frequency with propranolol was 3.23; with placebo, it was 5.56 (no variance data reported). Similar results were reported for ***HA severity*** (p=0.003) and ***HA duration*** (p=0.002).	Dropouts: 7 (18%), 2 due to AEs (propranolol) No carry-over effect Abstract reporting limited results
Lamsudin and Sadjimin, 1993	SPPG QS: 3 (r, db, dd)	N = 83 Age: N/S 59% female Classic or common migraine; ≥ 2 attacks/mo Chron: N/S Rec: Hospital outpatient depts	***Flunarizine:*** 5 mg, 2x/day; n = 40 ***Nifedipine:*** 10 mg, 2x/day; n = 38 1-mo baseline period (placebo); 3-mo treatment period; no follow-up Use of acute meds permitted	***HA index:*** Calculated for HAs of disabling, severe, or moderate intensity only (not mild); = $3(FxD)_{disabling} + 2(FxD)_{severe} + 1(FxD)_{moderate}$, where F = frequency (no. of HAs/mo) and D = duration (hrs)	Both treatments significantly reduced ***HA index***, compared to baseline values, from one month on. In the nifedipine group, mean scores (± SD) were 26.28 (± 25.93) for the baseline period and 9.07 (± 13.78) for the final treatment month ($p<0.00001$). In the flunarizine group, the corresponding scores were 26.41 (± 24.56) and 6.69 (± 14.35), respectively ($p<0.00001$). There were no significant differences between the two treatments for this outcome (no p-values reported).	Dropouts: 5 (6%), none due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Lance and Anthony, 1968	SPPG QS: 4 (r, db+, dd)	N = 50 Age: 39 (range: N/S) 84% female Migraine; ≥ 2-8 *severe* HAs/mo; av. 24- to 48-hr HA duration Chron: N/S (range: N/S) Rec: Neuro. clinic	***Placebo***: n = 25 ***Pizotifen:*** 0.025 mg, 3x/day on Day 1; 0.05 mg, 3x/day on Day 3; 1.0 mg, 3x/day from Day 4 through 1 mo; n = 25 No baseline period described; 1-mo treatment period; no follow-up Nothing on acute migraine meds	***HA frequency:*** Definition N/S ***HA intensity:*** Definition N/S	Twelve of 25 pts (48%) treated with pizotifen improved (obtained ≥ 50% reduction in ***HA frequency*** or ***intensity*** [N/S] from pre- to post-treatment), whereas 9/25 pts (36%) treated with placebo improved. Pizotifen was more effective at reducing ***HA frequency*** or ***intensity*** than placebo, but not at a statistically significant level (p = 0.4). Investigators did not report pre- or post-treatment mean values for either ***HA frequency*** or ***intensity***.	Dropouts: 5 pts (12%), included in efficacy analyses, withdrew from trial (2 due to AEs, treatments N/S) Not clear if baseline data gathered Not clear how data obtained
Lance, Fine, and Curran, 1963	SPPG QS: 3 (nr, db+, dd)	N = 90 Age: N/S 71% female Classical or common migraine; ≥ 2 incapacitating HAs/mo Chron: N/S Rec: HA clinic	***Placebo:*** n = 34 ***Methysergide:*** 2 mg, 3x/day; n = 56 No baseline period described; 1-mo treatment period; patients who responded well were maintained on the same drug and followed up for up to 9 mos; patients who did not respond to initial drug were crossed over to alternative drug for 1 month and re-evaluated at that time; we considered only the initial, 1-mo controlled portion of the trial Nothing on acute meds	***HA frequency:*** No. of attacks; investigators reported no. of patients HA-free, > 50% improved, unchanged, and worse at end of treatment period	Methysergide was significantly more effective than placebo at reducing ***HA frequency*** (p<0.001). 38/56 patients (68%) taking methysergide and 7/34 (21%) taking placebo reported a 50% or greater reduction in HA frequency compared with baseline values.	Dropouts: 6 (7%), all due to AEs (all methy-sergide); all 6 dropouts were included in the efficacy analysis Report described results of treatment of patients with several different types of HA, and from controlled and uncontrolled portions of the trial; data reported here concern only those *migraine* patients who participated in the *controlled* portion of the trial Not clear how baseline values established

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Langohr, Gerber, Koletzki, et al., 1985	CrOv (5 groups, 2 periods) QS: 3 (r, db, dd)	N = 63 Age: 44 (range: 24-60) 67% female Common or classical migraine (Ad Hoc); ≥ 1 HA/wk Chron: 21 yrs (range: 5-41) Rec: N/S	***Placebo:*** n = 27* ***Metoprolol:*** Dosage gradually increased to maximum of 100 mg/day; n = 21* ***Clomipramine:*** Dosage gradually increased to maximum of 100 mg/day; n = 20* Patients randomized to five treatment groups: clomipramine followed by placebo; placebo followed by clomipramine; metoprolol followed by placebo; placebo followed by metoprolol; clomipramine followed by metoprolol 6-wk baseline period; two 4-wk treatment periods; 4-wk washout; 6-wk follow-up Use of acute meds permitted	***HA frequency:*** No. of attacks; reduction from pre-to post-treatment ***HA duration***	A time series analysis (ARIMA) performed by the investigators showed that metoprolol was significantly better than clomipramine at reducing ***HA frequency*** ($p<0.05$). No significant differences could be established between metoprolol and placebo, or between clomipramine and placebo (no p-values reported). Investigators also reported the number of patients reporting a ***> 50% improvement in HA frequency,*** based on conventional statistical methods. The numbers were as follows: with clomipramine, 5/20 patients (24%); with metoprolol, 9/21 patients (44%); and with placebo, 7/27 patients (26%) (no p-values reported).	Dropouts: 27 (43%), 18 due to AEs associated with clomipra-mine; also, 2 patients who completed the trial were (for some unspecified reason) excluded from the investi-gators' efficacy analysis
Lawrence, Hossain, and Littlestone, 1977	SPPG QS: 4 (r, db+, dd)	N = 36 Age: N/S (range: 16-64) 72% female Common or classical migraine; ≥ 4 HAs/mo Excl: Pts taking MAOIs Chron: 16 (range: 2-36) Rec: 3 GP clinics	***Placebo***: n = 14 ***Pizotifen:*** 0.5 mg, 1x/day for 2 days; 0.5 mg, 2x/day for 2 days; 0.5 mg, 3x/day for 10 days; then 1.0 mg, 3x/day for 10 wks; n = 14 No baseline period described; one 3-mo treatment period; no follow-up Pts permitted to take mild hypnotics, analgesics, and ergotamine during trial, but not migraine prophylactic meds	***HA Index:*** Calculated weekly by multiplying no. of HAs by ***HA intensity*** score ***HA frequency:*** Definition N/S, but recorded daily by pts ***HA Intensity:*** Rated on 3-point scale daily by pt	Results were reported as weekly individual ***HA index*** values, categorized according to degree of improvement. However, the criterion for determining "improvement" was not specified. Investigators reported that pizotifen was more effective than placebo at reducing ***HA index***, but did not report whether they analyzed the differences for statistical significance (no p-value given). From the last 4 weeks of data, we calculated mean scores of 8.6 (± 10.3) (SD in parentheses) and 14.9 (± 10.1) for patients treated with pizotifen and placebo, respectively. We calculated an effect size of 0.62 (-0.14 to 1.4) for the difference between the two treatments. The effect size suggests that pizotifen is better than placebo, but not at a statistically significant level.	Dropouts: 8 pts (22%), not included in efficacy analyses, withdrew, none due to AEs; 1 additional pt, included in efficacy analyses, withdrew due to AEs (placebo) Not clear how baseline data gathered or how results determined from those data

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Leandri, Rigardo, Schizzi, et al., 1990	CrOv QS: 4 (r, db+, dd)	N = 36 Age: N/S 73% female Migraine w/o aura (IHS); 2-8 attacks/mo in previous yr; no TTH; no prophylactic med in previous 4 mos Chron: 8 yrs (range: 1-25) Rec: N/S	***Placebo:*** n = 30* ***Nicardipine:*** 20 mg, 2x/day (dosage reduced by half for first 3 days); n = 30* 2-mo baseline period; two 2-mo treatment periods; no washout; no follow-up Acute meds (analgesics or ergotamine) permitted	***HA index:*** Monthly no. of attacks times mean severity ***HA frequency:*** Monthly no. of attacks ***HA severity:*** Monthly mean severity; graded daily on scale of 0-3 (no HA; mild HA; strong HA interfering with work or other activity; very strong HA necessitating bed rest) ***HA duration:*** Monthly mean (hrs)	Both nicardipine ($p<0.01$) and placebo ($p<0.05$) significantly reduced ***HA index*** compared with the pre-treatment period. Nicardipine was significantly better than placebo for this outcome ($p<0.01$). Mean HA index scores (± SD) were 12.61 (± 10.96) pre-treatment, 8.09 (± 7.58) after treatment with placebo, and 2.35 (± 2.39) after treatment with nicardipine. Separate analysis of the HA index scores for the two treatment orders suggested that, as a group, patients who took nicardipine first achieved significant improvement over baseline scores and maintained this improvement through the placebo period. Patients starting on placebo improved significantly only after crossing over to nicardipine. Nicardipine was also significantly better than placebo for ***HA frequency***, ***HA severity***, and ***HA duration*** ($p<0.01$ for all three outcomes).	Dropouts: 6 (17%), 3 due to AEs (1 nicardipine, 2 placebo)
Lindegaard, Övrelid, and Sjaastad, 1980	CrOv (analyzed as SPPG) QS: 2 (r, db, dnd)	N = 28 Age: N/S (range: 16-60) 68% female Classic or common migraine (Ad Hoc); ≥ 3 HAs/mo Chron: 17 yrs Rec: Neuro dept out-patients	***Placebo:*** n = 13 ***Naproxen (Naprosyn®):*** 250 mg, 2x/day; n = 15 Baseline period of at least 2 mos (drug-free); two 6-wk treatment periods; one-week washout; no follow-up Patients could take dextropropxyphene for acute attacks	***HA index:*** Frequency times severity ***HA frequency:*** No. of attacks/wk ***HA severity:*** Severity of each attack graded on scale of 1-3 ***HA duration:*** Hrs per wk	Because of a positive treatment-period interaction, we analyzed first-period data only. Mean ***HA index*** (± SEM) was 3.4 (± 0.72) among patients taking naproxen during the first treatment period and 4.0 (± 0.87) among patients taking placebo. Investigators did not analyze the first-period data separately. Mean ***HA frequency*** (± SEM) was 1.2 (± 0.24) in the naproxen group and 1.4 (± 0.33) in the placebo group.	Dropouts: Not described Low quality score (2); dropouts not described Investigators recommended further studies with higher doses of naproxen

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Louis, 1981	SPPG QS: 4 (r, db+, dd)	N = 58 Age: 29 (median) (range: 20-47) 50% female Classic or common migraine; attacks clearly distinguish-able from TTHs; ≥ 6 attacks in previous 6 mos Chron: N/S Rec: General practice out-patients	***Placebo:*** n = 29 ***Flunarizine:*** 5 mg, 2x/day; n = 29 No baseline period described; 3-mo treatment period; no follow-up Use of acute meds permitted	***HA frequency:*** No. of attacks per 3 mos ***Frequency of severe HA:*** No of days with severe HA per 3 mos ***HA severity:*** Outcome measure not described ***HA duration:*** Outcome measure not described	The median percentage reduction in ***HA frequency*** at 3 mos, compared with pre-treatment values, was 57% in the flunarizine group (range: 0-100%) and 14% in the placebo group (range: 0-56%). The difference between the two treatments was statistically significant ($p<0.001$) in favor of flunarizine. We calculated an ES for ***HA frequency*** based on categorical data reported on the number of patients with a median of 0, 1, 2, 3, 4, and 5 attacks per 3-mo treatment period. For the flunarizine group, the number of patients in these six frequency groups was 5, 8, 8, 7, 0, and 1, respectively; in the placebo group, the number of patients in the six groups was 0, 0, 9, 15, 3, and 2, respectively. The investigators' analysis found a significant difference in favor of flunarizine for this outcome ($p<0.0001$). Flunarizine was also significantly better than placebo at reducing themedian ***frequency of severe HAs*** ($p<0.001$; data reported only in graphic form). Neither ***HA severity*** nor ***duration*** were affected by flunarizine.	Dropouts: 0 Baseline values based on patient history over 6 mos preceding trial

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Louis, Schoenen, and Hedman, 1985a	CrOv QS: 4 (r, db+, dd)	N = 31 Age: 36 (range: 18-57) 81% female Chron: 19 (range: 2-40) Migraine; hist. of Ms ≥ 2 yrs; ≥ 3 -10 HAs/mo with duration ≥ 2 hrs; must have met 4 of 6 criteria that included prodromas, hemicrania, & phono- or photophobia Excl: Inability to distinguish HA types; current use of prophylactic HA meds Rec: N/S, but were out-patients	***Metoprolol:*** 50 mg, 2x/day; n = 31* ***Clonidine:*** 50 µg, 2x/day; n = 31* 4-wk baseline; two 8-wk treatment periods; 4-wk washout between treatment periods; no follow-up Acute migraine meds permitted during trial	***HA index:*** Calculated by multiplying no. of migraine days by HA intensity rating for each attack (1=mild; 2=moderate; 3=severe) and summing them ***HA frequency:*** Definition N/S, but obtained from pts' diaries	The median ***HA index*** scores after treatment with clonidine or metoprolol were 10.2 and 8.4, respectively. Metoprolol was significantly better than clonidine at reducing ***HA index*** ($p<0.05$). The median ***HA index*** score at baseline was reduced from 11.2 to 10.2 after treatment with clonidine, a reduction that was not statistically significant ($p>0.05$). However, the median ***HA index*** score was reduced from 11.2 at baseline to 8.4 after treatment with metoprolol, a reduction that was statistically significant ($p<0.001$). Of pts treated with clonidine, 8/29 (28%) improved (achieved > 50% reduction in ***HA frequency*** from pre- to post-treatment). Of those treated with metoprolol, 10/27 (37%) improved.	Dropouts: 8 (26%), 4 due to AES (3 clonidine, 1 washout period); data from these pts were included in efficacy analyses All results reported as median values per 4 wks

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Louis and Spierings, 1982	SPPG QS: 3 (r, db, dd)	N = 75 Age: 37 (median) (range: 17-57) 56% female Classical or common migraine (Ad Hoc); HAs moderate-severe and throbbing; ≥ 6 attacks in past 6 mos Chron: 17 yrs (median) (range: 2-32) Rec: General practices	***Pizotifen:*** 2-3 mg/day in 3 administrations (dose adjusted during first month of treatment); n = 30 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 36 No baseline period described; 4-mo treatment period Acute meds permitted	***HA frequency:*** No. of attacks/mo ***HA severity:*** Each attack graded on 4-pt scale (not described) ***HA duration:*** Not described	Both drugs had a significant effect on ***HA frequency*** from the second month on (no p-values reported). The mean reduction in the number of attacks over the 4-mo treatment period was 54% in the flunarizine group and 45% in the pizotifen group. There were no significant differences between the two drugs for this outcome (no p-value reported). Both drugs also significantly reduced ***HA severity*** compared to pre-treatment values ($p<0.001$ for both groups). From month 2 on, flunarizine was significantly better than pizotifen for this outcome ($p=0.026$ for month 4). Neither treatment significantly affected ***HA duration.***	Dropouts: 9 (12%), 2 due to AEs (1 each flunarizine and pizotifen) Not clear how baseline/pre-treatment values established (no baseline period described)
Lücking, Oestreich, Schmidt, et al., 1988 (Study 1)	SPPG QS: 3 (nr, db+, dd)	N = 434 Age: 42 82% female Classical or common migraine (Ad Hoc); ≥ 2 attacks/mo in past 6 mos or single attacks lasting several days Chron: N/S Rec: Medical practices	***Propranolol:*** 40 mg, 2x/day for 2 wks, then 3x/day; n = 170 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 166 2-wk washout period; 4-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo ***HA duration:*** Overall attack duration (hrs/mo)	Mean ***HA frequency*** (± SD) was reduced in the flunarizine group from 6 (± 6) after one month of treatment to 4 (± 4) after 4 months. A similar reduction was observed in the propranolol group, from 6 (± 6) to 4 (± 5). Mean ***HA duration*** (± SD) was reduced from 17 (± 33) after one month to 10 (± 16) after 4 months in the flunarizine group, and from 17 (± 24) to 11 (± 18) in the propranolol group. There were no statistically significant differences between the two treatments for these outcomes (no p-values reported).	Dropouts: 98 (23%), 17 due to AEs (6 flunarizine, 11 propranolol) Not randomized 1-mo results used in lieu of pre-treatment/ baseline data Most patients had classical migraine

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Lücking, Oestreich, Schmidt, et al., 1988 (Study 2)	SPPG QS: 3 (nr, db+, dd)	N = 87 Age: 43 74% female Classical or common migraine (Ad Hoc); ≥ 2 attacks/mo in past 6 mos or single attacks lasting several days Chron: N/S Rec: Hospital outpatient depts	***Propranolol:*** 40 mg, 2x/day for 2 wks, then 3x/day; n = 34 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 35 2-wk washout period; 4-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo ***HA duration:*** Overall attack duration (hrs/mo)	Mean ***HA frequency*** (± SD) was reduced in the flunarizine group from 6 (± 6) after one month of treatment to 4 (± 5) after 4 months. A similar reduction was observed in the propranolol group, from 5 (± 6) to 3 (± 5). Mean ***HA duration*** (± SD) was reduced from 25 (± 39) after one month to 19 (± 29) after 4 months in the flunarizine group, and from 19 (± 37) to 14 (± 14) in the propranolol group. There were no statistically significant differences between the two treatments for these outcomes (no p-values reported).	Dropouts: 18 (21%), 6 due to AEs (2 flunarizine, 4 propranolol) Not randomized 1-mo results used in lieu of pre-treatment/ baseline data Most patients had classical migraine
Ludin, 1989	SPPG QS: 4 (r, db+, dd)	N = 59 Age: 34 71% female Common or classical migraine; ≥ 6 attacks in past 6 mos Chron: N/S Rec: N/S	***Propranolol:*** 40 mg, 3x/day; n = 32 ***Flunarizine:*** 10 mg, 1x/day; n = 27 1-mo baseline period (placebo); 4-mo treatment period; no follow-up Patients allowed to use their usual acute meds	***HA index:*** Total monthly duration times severity ***HA frequency:*** No. of attacks/mo ***HA severity:*** Each attack graded on scale of 1-3 (no interference with daily activities, interference with daily activities, normal daily activities impossible); mean attack severity calculated for each month ***HA duration:*** In hrs; mean attack duration calculated for each month of trial	Mean ***HA index*** (± SD) was not significantly reduced in the flunarizine group (no p-value reported) and was actually slightly higher during the last month of treatment (93.0 [± 154.1]) than during the baseline period (92.9 [± 90.3]). In the propranolol group, the mean HA index was reduced over the same period of time from 121.4 (± 123.2) to 66.9 (± 74.1) ($p<0.005$). Both treatments significantly reduced mean ***HA frequency*** compared with baseline values. Pre-treatment mean frequency (± SD) in the flunarizine group was 6.6 (± 4.9); during the last month of treatment, it was 4.8 (± 6.2) ($p<0.01$). Corresponding values in the propranolol group were 6.1 (± 3.9) and 3.7 (± 4.2), respectively ($p<0.0005$). 13/27 (48%) of patients in the flunarizine group achieved a 50% or more reduction in monthly HA frequency during the trial, as did 16/32 (50%) of patients in the propranolol group. Propranolol, but not flunarizine significantly reduced mean ***HA intensity***. Neither treatment affected mean ***HA duration***. Investigators reported that there were no significant differences between the two treatments for any of the outcome measures analyzed (no p-values reported for between-group comparisons).	Dropouts: 11 patients (19%) withdrew before completing the trial, 5 due to AEs (2 flunarizine, 3 propranolol); these 11 patients were nonetheless included in the efficacy analysis (last available scores used for later timepoints)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Lundberg, 1969	SPPG QS: 3 (r, db, dd)	N = 50 Age: 35 74% female Classic or common migraine; ≥ 1 attack/mo Chron: N/S Rec: Referrals to investigator	***Placebo:*** n = 23 ***Flumedroxone:*** 5 mg, 2x/day; n = 21 No baseline period; 1-mo treatment period; open trial followed double-blind trial Acute meds (ergotamine or analgesics) permitted	***HA frequency:*** No. of attacks/mo	Flumedroxone was significantly better than placebo at reducing ***HA frequency*** compared with pre-treatment values ($p<0.0005$). After 1 month of treatment, 1 patient in the flumedroxone group (5%) was unchanged, 13 (62%) had fewer attacks than before, and 7 (33%) were completely free of attacks. Corresponding figures in the placebo group were 14 patients (61%), 8 (35%), and 1 (4%), respectively.	Dropouts: 6 (12%), none due to AEs Baseline values taken from patient histories "Small number" of patients had been treated with progestogens or methysergide before, with unsatisfactory results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Malvea, Gwon, and Graham, 1973	CrOv QS: 2 (r, ndb, dd)	N = 31 Age: N/S (range: 25-57) 86% female Common migraine; ≥ 1 HA/wk Chron: N/S Rec: Clinic of unspecified type	***Placebo:*** n = 29* ***Propranolol:*** Dose N/S; n = 29* 30-day baseline period (no prophylactic med); two 6-wk treatment periods; no washout; no follow-up Acute meds (analgesics, narcotics, ergots) permitted	***HA index:*** Sum of severity scores; severity of each attack graded on scale of 1-3 (mild/ annoying, moderate/ interfering, severe/ incapacitating)	Mean total ***HA index*** scores per day were 25.4 during the baseline period, 23.3 on placebo, and 18.6 on propranolol (no variance data reported). Investigators did not report whether they found the difference between placebo and propranolol to be statistically significant.	Dropouts: 2 (6%), neither due to AEs Low quality score (2); not double-blind
Markley, Cheronis, and Piepho, 1984	CrOv QS: 3 (r, db, dd)	N = 20 Age: 33 86% female Common or classic migraine; ≥ 3 HAs/mo in past yr Chron: 13 yrs Rec: N/S	***Placebo:*** n = 14* ***Verapamil:*** 80 mg, 3x/day; n = 14* 4-wk baseline period (no prophylactic med); two 8-wk treatment periods; no washout; no follow-up Use of acute meds permitted	***HA index:*** Severity times duration for each attack; individual attack scores then summed for each week ***HA frequency:*** No. of HAs per week ***HA severity:*** Each attack graded on scale of 1-5 (warning of potential HA, but no pain; mild; moderate; severe; excruciating) ***HA duration:*** Recorded (in hrs) for each attack	Verapamil was significantly better than placebo for ***HA index*** ($p<0.005$). Mean weekly HA index scores, post-treatment, were 72.6 for verapamil and 116.4 for placebo (no variance data reported). Post-treatment mean weekly ***HA frequency*** was also significantly lower with verapamil (2.8) than with placebo (3.4) ($p<0.05$; no variance data reported). Verapamil was also significantly better than placebo for ***HA duration*** ($p<0.05$). ***HA severity*** was not significantly affected (no data and no p-value reported).	Dropouts: 6 patients (30%) withdrew during 1st treatment period with intractable HAs; 2 others (10%) withdrew before completing trial (one due to AEs with verapamil), but were included in the efficacy analysis 8/14 patients included in the efficacy analysis had had no success when treated with prophylactic med in past

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Martucci, Manna, Mattesi, et al., 1983	CrOv QS: 3 (r, db, dd)	N = 90 Age: 37 (range: 20-50) 60% female Common migraine (Ad Hoc); history ≥ 5 yrs; no migraine preventive therapy in previous 6 mos Chron: N/S Rec: HA clinics	***Placebo:*** n = 79* ***DHE (timed-release):*** 5 mg, 2x/day; n = 79* No baseline period described; two 45-day treatment periods; no washout; no follow-up Patients permitted to take their usual meds for acute attacks	***HA index:*** Severity times frequency ***HA frequency:*** No. of attacks ***HA severity:*** Not described; severity graded each day on scale of 0-4 (no HA; no medication required; no disability after medication; partial disability with medication; total disability, even with medication) ***HA duration:*** Mean per attack (in hrs)	Results for all outcomes were reported separately for "daily migraine" (occurring during the day), "night migraine" (patient awakens with HA), and "awakening migraine" (onset within 1 hr of awakening). It was not clear whether this division represented a stratified analysis of different *HA episodes* or of different *subgroups of patients*. Mean ***HA index*** was lower with DHE than with placebo for all three HA types/patient groups (19.47 vs. 26.92 for daily; 0.28 vs. 1.63 for night; 11.57 vs. 16.49 for awakening); no variance data or p-values were reported. ***HA frequency*** was significantly lower with DHE than with placebo in all three HA types/patient groups ($p<0.01$, daily; $p<0.005$, night; $p<0.02$, awakening). ***HA severity*** was significantly lower with DHE than with placebo for night migraines ($p<0.05$); otherwise, there were no significant differences between the two treatments for ***HA severity*** or ***duration***.	Dropouts: 11 (12%), 6 due to AEs (all DHE)
Masel, Chesson, Peters, et al., 1980	CrOv QS: 4 (r, db+, dd)	N = 40 Age: 35 (median) (range: 21-64) 92% female Migraine; > 1 attack/mo Chron: N/S Rec: Referrals to neuro dept	***Placebo:*** n = 25* ***Aspirin + dipyridamole:*** 325 + 25 mg, 3x/day; n = 25* No baseline period described; two 3-mo treatment periods; no washout; no follow-up All patients given acetaminophen 325 mg + codeine 30 mg to take for acute migraine attacks; aspirin and antihistamines *not* permitted as treatments for acute attacks	***HA frequency:*** No. of HAs/mo ***HA severity:*** Each attack graded on continuum from 0-100 (no pain-maximum pain tolerable)	***HA frequency*** was significantly lower with aspirin + dipyridamole than before treatment ($p<0.01$) or with placebo ($p<0.01$; Mann Whitney U-test). Median frequency was 2.00 pre-treatment, 2.33 with placebo, and 1.33 with aspirin + dipyridamole. Similar results were reported for ***HA severity***.	Dropouts: 15 (38%), none due to AEs High dropout rate (38%) Not clear how pre-treatment values established

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mastrosimone, Iaccarino, and de Caterina, 1992	SPPG QS: 4 (r, db+, dd)	N = 61 Age: 43 (range: 24-51) 72% female Classical or common migraine (Ad Hoc); > 2-yr history; markedly reduced sense of well-being during attacks; > 4 HAs during anamnestic baseline period Chron: 12 yrs Rec: N/S	***Pizotifen:*** 0.5 mg, 3x/day; n = 26 ***Cyclandelate:*** 800 mg, 2x/day; n = 35 1-mo anamnestic baseline period (no migraine meds); 1-mo placebo baseline period; 3-mo treatment period; no follow-up Acute meds permitted	***Daily total pain index:*** Score calculated every day = sum of severity scores for every hr of day, where severity graded on scale of 0-4 (no HA - very severe HA); mean daily score/mo calculated ***HA frequency:*** No. of attacks/mo	Both drugs reduced the ***total pain index*** significantly in comparison to baseline values from the first month of treatment on ($p<0.001$ for both treatments and all months). Cyclandelate was signficantly better than pizotifen, beginning in the first month and continuing through the second and third months of treatment ($p<0.001$ for all three months). During the third treatment month, the total pain index was reduced by 64.0% in the cyclandelate group and 52.1% in the pizotifen group. Very similar results were reported for ***HA frequency***. During the third month of treatment, HA frequency was reduced by 77.6% in the cyclandelate group and 31.5% in the pizotifen group.	Dropouts: 0/61 during active treatment periods; 23/84 patients were excluded before active treatment began for noncompliance or as placebo responders (> 40% reduction in frequency of attacks during placebo baseline period compared to anamnestic baseline period)
Mathew, 1978	CrOv QS: 2 (r, db, dnd)	N = 12 Age: N/S (range: N/S) % female N/S Common or classical migraine Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 12* ***Oxitriptan (5-HTP):*** 300 mg/day; n = 12* No baseline described; two 8-wk treatment periods; no washout; no follow-up No mention of acute migraine meds	***HA index:*** Not defined	Investigators reported that "5-HTP was not superior to placebo in preventing migraine attacks," but did not provide further information.	Dropouts: N/S Information obtained from abstract

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mathew, 1981	SPPG QS: 2 (r, ndb, dd)	***Migraine-only:*** N = 340 Age: 36 94% female Chron: N/S Rec: N/S ***Mixed HA:*** N = 375 Age: 40 96% female Chron: N/S Rec: N/S	***Control (abortive admin. of ergotamine + analgesic)***: n = 33 (migraine), 35 (mixed); total ergotamine intake ≤ 6 mg/wk ***Propranolol***: n = 38 (migraine), 38 (mixed); 20 mg 3x/day initially; increased to 40 mg 3 or 4x/day within first month of treatment, as tolerated ***Amitriptyline***: n = 32 (migraine), 31 (mixed); 25 mg/day for 2 wks, then increased to 50-75 mg/day in first month, as tolerated ***Biofeedback (combined EMG + thermal) + relax. (AT phrases)***: n = 31 (migraine), 31 (mixed); ten 1-hr sessions over 6 mos; home practice ≥ 30 min, at least 1x/day ***Propranolol + amitriptyline***: n = 38 (migraine), 36 (mixed); combined using dosages described above ***Propranolol + biofeedback (as above)***: n = 33 (migraine), 34 (mixed); combined using dosage and procedure described above ***Amitriptyline + biofeedback (as above)***: n = 38 (migraine), 39 (mixed); combined using dosage and procedure described above ***Propranolol + amitriptyline + biofeedback (as above)***: n = 30 (migraine), 37 (mixed); combined using dosages and procedure described above 1-mo baseline period; 6-mo treatment period; no follow-up Use of acute meds permitted	***HA index***: Average weekly HA index, derived from frequency and severity ratings ***HA frequency:*** Definition N/S ***HA intensity:*** Scale used for grading N/S, but recorded for each attack	Improvement was expressed as the percentage of change in mean weekly ***HA index*** scores from pre-treatment to the last 3 mos of treatment. ***Migraine results:*** Each active treatment group experienced significantly better improvement than did the control group (no p-values reported). The improvement percentages ranged from 35-74% for the active treatment groups, compared with 20% for the control group. The combination of propranolol + biofeedback yielded the best results (74%); adding amitriptyline to this combination did not produce a significant change (73%). Propranolol alone resulted in a 62% improvement, amitriptyline alone in a 42% improvement ($p < 0.01$ in favor of propranolol). Propranolol + amitriptyline (64%) was not significantly better than propranolol alone (62%) ($p<0.50$). Treatment with biofeedback alone resulted in a 35% improvement. Adding biofeedback to treatment with propranolol or amitriptyline improved both (propranolol, from 62% to 74%; amitriptyline, from 42 to 48%). ***Mixed HA results:*** Percentage improvement scores in the active treatment groups ranged from 48%-76%, compared to 18% for the control group. The most effective treatment was the combination of propranolol + amitriptyline + biofeedback (76%). Amitriptyline alone was significantly better than propranolol alone (60% vs. 52%) ($p < 0.01$), and the combination of propranolol + amitriptyline (69%) was superior to either drug on its own ($p < 0.01$). Biofeedback alone yielded a 48% improvement. Adding biofeedback to the active drug therapies produced an improvement in every case (from 52% to 62% for propranolol alone; from 60% to 66% for amitriptyline alone; and from 69% to 76% for propranolol + amitriptyline).	Dropouts: Migraine-only, 67 (20%), 18 due to AEs; mixed HA, 94 (25%), 29 due to AEs Low quality score (2); not double-blind

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mathew, Saper, Silberstein, et al., 1995	SPPG QS: 4 (r, db+, dd)	N = 107 Age: 46 78% female Migraine w/ or w/o aura (IHS); history ≥ 6 mos; ≥ 2 attacks in previous 3 mos; patients with chronic daily HA or TTH on ≥ 15 days/mo excluded Chron: 25 yrs Rec: HA and neuro clinics	***Placebo:*** n = 36 ***Divalproex sodium:*** Dose titrated to achieve serum level of approximately 70-120 mg/L; average dose 1087 mg/day; n = 69 4-wk baseline phase (placebo); 12-wk treatment phase (4 wks dose adjustment + 8 wks maintenance); no follow-up Patients permitted to use symptomatic meds to treat acute attacks, but use of such meds must average < 3 days/wk	***HA frequency:*** Mean 4-wk attack frequency; percentage reduction in mean 4-wk attacks frequency; percentage of patients reporting a ≥ 50% reduction in frequency ***HA severity:*** Peak severity per attack, on scale of 0-4 (none-excruciating) ***HA duration:*** Per attack, in hrs	Divalproex sodium was significantly better than placebo at reducing ***HA frequency***. Mean 4-wk HA frequencies at baseline were 6.4 in the placebo group and 6.0 in the divalproex sodium group; during the treatment phase, these numbers were reduced to 5.7 and 3.5, respectively ($p \leq 0.001$; no variance reported). Mean change scores (from baseline to treatment phase) were also significantly higher in the divalproex sodium group ($p < 0.001$; mean change scores not reported). The proportions of patients reporting a 50% or greater reduction in mean 4-wk attack frequency were 14% in the placebo group (5/36) and 48% in the divalproex sodium group (33/69). Divalproex sodium was significantly better than placebo for this outcome ($p < 0.001$). No significant differences were observed between the two treatments for ***HA severity*** or ***duration***.	Dropouts: 17 (16%), 11 due to AEs (9 divalproex sodium, 2 placebo); 15 of the 17 dropouts provided some efficacy data and were included in the efficacy analysis Only patients who were previously untreated or had failed ≤ 2 trials of prophylactic med were included
McArthur, Marek, Pestronk, et al., 1989	CrOv QS: 2 (nr, db, dd)	N = 24 Age: N/S % female N/S Classic migraine (Ad Hoc) Chron: N/S Rec: Personal referral and ads	***Placebo:*** n = 14* ***Nifedipine:*** 20 mg, 3x/day for 3 days; increased to 30 mg, 3x/day if no AEs; n = 14* 1-mo baseline period (no prophylactic med); two 3-mo treatment periods; 1-wk washout; no follow-up Use of acute meds permitted	***HA frequency:*** No. of attacks of classic migraine per month	All patients (n = 14) who completed at least 10 wks of treatment in each phase of the trial were included in the efficacy analysis. There was no significant difference between nifedipine and placebo for post-treatment ***HA frequency*** (p=0.56). Mean HA frequency (± SEM) during the third month of treatment was 1.9 (± 0.5) with nifedipine and 2.1 (± 0.4) with placebo.	Dropouts: 10 (42%), 6 due to AEs (5 nifedipine, 1 placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mendenopoulos, Manafi, Logothetis, et al., 1985	SPPG QS: 5 (r+, db+, dd	N = 30 Age: 44 (median) (range: 20-65) 80% female Classical migraine (Ad Hoc); ≥ 1-yr history; ≥ 4 mod-severe attacks in previous 3 mos; no other types of HA; no prophylactic med in last 2 mos Chron: 5 yrs Rec: Neuro and psychiatric dept	***Placebo:*** n = 11 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 9 1-mo baseline period (medication-free); 3-mo treatment period; 15 patients (8 placebo, 7 flunarizine) continued in double-blind trial for additional month Acute meds permitted during treatment period	Severity of each attack (HA and other symptoms) graded on scale of 1-4 (mild, mild to moderate, moderate, rather severe); following outcome measures calculated: ***Migraine index:*** No. of attacks/mo times mean monthly severity of attack ***Corrected migraine index:*** Migraine index times mean monthly duration of attack ***HA frequency:*** Mean no. of attacks/mo ***Attack severity:*** Mean monthly severity ***Attack duration:*** Mean duration/mo (in hrs)	Flunarizine was significantly ($p<0.05$) better than placebo for reduction in the ***corrected migraine index*** from pre-treatment to end of treatment (after 3 mos in 5 patients and after 4 mos in 15 patients). In the flunarizine group, the mean corrected migraine index (± SEM) was 34.7 (± 10.2) pre-treatment and 6.2 (± 2.5) at the end of treatment; in the placebo group, the corresponding means were 37.0 (± 9.3) and 61.6 (± 18.9), respectively. Mean ***migraine index*** scores in the flunarizine group were reduced from 13.3 pre-treatment to 3.6 after 3 mos. In the placebo group, scores rose slightly over the same period of time from 17.5 to 18.6 (no variance data or p-values reported). Differences between the two treatments for reduction in ***HA frequency*** were statistically significant only during the third month of treatment ($p=0.033$).	Dropouts: 10 patients (33%) withdrew before the end of the baseline period; 5 (17%) withdrew after completing 3 mos of treatment (3 placebo, 2 flunarizine), none due to AEs 10/20 patients completing the trial had been treated with prophylactic med before, generally with moderate or unsatisfactory results
Meyer and Hardenberg, 1983	CrOv QS: 3 (r, db+, dnd)	N = 35 Age: 41 78% female Classic or common migraine (n = 27) or cluster HA (n = 8) (Ad Hoc); ≥ 2 HAs/mo Chron: N/S Rec: N/S	***Nimodipine, 60 mg/day:*** 20 mg, 3x/day; n = 27* (migraine) ***Nimodipine, 120 mg/day:*** 40 mg, 3x/day; n = 27* (migraine) 1-wk baseline period (no prophylactic med); two 8-wk treatment periods; 1-wk washout; no follow-up Acute meds permitted, with some restrictions	***HA frequency:*** Mean frequency/mo (not clear whether no. of attacks or no. of HA days) ***HA severity:*** Outcome measure not described; each HA graded as mild, moderate, or severe ***HA duration:*** Not described	Both doses of nimodipine significantly reduced mean ***HA frequency*** per month in comparison to baseline values (no p-values reported). There was no significant difference between the two doses for this outcome (no p-value reported). Pre- and post-treatment mean frequencies themselves were not reported. Neither dose significantly reduced ***HA severity*** or ***duration*** (no data and no p-values reported).	Dropouts: Not described

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Micieli, Trucco, Agostinis, et al., 1985	CrOv QS: 3 (r, db, dd)	N = 22 Age: 47 55% female Common migraine; no interval HA; no prophylactic med in previous 6 mos Chron: 23 yrs Rec: N/S	***Pizotifen:*** 0.5 mg, 3x/day; n = 20* ***Nimodipine:*** 40 mg, 3x/day; n = 20* 1-mo baseline period (placebo); two 3-mo treatment periods; 1-mo washout (placebo); no follow-up Acute meds permitted	***HA index:*** Not described ***HA frequency:*** No. of attacks/mo	Post-treatment mean scores for ***HA index*** and ***HA frequency*** were reported only for the first treatment period and only for the two treatment groups combined. Reductions were significant from baseline to 3 mos ($p<0.001$ for both outcomes). Investigators reported that an ANOVA analysis showed no significant differences between the two treatments (no p-values reported).	Dropouts: 2 (9%); reasons for withdrawal not stated Abstract reporting limited results
Migraine-Nimodipine European Study Group, 1989a	SPPG QS: 4 (r, db+, dd)	N = 89 Age: 34 79% female Classic migraine (Ad Hoc); 2-8 migraine days/mo (including baseline period); ≥ 2 classic attacks in previous 6 mos; no cluster HA; TTH ≤ 6 days/mo Chron: 13.5 yrs (median) Rec: Neuro depts	***Placebo:*** n = 46 (intention-to-treat); n = 39 (valid for efficacy analysis) ***Nimodipine:*** 40 mg, 3x/day; n = 43 (intention-to-treat); n = 33 (valid for efficacy analysis) 4-wk baseline period; 12-wk treatment period; no follow-up Nothing on acute meds	***HA index:*** No. of migraine days times HA severity per 4 wks; included attacks with and without aura ***HA frequency:*** No. of migraine days per 4 wks	An *intention-to-treat analysis* showed no significant difference between nimodipine and placebo for reduction in ***HA index*** from pre- to post-treatment (no p-value reported). Mean monthly HA index values in the nimodipine group were 7.7 during the baseline period and 2.1 during the treatment period (no variance data reported). Corresponding values in the placebo group were 8.1 and 0.9, respectively. Results were similar when the smaller group of *patients valid for the efficacy analysis* were considered. Mean monthly ***HA index*** scores in the nimodipine group were 11.35 during the baseline period, 3.24 after one mo of treatment, 2.69 after two months, and 2.47 after three mos. Corresponding scores in the placebo group were10.30, 3.46, 3.08, and 1.00, respectively (no variance data reported). The difference between the two groups was not significant (no p-value reported). Similar results were reported for ***HA frequency.***	Dropouts: 17 patients (19%) were excluded from the analysis of efficacy, 7 due to AEs (3 nimodipine, 4 placebo); the other 10 were excluded at the completion of the baseline period Patients who had tried 2 or more prophylactic drugs w/o success were excluded

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Migraine-Nimodipine European Study Group, 1989b	SPPG QS: 4 (r, db+, dd)	N = 192 Age: 38 78% female Common migraine (Ad Hoc); 2-8 migraine days/mo (including baseline period); ≤ 1 attack of classic migraine in previous 6 mos; no cluster HA; TTH ≤ 6 days/mo Chron: 16 yrs (median) Rec: Neuro depts	***Placebo:*** n = 98 (intention-to-treat); n = 85 (valid for efficacy analysis) ***Nimodipine:*** 40 mg, 3x/day; n = 94 (intention-to-treat); n = 76 (valid for efficacy analysis) 4-wk baseline period; 12-wk treatment period; no follow-up Nothing on acute meds	***HA index:*** No. of migraine days times HA severity per 4 wks ***HA frequency:*** No. of migraine days per 4 wks	An *intention-to-treat analysis* showed no significant difference between nimodipine and placebo for reduction in ***HA index*** from pre- to post-treatment (p=0.91). Mean monthly HA index values in the nimodipine group were 9.27 during the baseline period and 4.19 during the treatment period (no variance data reported). Corresponding values in the placebo group were 8.78 and 3.87, respectively. Results were similar when the smaller group of *patients valid for the efficacy analysis* were considered. Mean monthly ***HA index*** scores in the nimodipine group were 9.39 during the baseline period, 5.35 after one mo of treatment, 5.67 after two months, and 3.29 after three mos. Corresponding scores in the placebo group were 8.55, 4.87, 3.40, and 3.50, respectively (no variance data reported). Analysis of covariance showed no significant difference between the two treatments for this outcome (p=0.58). Similar results were reported for ***HA frequency***.	Dropouts: 31 patients (16%) were excluded from the analysis of efficacy, 4 due to AEs; 12 of the 31 were excluded for protocol violations during the baseline period Patients who had tried 2 or more prophylactic drugs w/o success were excluded
Mikkelsen and Falk, 1982	CrOv QS: 4 (r, db+, dd)	N = 38 Age: 35 (median) (range: 18-52) 87% female Classic or common migraine (Ad Hoc); history > 1 yr; > 2 HAs/mo Chron: N/S Rec: Neuro dept	***Placebo:*** n = 31* ***Tolfenamic acid:*** 100 mg, 3x/day; n = 31* No baseline period described; two 10-wk treatment periods; 2-wk washout; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks ***HA severity:*** Recorded for each attack on scale of 1-5 (not described) ***HA duration:*** Total duration (in hrs)	Tolfenamic acid was significantly better than placebo for ***HA frequency*** (p<0.01). 22 patients had fewer attacks on tolfenamic acid; 6 had fewer attacks on placebo, and 3 had the same number of attacks with both interventions. Based on individual patient data reported by investigators, we were able to calculate the mean within-patient difference in HA frequency for tolfenamic acid vs. placebo. The mean difference was 2.3 (± 3.2). Tolfenamic acid was significantly better than placebo for both ***HA severity*** and ***HA duration*** (p<0.01 for both outcomes).	Dropouts: 7 (18%), 3 due to AEs (2 tolfenamic acid, 1 placebo)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986	CrOv QS: 4 (r, db+, dd)	N = 39 Age: 38 (median) (range: 15-65) 84% female Classic or common migraine (Ad Hoc); ≥1-yr history; ≥ 3 HAs/mo Chron: N/S Rec: Neuro dept	***Placebo:*** n = 31* ***Propranolol:*** 40 mg, 3x/day; n = 31* ***Tolfenamic acid:*** 100 mg, 3x/day; n = 31* No baseline period described; three 12-wk treatment periods; no washout; no follow-up Data analyzed for last 11 wks of each treatment period only Acute meds permitted	***HA frequency:*** No. of attacks ***HA severity:*** Mean severity per attack; each attack graded on scale of 1-10 (not described) ***HA duration:*** Total duration of attacks (in hrs); mean duration per attack (in hrs)	There was a significant difference among the three treatments for ***HA frequency*** ($p<0.005$, Friedmann's test), with the number of attacks significantly larger with placebo. No significant difference was found between tolfenamic acid and propranolol for this outcome (95% confidence limits, -1.6 to +1.5 attacks). Based on individual patient data reported by investigators, we calculated mean within-patient differences in ***HA frequency*** for the various treatment comparisons. For tolfenamic acid vs. placebo, the mean difference was 2.29 (± 5.2); for propranolol vs. placebo, it was 2.5 (± 4.8); and for tolfenamic acid vs. propranolol, it was -0.23 (± 4.6). Tolfenamic acid, but not propranolol, was significantly better than placebo for ***HA intensity***. There was no significant difference between the two active treatments for this outcome. None of the three interventions significantly reduced mean ***HA duration (per attack)***. Tolfenamic acid and propranolol were both significantly better than placebo, and not different from one another, for ***total HA duration***.	Dropouts: 8 (21%), 3 due to AEs (2 propranolol, 1 tolfenamic acid) Statistical analysis showed no carry-over effect

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Mondrup and Møller, 1977	CrOv QS: 4 (r, db+, dd)	N = 32 Age: 35 (range: 17-54) 76% female Chron: 12 (range: 1-40) Common or classical migraine (Ad Hoc); ≥ 2 Ms/mo for > 1 yr Excl: Previous use of clonidine Rec: Neurology dept. of hospital in Denmark	***Placebo:*** n = 21* ***Clonidine:*** 50 µg, 2x/day for 1 wk; dose then increased to 75 µg, 2x/day for 11 wks; n = 21* Baseline period (length N/S); two 12-wk treatment periods; three 4-wk washout periods, 1 before and after each treatment period; no follow-up Acute migraine meds permitted during trial	***HA index:*** Calculated by multiplying the HA intensity ratings (1=mild; 2=moderate; 3=severe) and summing them ***HA frequency:*** Recorded by pt as "dates of attacks" and reported as "no. of HA days"	Results were reported only as median differences. For ***HA index***, the median difference between clonidine and placebo was -4 (with 95% confidence limits of from -10 to +5 days). For comparisons of pre- to post-treatment results for ***HA index***, investigators reported only that there were no significant differences between the two treatments (no p-value given). For ***HA frequency***, the median difference between clonidine and placebo was -2 days (with 95% confidence limits of from -6 to +2 days). Investigators reported that there was no statistically significant difference between the two treatments for ***frequency*** (no p-value given). A comparison of ***HA frequency*** from baseline to post-treatment revealed a 16% reduction from treatment with clonidine and a 30% reduction from treatment with placebo. Investigators reported that the difference between the two treatments was not significant (no p-value given).	Dropouts: 11 (34%), none due to AEs Data recorded by pts and assessed every 4 wks by investigators Investigators reported that the large no. of withdrawals and small no. of pts may have biased results
Monro, Swade, and Coppen, 1985	SPPG QS: 4 (r, db+, dd)	N = 38 Age: N/S % female N/S Classical or common migraine (World Fed Neurol); ≥ 1 attack/wk Chron: N/S Rec: N/S	***Placebo:*** n = 18 ***Mianserin:*** 30 mg, 1x/day (at night) for first wk; then 60 mg, 1x/day (at night) for duration of trial; n = 16 2-wk baseline period (placebo); 16-wk treatment period; no follow-up Acute attacks treated with metoclopramide + acetaminophen (po), ergotamine + caffeine (po), or ergotamine (in)	***HA frequency:*** Mean no. of attacks/4 wks ***HA severity:*** Sum of severity ratings for each 4-wk segment of treatment period (each HA graded on scale of 1-3)	Compared with pre-treatment values, mianserin resulted in a significant reduction in ***HA frequency*** at 4 and 12 wks ($p<0.01$ and $p<0.05$, respectively). Placebo did not produce a significant reduction at any timepoint (no p-values reported). When the two treatments were directly compared for this outcome, there was no significant difference between them (no p-value reported). Mean HA frequencies were reported only in graphic form and could not be reliably read off the graph. Similar results were reported for ***HA severity***.	Dropouts: 4 (11%) (no reasons specified)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Murphy, Heptinstall, and Mitchell, 1988	CrOv QS: 3 (r, db, dd)	N = 72 Age: 46 (range: 24-72) 74% female Common or classical migraine; ≥ 1 HA/mo for ≥ 2 yrs Chron: N/S Rec: Migraine self-help group; media publicity	***Placebo:*** n = 59* ***Feverfew:*** 1 cap/day (cap weights ranged from 70-114 mg [mean 82 mg]); n = 59* 1-mo baseline (placebo); two 4-mo treatment periods; no washout; no follow-up No meds permitted during trial for acute migraine attacks	***HA frequency:*** No. of attacks ***HA intensity:*** Recorded daily by patients on 4-point scale (0=no pain; 1=mild, not interfering with daily activities; 2=severe, reducing working capacity; 3=very severe, requiring rest in bed)	For ***HA frequency***, the post-treatment mean values (± SEM) were 3.6 (± 0.2) and 4.7 (± 0.3) for patients treated with feverfew and placebo, respectively. Investigators reported that feverfew was significantly better at reducing HA frequency than was placebo ($p < 0.005$). Investigators did not report having analyzed the pre- to post-treatment differences for statistical significance.	Dropouts: 12 patients (17%) withdrew and were not included in efficacy analyses, 5 due to AEs (feverfew 2, placebo 3); another patient lost her diary twice, so was also excluded from efficacy analyses 18 (24%) of 76 patients originally selected for the study had previously used feverfew; of the 59 patients completing the trial, 42 had never previously taken the active drug; on entry to trial, 5 patients were still using the treatment
Nanda, Johnson, Gray, et al., 1978	CrOv QS: 4 (r, db+, dd)	N = 43 Age: N/S 74% female Migraine; > 2 attacks/mo Chron: N/S Rec: Migraine clinic	***Placebo:*** n = 33* ***Acebutolol:*** 400 mg, 2x/day (dose gradually increased over first 2 wks); n = 33* 4-wk baseline period; two 12-wk treatment periods; 4-wk washout (placebo); no follow-up Patients permitted to take their usual meds for acute attacks	***HA frequency:*** No. of HAs per 4 wks ***HA severity:*** Mean attack severity; each attack graded on scale of 1-10 (not described) ***HA duration:*** Mean duration per attack (in hrs)	Both acebutolol and placebo significantly reduced mean ***HA frequency*** compared with baseline values ($p<0.01$), but there was no significant difference between the two interventions (no p-values reported). Overall mean frequencies were not reported. Neither intervention significantly affected HA severity or duration (no p-values and no further results reported).	Dropouts: 10 (23%), none due to AEs No carry-over effect High dropout rate (23%)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Nappi, Sandrini, Savoini, et al., 1987	SPPG QS: 2 (r, db-, dd)	N = 40 Age: N/S % female N/S Common migraine (Ad Hoc); history of ≥ 2 yrs; ≥ 3 attacks/mo; no prophylactic treatment in last 2 mos Chron: N/S Rec: Outpatients at HA clinic	***Flunarizine:*** 5 mg, 1x/day (bedtime); n = 18 ***Cyclandelate:*** 800 mg, 2x/day; n = 19 1-mo baseline period (no medication); 1-mo placebo period; 3-mo active treatment period; no follow-up Acute meds permitted	***HA index:*** No. of attacks/mo times severity; severity of each attack graded on scale of 1-3 (working capacity not affected; not able to work; bed rest required) ***HA frequency:*** No. of migraine days/mo	***HA index*** scores were significantly lower during the second ($p<0.05$) and third ($p<0.001$) months of treatment with cyclandelate than during the baseline (placebo) period. Flunarizine produced significantly lower scores, compared to baseline (placebo) values, beginning with the first month of treatment ($p<0.01$; for mos 2 and 3, $p<0.001$). The percentage reduction in HA index scores from baseline (placebo) to the third treatment month was significantly greater in the flunarizine group than in the cyclandelate group ($p<0.02$). HA index scores and percentage reduction data were reported only in graphic form and could not be reliably read off the graphs. Both drugs significantly reduced ***HA frequency***, cyclandelate beginning in the first month of treatment, flunarizine in the second month. Investigators did not state whether they found any significant differences between the two treatments for this outcome. Data on frequency were reported only in graphic form and could not be reliably read off the graphs.	Dropouts: 3 (8%), all due to AEs (2 flunarizine, 1 cyclandelate)
Nattero, Biale, and Savi, 1991	CrOv QS: 2 (r, ndb, dd)	N = 110 Age: 38 (range: 17-66) 63% female Common migraine (IHS); frequency N/S Chron: N/S (range: N/S) Rec: N/S	***Lisuride:*** 0.075 mg, 3x/day; n = 43* ***Pizotifen:*** 1.5 mg, 3x/day; n = 43* 4-wk run-in with acute, but not prophylactic, migraine meds permitted; two 16-wk treatment periods; 4-wk washout between treatment periods; no follow-up Analgesics permitted; no mention of other acute migraine meds	***HA frequency:*** Defined as "frequency of HAs/4 wks" ***HA intensity:*** Recorded daily by pts on 3-point scale	Ten of 43 pts (23%) and 15/43 pts (35%) reduced ***HA frequency*** by ≥ 50% from baseline to post-treatment in the lisuride and pizotifen groups, respectively. Each treatment group improved significantly from pre- to post-treatment ($p < 0.05$, each case). Investigators did not report between-group results.	Dropouts: 63 pts (57%) withdrew due to unspecified reasons; treatment groups N/S; 4 additional pts were not included in efficacy analyses Information obtained from abstract

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Neuman, Demarez, Harmey, et al., 1986	SPPG QS: 3 (nr, db+, dd)	N = 40 Age: 47 45% female Migraine; ≥ 3 attacks/mo; no anti-migraine therapy in 15 days prior to trial Chron: N/S Rec: N/S	***Placebo:*** n = 20 ***DHE (timed-release):*** 5 mg, 2x/day; n = 20 No baseline period described; 1-mo treatment period; no follow-up Acetaminophen permitted for the treatment of acute attacks	***HA frequency:*** No. of attacks per month ***HA severity:*** Mean per attack; each attack graded on scale of 1-3 (mild; requires treatment, but not incapacitating; incapacitating)	DHE was significantly better than placebo at reducing ***HA frequency*** ($p<0.001$). Pre-treatment mean HA frequency (± SD) was 3.3 (± 0.6) in both treatment groups. After 1 month, mean frequency was 1.3 (± 0.6) in the DHE group and 3.0 (± 1.0) in the placebo group. Similar results were reported for ***HA severity.***	Dropouts: 0 Not clear how baseline values established Not randomized
Noone, 1980	CrOv QS: 4 (r+, db, dd)	N = 21 Age: N/S % female N/S Common or classical migraine; ≥ 3 attacks in previous 8 wks Chron: N/S Rec: 2 private practices	***Placebo:*** n = 10* ***Clomipramine:*** 10 mg, 3x/day; n = 10* No baseline period; two 8-wk treatment periods; no washout; no follow-up Use of acute meds permitted	***HA frequency:*** Median no. of attacks ***HA severity:*** No. of severe attacks divided by the total no. of attacks (severe = requires patient to stop what he is doing and lie down) ***HA duration***	Both interventions significantly reduced ***HA frequency*** from pre-treatment levels ($p=0.0039$ for both comparisons), but there was no significant difference between the two treatments for this outcome ($p=0.46$). The median HA frequency pre-treatment was 6 (range: 3-18). Post-treatment median frequencies were 3 (2-12) for clomipramine and 3.5 (1-20) for placebo. Neither intervention significantly affected ***HA severity*** or ***HA duration.***	Dropouts: 11 (52%), 2 due to AEs (both clomipramine) Very high dropout rate No washout Not clear how pre-treatment values established (no baseline period)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Olerud, Gustavsson, and Furberg, 1986	SPPG QS: 4 (r, db+, dd)	N = 28 Age: N/S (range: 17-61) 79% female Classic or common migraine (Ad Hoc); ≥ 2 attacks/mo in previous 4 mos Chron: N/S (range: 2-45 yrs) Rec: N/S	***Propranolol:*** 40-80 mg, 2x/day; n = 14 ***Nadolol:*** 40-160 mg, 1x/day; n = 13 Baseline period (placebo) of at least 1mo; 6-mo treatment period; no follow-up Acute meds (analgesics or ergotamine) permitted	***HA frequency:*** No. of attacks per month ***HA severity:*** Each attack graded on scale of 1-4 (mild, moderate, severe, incapacitating); median severity per attack reported ***HA duration:*** Median duration (in hrs) per attack	Both drugs significantly reduced median ***HA frequency*** compared with baseline values ($p<0.01$ for both comparisons); there was no significant difference between the two drugs for this outcome (no p-value reported). In the propranolol group, median HA frequency (with range) was reduced from 3.6 (1.6-15.0) pre-treatment to 1.9 (0.3-5.6) during treatment. In the nadolol group, the corresponding figures were 5.6 (2.5-25.5) and 2.7 (0.0-23.6), respectively. 8/14 patients in the propranolol group (57%) and 5/13 in the nadolol group (38%) reported a > 50% reduction in HA frequency; the investigators did not analyze this result. Neither treatment significantly affected ***HA severity*** or ***duration***.	Dropouts: 1 patient (4%) withdrew after 3 mos due to AEs associated with nadolol, but was included in the efficacy analysis; one patient in the propranolol group completed the trial, but was not included in the efficacy analysis due to incomplete data
Olsson, Behring, Forssman, et al., 1984	CrOv QS: 4 (r, db+, dd)	N = 56 Age: 37 (range: 19-59) 73% female Classical or common migraine (World Fed of Neurology); 3-10 attacks/mo; patients with other types of vascular HA, chronic daily HA, and "non-separable" TTH excluded Chron: 21 yrs (range: 5-43) Rec: Neuro depts	***Propranolol:*** 40 mg, 2x/day; n = 53* ***Metoprolol:*** 50 mg, 2x/day; n = 56* 4-wk baseline period (placebo); two 8-wk treatment periods; 4-wk washout (placebo); no follow-up Acute meds (ergotamine or analgesics) permitted	***HA index:*** Severity times no. of migraine days; severity of each attack graded on scale of 1-3 (light, moderate, severe) ***HA frequency:*** No. of attacks per 4 wks; no. of migraine days per 4 wks	There were no statistically significant differences between metoprolol and propranolol for any of the outcomes measured (p-values not reported). Both drugs significantly reduced ***HA index*** in comparison with baseline values ($p \leq 0.001$ for both comparisons). Median HA index scores were 12.4 during the baseline period (n = 56), 8.7 during treatment with propranolol (n = 53), and 9.7 during treatment with metoprolol (n = 56). 16/53 patients (30%) reported a 50% or greater reduction in ***HA index*** scores with propranolol in comparison with baseline values, as did 21/56 (37%) with metoprolol.	Dropouts: 3 (5%), none due to AEs; all three included in efficacy analysis to point of withdrawal 16% of patients had tried preventive meds before

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
O'Neill and Mann, 1978	CrOv QS: 2 (nr, db, dd)	N = 12 Age: 35 (range: 18-53) 42% female Classical or common migraine; ≥ 1 HA/mo Chron: 15 yrs (range: 3-40) Rec: N/S	***Placebo:*** n = 12* ***Aspirin:*** 650 mg, 2x/day; n = 12* No baseline period described; two 3-mo treatment periods; no washout; no follow-up Abortive therapy permitted for acute attacks	***HA frequency:*** No. of attacks per 3-mo treatment period	Investigators defined a positive treatment response to aspirin as a > 50% reduction in ***HA frequency*** compared with placebo. 9/12 patients (75%) had such a response ($p \leq 0.0001$). Based on individual patient data reported by investigators, we calculated the mean within-patient difference in HA frequency; it was 5.7 (± 3.4).	Dropouts: 1 patient (8%) withdrew after 4 mos (3 on placebo, 1 on aspirin) due to AEs (aspirin), but was included in the efficacy analysis Low quality score (2); not randomized
Orholm, Honoré, and Zeeberg, 1986	SPPG QS: 3 (r, db, dd)	N = 65 Age: N/S 85% female Migraine; history ≥ 3 yrs; ≥ 6 attacks in previous 2 mos; avg duration ≥ 4 hrs; not using prophylactic med Chron: N/S Rec: 25 general practices	***Placebo:*** n = 28 ***Femoxetine:*** 200 mg/day initially, increasing over first nine days to 600 mg/day; if AEs experienced, dose could be reduced to 400 mg/day; n = 25 No baseline period described; 16-wk treatment period; no follow-up Nothing on use of acute meds	***HA index:*** Not defined; median HA index/two-wk period reported ***HA frequency:*** Number of attacks; median/two-wk period reported	Investigators employed a nonparametric type of ANOVA analysis, assessing treatments, time course, and interaction between treatment and time course simultaneously. This analysis revealed no significant variation with time regardless of treatment, no difference between treatments disregarding time-course, and no interaction between treatment and time. ***HA index, wks 1-2 vs. wks 15-16:*** In the femoxetine group, the median HA index during wks 1-2 was 7.3; during wks 15-16, it was 6.3. In the placebo group, the median HA index for wks 1-2 was 6.8; for wks 15-16, it was 4.5 (no ranges specified). At the end of the study, the 95% confidence limits for the difference between femoxetine and placebo for this outcome were -1.8 to 4.4. ***HA frequency, wks 1-2 vs. wks 15-16:*** In the femoxetine group, median HA frequency was 2.1 in wks 1-2 and 2.3 in wks 15-16. In the placebo group, these values were 2.3 and 2.0, respectively (no ranges specified). At the end of the study, the 95% confidence limits for the difference between femoxetine and placebo for this outcome were -1.1 to 1.0.	Dropouts: 12 (18%), 6 due to AEs (2 placebo, 4 femoxetine)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Osterman, 1977	CrOv QS: 4 (r, db+, dd)	N = 30 Age: 37 (range: 23-49) 70% female Common or classical migraine (Ad Hoc); ≥ 2-3 HAs/mo Chron: 20 (range: 4-34) Rec: Neuro. dept. of hospital; 13 pts had never been treated with prophylactic meds	***Placebo:*** n = 27* ***Iprazochrome (Divascan®):*** 2.5 mg, 1x/evening on Day 1; dosing schedule gradually increased by 1 cap/day to a total of 2 caps, 3x/day (15 mg/day) on Day 11 and until end of trial; n = 27* ***Pizotifen:*** 0.5 mg, 1x/evening on Day 1; dosing schedule gradually increased by 1 cap/day to a total of 2 caps, 3x/day (3 mg/day) on Day 11 and until end of trial; n = 27* No baseline period described; three 8-wk treatment periods; no washout, but first 2 wks of data from each treatment period excluded from analysis; no follow-up Ergotamine and other acute migraine meds permitted	***HA index:*** Calculated weekly by multiplying no. of HAs by respective ***HA intensity*** scores ***HA frequency:*** Defined as "occurrence of HA" ***HA intensity:*** Rated on 3-point scale daily by pt	Results were reported as the "total mean of the individual ***HA indices***/wk" for each treatment group. The total post-treatment mean values for pts treated with pizotifen, iprazochrome, and placebo were 1.6, 2.1, and 2.4, respectively. Investigators did not report pre-treatment mean values. They also did not report whether they analyzed pre- to post-treatment results for statistical significance. ***HA index*** was reduced significantly better by pizotifen than by placebo ($p < 0.001$) or by iprazochrome ($p < 0.01$). However, there were no significant differences between iprazochrome and placebo for this outcome (no p-value given).	Dropouts: 2 (7%) pts withdrew early & were not included in efficacy analyses (1 due to AEs from pizotifen); efficacy data also obtained from 1 additional pt, treated with only iprazo-chrome & placebo, who withdrew early Not clear if baseline data gathered
Palferman, Gibberd, and Simmonds, 1983	CrOv QS: 4 (r, db+, dd)	N = 16 Age: 41 80% female Migraine Chron: 18 yrs Rec: N/S	***Placebo:*** n = 10* ***Propranolol:*** 40 mg, 3x/day; n = 10* No baseline period described; two 8-wk treatment periods; no washout; no follow-up	***HA index:*** Sum of severity scores per 4 wks; severity graded daily on scale of 0-4 (no HA, mild, moderate, severe, worst possible) ***HA frequency:*** No. of days with HA	Mean ***HA index*** scores were 52 on placebo and 47 on propranolol (no variance reported). The difference between the two treatments was not statistically significant ($p>0.05$). Similar results were reported for ***HA frequency***.	Dropouts: 6 (38%), 1 due to AEs (placebo) Trial also included 20 patients with nonmigraine HAs, who are not described here

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Pedersen and Møller, 1966	CrOv QS: 4 (r, db+, dd)	N = 102 Age: N/S % female N/S Classic or common migraine (Ad Hoc); ≥ 1 HA/mo Chron: N/S ("fresh cases" to those lasting "many years") Rec: Neuro dept	***Placebo:*** n = 60* ***Methysergide (prolonged-action):*** 6 mg/ day (dosing schedule not described); n = 60* No baseline period described; two 6-wk treatment periods; 1-wk transition period (3 mg methysergide + placebo/day for all patients); no follow-up Ergotamine tartrate prescribed for acute treatment of severe attacks	***HA frequency:*** No. of patients with a > 50% reduction in no. of HAs per 6-wk treatment period compared with pre-treatment values; mean within-patient difference between number of attacks in placebo period and in methysergide period ***HA severity:*** Each attack graded as "mild," "moderate," or "severe"; investigators analyzed the difference in the distribution of the various degreees of severity	***HA frequency:*** 34/60 patients (57%) reported a 50% or greater reduction in the number of HAs during treatment with methysergide compared to pre-treatment values; 16/60 patients (27%) reported a reduction of this magnitude during treatment with placebo. The investigators' analysis found the difference between the two treatments to be statistically significant (no p-value reported). Investigators also calculated the difference between the number of attacks in the placebo period and in the methysergide period for each patient and then calculated the mean difference for the entire group (no individual patient or group mean data reported). Their analysis found that the reduction in ***HA frequency*** with methysergide was statistically significant (p=0.05; two-tailed test). Methysergide was significantly better than placebo for ***HA severity*** (no measure of statistical significance reported).	Dropouts: 42 (41%), 7 due to AEs Not clear how pre-treatment values established Carry-over effect detected High dropout rate (41%)
Penzien, Johnson, Carpenter, et al., 1990	SPPG QS: 2 (r, ndb, dd)	N = 22 Age: N/S % female N/S Migraine Chron: N/S Rec: N/S; U.S.	***Relax. + thermal BF + cog.-beh. coping skills (home-based):*** n = 11; three sessions (time N/S) x 6 wks + telephone consultations; therapist N/S; home practice (amt. N/S) ***Propranolol (60-160 mg Inderal® LA):*** n = 11; two sessions x 6 wks + telephone consultations	***HA index:*** Definition N/S Both groups monitored HAs daily by diary for 4, 6, & 4 wks for pretreat., treatment, & posttreat., respectively.	Authors reported that there were no significant differences between treatments for reductions in ***HA index*** (mean reductions: behavioral, 42%; propranolol, 44%). Both groups reduced ***HA index*** significantly from pre- to posttreat. (p-values not given). Forty-six percent (5/11) and 55% (6/11) of pts in the behavioral and propranolol groups, respectively, were improved (achieved > 50% reduction in ***HA index*** from pre- to posttreat.). Thirty-six percent (4/11) and 18% (2/11), respectively, were moderately improved (achieved 25-50% reduction), and 18% (2/11) and 27% (3/11), respectively, were not improved (< 25% reduction).	Dropouts: 0 Abstract reporting preliminary results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Pini, Ferrari, Guidetti, et al., 1985	SPPG QS: 2 (nr, db, dd)	N = 29 Age: 40 83% female Common or classic migraine; history > 5 yrs Chron: N/S Rec: Out-patients at university HA study center	***Placebo:*** n = 14 (see note) ***Flunarizine:*** 10 mg, 2x/day for 2 wks; then 10 mg, 1x/day (bedtime); n = 14 (see note) 2-mo baseline period (placebo); treatment period lasted "up to 120 days"; no follow-up Acute meds permitted	***HA index:*** Not described ***Corrected HA index:*** Not described ***HA severity:*** Not described	Flunarizine significantly reduced ***HA index*** compared with baseline values (p=0.013); placebo did not (p=0.308). Mean pre- and post-treatment HA index scores (± SD) were 0.54 (± 0.26) and 0.31 (± 0.38), respectively, in the flunarizine group (a reduction of 42.6%), and 0.33 (± 0.26) and 0.30 (± 0.32), respectively, in the placebo group (a reduction of 9.1%). The two treatments were not directly compared by investigators. Similar results were reported for the ***corrected HA index***. Neither flunarizine nor placebo significantly affected ***HA severity*** (no data reported).	Dropouts: 0 Article reports that "half" of 29 patients received placebo, and "half" flunarizine. We used n = 14 for both groups in our calculations Low quality score (2); not randomized
Pita, Higueras, Bolaños, et al., 1977	CrOv QS: 3 (r, db, dd)	N = 9 Age: 32 (range: 23-39) 78% female Classic or common migraine (Ad Hoc); ≥ 3-4 HAs/mo; previously unresponsive to preventive therapy Chron: 13 yrs (range: 1-27) Rec: Referrals from neurologists and psychiatrists	***Placebo:*** n = 8* ***Propranolol:*** 40 mg, 4x/day; n = 8* No baseline period described; two 2-mo treatment periods; no washout; patients who reported success with propranolol continued treatment and were followed up at two-month intervals Acute meds permitted	***HA frequency:*** Mean no. of attacks per 2-mo treatment period	Propranolol was significantly better than placebo at reducing ***HA frequency*** (p=0.01). Mean frequency was 7.5 (± 5.1) during treatment with placebo and 2.25 (± 1.2) with propranolol.	Dropouts: 1 (11%), due to AEs associated with propranolol No carry-over effect

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Pradalier, Serratrice, Collard, et al., 1989b	SPPG QS: 4 (r, db+, dd)	N = 55 Age: 37 (range: 18-65) 76% female Migraine w/ or w/o aura (IHS); ≥ 2-yr history; 2-8 HAs/mo; no preventive med in two wks preceding trial Chron: N/S Rec: N/S	***Placebo:*** n = 24 ***Propranolol (long-acting):*** 160 mg, 1x/day; n = 31 4-wk baseline period (placebo); 12-wk treatment period; no follow-up Patients permitted to take their usual med for acute attacks	***HA frequency:*** No. of attacks per month	Propranolol was significantly more effective than placebo at reducing ***HA frequency*** (p=0.01). Mean HA frequencies (± SD) in the propranolol group were 6.11 (± 0.93) at the start of treatment and 3.15 (± 0.77) after 12 wks; corresponding figures in the placebo group were 6.00 (± 1.37) and 6.41 (± 1.70), respectively.	Dropouts: 14 (25%), none due to AEs; all 14 dropouts were included in the efficacy analysis Most patients had tried some type of preventive med before
Presthus, 1971	CrOv QS: 3 (r, db, dd)	N = 21 Age: 43 (range: 24-53) 52% female Classic or common migraine Chron: N/S Rec: N/S	***Methysergide:*** 1 mg, 3x/day; n = 19* ***Pizotifen:*** 0.5 mg, 3x/day; n = 19* No baseline period described; two 5-wk treatment periods; 1-wk washout (no medication); no follow-up; data from last 4 wks of each treatment period used for efficacy analysis Patients permitted to take meds for acute attacks	***HA frequency:*** No. of attacks during last 4 wks of treatment period ***HA intensity:*** Sum of intensity scores for all HAs during last 4 wks of treatment period ***HA duration:*** Sum of duration of all HAs during last 4 wks of treatment period	The investigator reported individual patient data and analyzed them using students T test and the Wilcoxon rank sum test. No statistically significant differences were found between the two treatments for ***HA frequency***, ***intensity***, or ***duration*** (p>0.10 for all three outcomes).	Dropouts: 2 (10%), 1 due to AEs (pizotifen)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Rascol, Montastruc, and Rascol, 1986	SPPG QS: 5 (r+, db+, dd)	N = 35 Age: 38 (median) (range: 28-59) 71% female Common or classical migraine (Ad Hoc); history ≥ 2 yrs; ≥ 6 attacks in last 6 mos Chron: N/S Rec: Out-patient HA clinic	***Pizotifen:*** Dose gradually increased over first week to 2.19 mg/day (three 0.73 mg tabs; partial doses taken in morning and at night [precise dosing schedule not described]); n = 14 ***Flunarizine:*** 10 mg, 1x/day; n = 21 No baseline period described; 4-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo; no. of migraine days (as % of total number of days in observation period) ***HA severity:*** Not described	Both treatments significantly reduced the mean ***number of attacks per month*** compared with pre-treatment values, flunarizine in months 2, 3, and 4 ($p<0.01$, all three months), and pizotifen in months 3 and 4 ($p<0.05$ for both months). After 4 months, the number of attacks was reduced by 65% in the flunarizine group and by 45% in the pizotifen group. The difference between the two groups was not statistically significant (no p-value reported). The ***number of migraine days per month*** was reduced over 4 months to 37% of the pre-treatment number in the flunarizine group and to 50% of the pre-treatment number in the pizotifen group. There were no significant differences between the two treatments for any month (no p-values reported). No actual HA frequencies (either no. of attacks or no. of migraine days) were reported. There were no significant differences between the two treatments for ***HA severity*** (no data and no p-values reported).	Dropouts: 3 (9%), 2 due to AEs (1 each flunarizine and pizotifen); these 3 patients included in efficacy analysis Approximately 2/3 of patients had never used prophylactic meds before Not clear how baseline/pre-treatment values derived (no baseline period described)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Rompel and Bauermeister, 1970	CrOv QS: 5 (r+, db+, dd)	N = 48 Age: N/S (range: 14-60) 69% female "Typical" migraine (with aura) Chron: N/S Rec: N/S	***Placebo:*** n = 48* ***Carbamazepine (Tegretol®):*** 200 mg, 3x/day; n = 45* No baseline period described; two 6-wk treatment periods; no washout; no follow-up Nothing on acute meds	***HA index:*** Not described, but appears to have somehow combined frequency and severity; investigators reported no. of patients much worse, slightly worse, unchanged, slightly to moderately improved, markedly to completely improved ***HA frequency:*** No. of attacks/mo	***HA index*** was markedly or completely improved in 26/45 patients taking carbamazepine (58%) and in 5/48 patients taking placebo (10%) (no p-value or other measure of statistical significance reported). Pre-treatment ***HA frequency*** averaged 2.97 HAs/month for the entire patient group. During the treatment phase, 30 attacks were reported by 45 patients during treatment with carbamazepine (0.67 attacks/patient); with placebo, 48 patients reported 186 attacks (avg 3.87 attacks/patient) (no p-value or other measure of statistical significance reported).	Dropouts: 3 (6%), 1 due to AEs (carbamazepine); dropouts not included in efficacy analysis Investigators suspected a carry-over effect, but could not demonstrate one statistically Not completely certain that HA index outcomes based on diary data Baseline values based on patients' histories
Ryan, 1968	CrOv QS: 3 (r, db+, dnd)	N = 62 Age: N/S % female N/S Classic or common migraine; ≥ 3-4 HAs/mo Chron: N/S Rec: N/S	***Placebo:*** n = 62* ***Methysergide:*** 2 mg, 2x/day; n = 62* ***Pizotifen:*** 2 mg, 2x/day; n = 62* No baseline period described; three 4-wk treatment periods; no washout; no follow-up Acute meds permitted	***HA index:*** Calculated per 4-wk treatment period; HA index = $(1xF_1) + (2xF_2) + (3xF_3)$, where F_1 = frequency of HAs of severity 1, F_2 = frequency of HAs of severity 2, etc.; severity of each attack graded on scale of 1-3 (slight, moderate, severe) ***HA frequency:*** No. of HAs per 4-wk treatment period	Mean ***HA index*** was 8.9 with pizotifen, 11.3 with methysergide, and 17.0 with placebo (no variance data reported). Mean ***HA frequency*** was 4.7 with pizotifen, 6.2 with methysergide, and 8.9 with placebo (no variance data reported). No statistical analysis of these results was described.	Dropouts: Not described Nothing on carry-over effect

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ryan, 1971	SPPG QS: 4 (r, db+, dd)	N = 60 Age: N/S (range: N/S) % female N/S Migraine; hist. of ≥ 3 HAs/mo Excl: Hypersen-sitivity to antimigraine or antiamine drugs; physical conditions possibly interfering with study meds; use of investigational drugs ≤ 1 mo prior to entering trial; use of concomitant meds Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 20 ***Pizotifen (BC-105):*** Dose increased daily by one capsule from 0.5 mg, 1x/day to 1.0 mg, 3x/day for 2 wks; after 2 wks, and at 4-wk intervals, pts were assessed and dosage was according to a protocol; n = 25 Previous interval treatment discontinued 4 wks prior to entering baseline; 4-wk baseline (control) period; 12-wk treatment period; 4-wk post-drug period; no follow-up Other acute migraine meds permitted	***HA index:*** Calculated as sum of no. of severe HAs x 3, moderate HAs x 2, and mild HAs x 1 ***HA frequency:*** Defined as "total no. of HAs of all severity in past 4 wks" ***HA intensity:*** Recorded daily by pt on 4-point scale (from "no HA" to "severe HA")	The mean ***HA index*** values for pizotifen and placebo decreased from 21.53 and 10.00 at baseline to 15.68 and 6.65, respectively, after 12 wks of treatment. Investigators reported that there were no differences between the two treatments, but did not report whether or not they analyzed the results for statistical significance. Both treatments were effective at reducing ***HA index*** from pre- to post-treatment, but neither did so at a statistically significant level (no p-values given). Investigators noted that the mean ***HA index*** at baseline was twice as large for the pizotifen group as for the placebo group.	Dropouts: 15 pts (25%) withdrew, 1 due to AEs (pizotifen); of the 15, 9 were not included in efficacy analyses; not clear whether remaining 6 were included or not
Ryan, 1978	CrOv QS: 2 (r, ndb, dd)	N = 40 Age: N/S 100% female Migraine; moderate or severe in intensity Chron: N/S Rec: N/S	***No treatment:*** n = 40* ***Norgestrel + ethinyl estradiol (Ovral®):*** 0.5 mg + 0.05 mg, 1x/day for 3 wks, followed by no treatment for 1 wk; n = 40* No baseline period described; two 2-mo treatment periods; no washout; no follow-up Acute meds permitted	***HA index:*** 2(no. of mild-moderate attacks) + 3(no. of severe attacks) ***HA frequency:*** No. of attacks per 2-mo treatment period	***HA index*** scores were worse during treatment with Ovral® than with no treatment. Mean ***HA index*** scores per 2-mo treatment period were 48.70 with Ovral® and 32.85 with no treatment (no variance data and no p-value reported). ***HA frequency*** was also higher with Ovral®: 464 HAs per 2-mo treatment period vs. 319 with no treatment (no p-value reported).	Dropouts: 0 Low quality score (2); not double-blind

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ryan, 1984	SPPG QS: 3 (r, db, dd)	N = 48 Age: N/S 73% female Common or classic migraine; ≥ 3 HAs/mo Chron: N/S Rec: N/S	***Propranolol:*** 160 mg/day (dosing schedule not described); n = 14 ***Nadolol, 160 mg/day:*** (Dosing schedule not described); n = 16 ***Nadolol, 80 mg/day:*** (Dosing schedule not described); n = 15 1-mo baseline period (placebo); 3-mo treatment period; no follow-up Patients permitted to use their usual meds for acute attacks	***HA index:*** Not defined, but included severity; severity of each attack graded on scale of 1-4 (mild, moderate, severe, disabling) ***HA frequency:*** No. of attacks per month	In the nadolol 80 mg group, mean ***HA index*** scores were reduced from 12.73 during the baseline period to 4.84 during the treatment period (no variance data and no p-values reported). In the nadolol 160 mg group, the corresponding figures were 10.43 and 5.83, respectively; and in the propranolol group, they were 14.71 and 8.01, respectively (no variance data and no p-values reported). The investigator did not compare the three treatments statistically for this outcome. Mean ***HA frequency*** scores in the nadolol 80 mg group were 6.13 during the baseline period and 2.74 during the treatment period (no variance data and no p-values reported). In the nadolol 160 mg group, the corresponding figures were 5.56 and 2.93, respectively; and in the propranolol group, they were 7.42 and 4.54, respectively (no variance data and no p-values reported). The investigator did not compare the three treatments statistically for this outcome.	Dropouts: 3 (6%), 1 due to AEs (nadolol 80 mg/day)
Ryan, Diamond, and Ryan, 1975	CrOv QS: 3 (r, db, dd)	N = 133 (Chicago, 61; St. Louis, 72) Age: 41 (median) (range: 20-64) 78% female Chron: 22 (median) (range: 1-53) Migraine; ≥ 3 Ms/mo Rec: 2 HA clinics, 1 in Chicago and 1 in St. Louis	***Placebo:*** n = 133* ***Clonidine:*** 0.025 mg, 2x/day for 2 wks; if relief insufficient, dose could be increased to 0.050 mg, 2x/day for 2 wks; if relief still insufficient, dose could be further increased to 0.075 mg, 2x/day for 4 wks; n = 133* No baseline period; two 8-wk treatment periods; one 2-day washout between treatment periods; no follow-up Other acute migraine meds permitted during trial	***HA index:*** Calculated by multiplying attacks by the HA intensity rating no. for each attack (1=mild; 2=moderate; 3=severe) and summing them ***HA frequency:*** Defined as no. of HAs per wk and reported as "change in mean weekly frequency," categorized according to intensity (severe, moderate, mild)	No overall mean scores were reported for ***HA Index***. No statistical difference was found for this outcome between pts receiving clonidine and pts receiving placebo (no p-value given). Neither treatment was found to reduce the ***frequency*** of mild, moderate, or severe HAs significantly from pre- to post-treatment. Investigators reported that there was no significant difference between the two treatments.	Dropouts: 0 Not clear how results determined from baseline data Investigators reviewed pts' diaries every 2 wks to assess frequency & intensity Investigators stated that the efficacy of the treatments could not be definitely established because pts were taking other meds concurrently

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ryan and Ryan, 1981	SPPG QS: 3 (r, db+, dnd)	N = 160 Age: N/S (range: 21-65) % female N/S Classic or common migraine; ≥ 3 HAs/mo; frequency "rather constant" over past 6 mos; no "mixed" HA Chron: N/S Rec: N/S	***Placebo:*** n = 40 ***Aspirin:*** 325 mg, 4x/day; n = 40 ***Dipyridamole:*** 75 mg, 4x/day; n = 40 ***Aspirin + dipyridamole:*** 325 + 75 mg, 4x/day; n = 40 4-wk baseline (no aspirin, dipyridamole, or other migraine-preventive med); one 8-wk treatment period; no follow-up Use of symptomatic meds permitted for acute attacks, but patients not allowed to take aspirin, dipyridamole, anturane, beta blockers, steroids, anti-inflammatory drugs, or antidepressants during trial	***HA index:*** Not defined ***HA frequency:*** No. of attacks per 4 wks	Because HA index was not defined, we preferred the results reported for HA frequency. Mean ***HA frequencies*** in the aspirin + dipyridamole group were 9.15 and 7.15 during the baseline period and weeks 5-8, respectively; corresponding figures in the aspirin group were 8.15 and 7.13; in the dipyridamole group, 8.13 and 8.12; and in the placebo group, 7.79 and 7.64 (no variance data and no p-values reported). Results for ***HA index*** were similar, except that dipyridamole reduced mean HA index slightly more than it did mean HA frequency (from 12.05 to 8.02).	Dropouts: Not described
Ryan, Ryan, and Sudilovsky, 1983	SPPG QS: 4 (r, db+, dd)	N = 80 Age: N/S (range: 18-60) 78% female Common or classical migraine; ≥ 3 HAs/mo Excl: Pts allergic to or with past failure to respond to beta-blockers; pts with cluster HAs Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 20 ***Nadolol:*** 80 mg/day; n = 20 ***Nadolol:*** 160 mg/day; dose gradually increased to full dose by 10th wk; at wk 20, dose tapered off to 80 mg/day; n = 20 ***Nadolol:*** 240 mg/day; dose gradually increased to full dose by 10th wk; at wk 20, dose tapered off to 80 mg/day; n = 20 2-mo baseline (placebo); 3-mo treatment period; no controlled follow-up Patients' usual acute migraine medications permitted, but prophylactics disallowed	***HA frequency:*** Not defined, but recorded at onset by pts in diaries ***HA intensity:*** Rating scale N/S, but recorded by pts in diaries	***HA frequency*** was reduced from mean scores of 6.9, 6.73, 6.8, and 8.45 at baseline (4-wk means of month 2 of baseline) to 4.25, 4.05, 2.10, and 3.28 after treatment (4-wk means of month 5) with placebo, 80 mg, 160 mg, and 240 mg of nadolol, respectively. Investigators did not report having analyzed the between-group or pre- to post-treatment differences for statistical significance (no variances or p-values reported).	Dropouts: 1 pt (1%) withdrew (not clear from which treatment group) and was not included in efficacy analyses; not clear whether dropout due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sances, Martignoni, Fioroni, et al., 1990	SPPG QS: 3 (nr, db+, dd)	N = 40 Age: 38 (range: 19-45) 100% female Migraine w/o aura (IHS); regular attacks the week before, or during, menstrual period, and HA-free the rest of the cycle; regular menstrual cycle Chron: N/S Rec: N/S	***Placebo:*** n = 17 ***Naproxen sodium:*** 550 mg, 2x/day; n = 18 2-mo baseline period (HA recording); one 3-menstrual-cycle treatment treatment period; this followed by 3-menstrual-cycle open phase, in which all patients took active drug (not considered here) Patients began treatment on the 7th day before the expected onset of menstruation and continued through the 6th day of menstrual flow	***HA index:*** Frequency + (Duration x Severity); severity of each attack graded on scale of 1-3 (mild, moderate, severe); duration reported in hrs for each attack ***HA frequency:*** No. of HA days	Mean ***HA index*** scores (± SD) for the baseline period were 75.1 (± 49.8) in the naproxen group and 78.6 (± 39.1) in the placebo group. For the third month of treatment, the scores were, respectively, 49.4 (± 38.6) and 69.1 (± 29.8). The improvement seen in the naproxen group was statistically significant ($p<0.01$); that seen in the placebo group was not (no p-value reported). There was no significant difference between the two groups for this outcome ($p>0.05$). 6/18 patients (33%) taking naproxen sodium reported a ≥ 50% improvement in ***HA index*** scores in month three compared to baseline values, as did 1/17 patients (6%) taking placebo. Similar results were reported for ***HA frequency;*** naproxen sodium was significantly better than placebo only for the third month ($p<0.05$).	Dropouts: 5 (13%), 2 due to AEs (intervention N/S) Not randomized
Sances, Martignoni, Rosettino, et al., 1989	SPPG QS: 2 (nr, db, dd)	N = 40 Age: N/S (range: 20-45) 100% female Only pts with migraine during menstrual periods; frequency N/S Chron: N/S (range: 2-31) Rec: N/S	***Placebo:*** n = 20 ***Lisuride:*** 0.05 mg, 3x/day; n = 20 2-mo run-in; 3-mo treatment period, followed by 3-mos of open, uncontrolled treatment; no follow-up Analgesic meds permitted	***HA index:*** Obtained from ***HA duration*** & ***intensity*** ratings and termed "pain total index" ***HA frequency:*** Recorded daily by pt as "days of HA" ***HA intensity:*** Not defined; rating scale N/S	No between-group results were provided. From baseline to 3 mos, lisuride reduced ***HA index*** from 81.7 (± 38) (SD) to 47.3 (± 32), a reduction that was statistically significant ($p < 0.001$). Placebo reduced ***HA index*** from 102 (± 50) at baseline to 95.8 (± 57) at 3 mos. Investigators reported that the difference was not significant ($p > 0.05$).	Dropouts: 4 (10%), all due to AEs (treatments N/S); not clear whether or not they were included in efficacy analyses Information provided in abstract Not clear how baseline data gathered

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Saper, Silberstein, Lake, et al., 1994	SPPG QS: 4 (r, db+, dd)	N = 122 Age: 38 (range: 20-59) (migraine) 93% female (migraine) Migraine (IHS); history ≥ 2 yrs; 4-12 attacks/mo with duration ≥ 4 hrs (n = 58); or CDH (n = 64) Chron: N/S Rec: 2 HA clinics	***Placebo:*** n = 26 (migraine) ***Fluoxetine:*** 20 mg/day for 2 mos; dose then increased to 20 mg, 2x/day for those patients who had shown no therapeutic response, but who tolerated drug; n = 31 (migraine) 4-wk baseline period (placebo); 12-wk treatment period; no follow-up Use of acute med permitted, with some restrictions	***HA index:*** Not described ***Frequency of severe HA:*** No. of days/wk with severe HA ***HA-free days:*** No. of HA-free days/wk	We analyzed results for migraine patients only. The investigators' ANOVA analysis found no significant differences between fluoxetine and placebo for ***HA index, frequency of severe HA***, or ***HA-free days;*** no data and no p-values were reported for any of these outcomes.	Dropouts: 14 (11%) overall, none due to AEs; 3 of the 14 dropouts were evidently included in the efficacy and AE analyses, but their identity and the basis on which they were included are not stated; only one migraine patient who began the trial was excluded from the efficacy and AE analyses
Sargent, Solbach, Damasio, et al., 1985	SPPG QS: 3 (r, db, dd)	N = 149 Age: 30 (range: 18-62) 79% female Common or classical migraine or combination of migraine and muscle-contraction HA; ≥ 1-yr history of migraine; avg of 12 migraine days over ≥ 6 attacks in last 3 mos Chron: 20 yrs Rec: N/S	***Placebo:*** n = 43 ***Propranolol:*** 40 mg, 2x/day for 2 wks, 3x/day for 12 wks, 2x/day for 1 wk; n = 44 ***Naproxen sodium:*** 550 mg, 2x/day; n = 42 2-wk baseline period (placebo); 3-wk dose escalation phase (propranolol); 12-wk treatment period; 1-wk dosage reduction period (propranolol); no follow-up Patients allowed to treat acute attacks with analgesic approved by investigator	***HA frequency:*** Reduction in no. of HA days/wk, baseline to post-treatment ***HA severity:*** Not described; severity graded every day on scale of 0-3 (none, mild, moderate, severe)	Efficacy data were reported for the 12-wk full dosage phase of the trial only. There were no significant differences among the study medications for median ***HA frequency*** (p=0.92 naproxen sodium vs. placebo; p=0.16 propranolol vs. placebo; p=0.17 naproxen sodium vs. propranolol). Mean difference scores (± SD) from baseline to post-treatment were -0.48 (± 2.02) for naproxen sodium, 0.21 (± 1.86) for propranolol, and -0.25 (± 1.57) for placebo. Similar results were reported for ***HA severity***.	Dropouts: 20 (13%), 3 due to AEs (all naproxen sodium) Baseline values derived from patients' histories

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Shafar, Tallett, and Knowlson, 1972	CrOv QS: 3 (r, db, dd)	N = 65 Age: N/S (range: 18-66) 84% female Chron: N/S) (range: N/S) Migraine; hist. ≥ 1 M/mo for ≥ 1 yr; Ms of "significant frequency & severity" Rec: Referred by GPs	***Placebo:*** n = 50* (42* in larger grp; 8* in smaller grp) ***Clonidine:*** 50 µg, 2x/day for 16 wks; n = 50* (42* in larger grp; 8* in smaller grp) Four-wk baseline; four 8-wk treatment periods, 2 active & 2 placebo; no washout between treatment periods; crossover point N/S, but assumed to be every 8 wks; 12-mo open follow-up using clonidine Other acute migraine meds permitted during trial	***HA index:*** Termed a "weighted score"; calculated by multiplying no. of HAs (frequency) by HA intensity rating for each attack (1=mild; 2=moderate; 3=severe) and summing them ***HA frequency:*** Definition N/S, but reported as mean no. of HAs/mo	Investigators performed a post hoc stratification, separating 8 pts with near-daily HAs from the 42 remaining pts. For the 42 pts with less frequent HAs, ***HA index*** decreased from 15.07 at baseline to 11.12 and 13.23 after treatment with clonidine and placebo, respectively. Clonidine was better than placebo at reducing ***HA index***, but not at a statistically significant level ($p<0.1$). For the group with less frequent HAs, each treatment reduced ***HA index*** from pre- to post-treatment, but authors did not report whether or not the reductions were statistically significant (p-values not given). For the group with more frequent HAs, ***HA index*** *increased* from 45.25 at baseline to 48.08 and 47.80 after treatment with clonidine and placebo, respectively. Investigators did not report whether or not they analyzed the treatment results for statistically significant differences for either between- or within-group comparisons.	Dropouts: 15 (23%), 1 due to AEs (clonidine) Not clear how baseline data gathered or how results determined from that data 14 of 50 pts returned incomplete records or failed to take correct no. of tablets. Nevertheless, investigators included their data in analyses because data from at least one 8-wk period per treatment was completed adequately. Consequently, length of treatment periods varied (larger group, 3-7 mos; smaller group, 3-9 mos)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Shekelle and Ostfeld, 1964	CrOv QS: 4 (r, db+, dd)	N = 16 Age: N/S (range: 22-46) 83% female Classic (n = 1) or common migraine (n = 16) or cluster HA (n = 1) (all Ad Hoc) Chron: N/S Rec: N/S	***Placebo:*** n = 13* ***Methysergide:*** 2 mg, 3x/day; n = 13* No baseline period described; two 5-wk treatment periods; no washout, but data analyzed from last 4 wks of each treatment period only; no follow-up Patients given mild analgesic to take for acute episodes	***HA frequency:*** No. of HA days during last 4 wks of placebo treatment minus no. of HA days during last 4 wks of methysergide treatment; calculated for each patient; results analyzed sequentially with Rushton's *t* test	***HA frequency:*** The only outcome analyzed by investigators was the difference in the total number of HA days reported by each patient on placebo and on methysergide. Their analysis of the data from individual patients showed methysergide to be significantly better than placebo at reducing the number of HA days ($p<0.05$).	Dropouts: 3 (19%), none due to AEs 1 patient included in the efficacy analysis had cluster HA
Shimell, Fritz, and Levien, 1990	SPPG QS: 4 (r, db+, dd)	N = 58 Age: 35 (range: 16-61) 70% female Common or classic migraine (Ad Hoc); 2-8 attacks/mo for past 6 mos; no prophylactic med in last mo Chron: N/S Rec: Outpatients at polyclinic and medical and neuro depts	***Propranolol:*** 60 mg, 3x/day; this dose achieved gradually over 20 days; n = 29 ***Flunarizine:*** 10 mg, 1x/day (at night); this dose achieved gradually over 4 days; n = 28 No baseline period described; 4-mo treatment period; no follow-up Nothing on acute meds	***HA frequency:*** No. of attacks/mo ***HA severity:*** Each attack graded as unbearable, severe, moderate, or slight; investigators reported only the percentage of patients whose HAs were severe in tensity before and after treatment ***HA duration:*** Not described	Both drugs reduced ***HA frequency*** significantly from wk 1 to wks 4 and 16. The mean number of attacks/mo in the flunarizine group was 4.57 in wk 1, 3.11 in wk 4, and 1.35 in wk 16 (no variance and no p-values reported). The corresponding numbers in the propranolol group were 5.71, 3.29, and 1.17 (no variance and no p-values reported). There was no significant difference between the two treatments for this outcome (no p-value reported). Neither treatment significantly affected ***HA severity*** or ***HA duration.***	Dropouts: 10 (17%); 1 patient left the country and was excluded from the analysis; 9 other patients withdrew before completing trial, 5 due to AEs (2 flunarizine, 3 propranolol); these 9 patients were included in the efficacy analysis 1-wk results used as baseline

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Shukla, Garg, Nag, et al., 1995	CrOv QS: 4 (r, db+, dd)	N = 36 Age: 30 79% female Migraine w/ or w/o aura (IHS); ≥ 4 attacks/mo in past yr Chron: 9 yrs Rec: HA clinic	***Placebo:*** n = 28* ***Nifedipine:*** 5 mg, 3x/day; n = 28* 2-wk baseline period (no prophylactic med); two 4-wk treatment periods; 2-wk washout; no follow-up Acute meds permitted	***HA index:*** Frequency times severity times duration ***HA frequency:*** No. of attacks/mo ***HA severity:*** Not clear how outcome calculated (categorical data only reported); severity graded every day on scale of 0-3 (no pain; mild, reducing activity by < 50%; moderate, reducing activity by > 50%, but not requiring bed rest; severe, requiring bed rest) ***HA duration:*** Mean duration (hrs)	Neither nifedipine nor placebo significantly reduced ***HA index*** in comparison with baseline values; there was no significant difference between the two interventions for this outcome (no p-values reported). Mean HA index scores (± SEM) were 808.6 (± 158.2) at baseline, 750.6 (± 141.8) after treatment with placebo, and 616.4 (± 150.0) after treatment with nifedipine. Nifedipine did significantly reduce ***HA frequency*** both in relation to baseline values and placebo values ($p<0.05$ for both comparisons). Mean HA frequency (± SEM) was 10.4 (± 1.76) during the baseline period, 10.1 (± 1.78) after treatment with placebo, and 6.3 (± 1.85) after treatment with nifedipine. Nifedipine also significantly reduced ***HA severity*** compared to baseline and placebo ($p<0.05$). It did not significantly affect ***HA duration*** (no p-values reported).	Dropouts: 8 (22%), none due to AEs
Sicuteri, 1973	SPPG QS: 2 (r, ndb, dd)	N = 40 Age: N/S 65% female Migraine Chron: N/S Rec: N/S	***Methysergide:*** 1 mg, 2x/day; n = 20 ***Oxitriptan (L-5-hydroxytryptophan or 5-HTP):*** 100 mg, 2x/day; n = 20 40-day baseline period; 40-day treatment period; no follow-up Nothing on acute meds	***HA Index:*** Calculated per 40-day period; HA index = $(1xF_1) + (2xF_2) + (3xF_3)$, where F_1 = frequency of moderate HAs, F_2 = frequency of medium HAs, and F_3 = frequency of severe HAs ***HA frequency:*** No. of HAs per 40-day period	Both oxitriptan and methysergide significantly reduced the ***HA index*** compared with pre-treatment values. The mean migraine index (± SEM) in the oxitriptan group was 9.7 (± 0.45) pre-treatment and 4.1 (± 0.52) post-treatment ($p<0.001$); the mean reduction from pre- to post-treatment was 5.6 (± 0.56). In the methysergide group, the mean migraine index (± SEM) was 9.9 (± 0.59) before treatment and 4.2 (± 0.66) post-treatment ($p<0.001$); the mean reduction from pre- to post-treatment was 5.9 (± 0.87). When the mean reductions in the migraine index were compared, there was no significant difference between the two treatments ($p>0.8$). Very similar results were reported for ***HA frequency***.	Dropouts: 0 Low quality score (2); not double-blind

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sjaastad and Stensrud, 1969	CrOv QS: 3 (r, db, dd)	N = 24 Age: 39 (range: 16-57) 92% female Common or classical migraine (Ad Hoc); 1-2 HAs/2 wks in baseline period (length N/S) Chron: N/S (range: N/S) Rec: N/S, but several pts had been hospitalized for migraine & others had participated in extensive trials of anti-migraine meds	***Placebo:*** n = 20* ***Pizotifen:*** 1 mg, 4x/day; n = 20* Length of baseline period not clear; two 8-wk treatment periods; no washout; some pts treated with pizotifen for 3-12 mos after trial; no other follow-up described Ergotamine and salicylates permitted	***HA frequency:*** Defined as "no. of HA days" ***HA intensity:*** Recorded by pt on 3-point scale	From individual data provided, we calculated overall mean reductions in ***HA frequency*** from baseline to 7 wks of 9.9 and 5.6 for placebo and pizotifen, respectively. Baseline data were not provided, and investigators did not report the statistical significance of the difference between the two results (no p-values given).	Dropouts: 4 pts (17%), not included in efficacy analyses withdrew, 1 due to AEs (pizotifen) Data from first week of each treatment period excluded from analysis

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sjaastad and Stensrud, 1971	CrOv QS: 3 (r, db, dd)	N = 30 Age: N/S (range: N/S) 87% female Chron: N/S) (range: N/S) Common or classical migraine (Ad Hoc); pts "generally severely affected" & had ≥ 1 HA/wk during baseline Rec: N/S	***Placebo:*** n = 26* ***Clonidine (Catapresan®):*** 25 µg, 3x/day; n = 26* One-wk baseline; two 3-wk treatment periods; 1-wk washout between treatment periods; no follow-up Other acute migraine meds permitted during trial	***HA index:*** Calculated as no. of HA days multiplied by intensity score (graded from 1+ to 3+) ***HA frequency:*** Results reported as average reduction in no. of HA days	Ten of 26 pts (38%) experienced at least a 50% reduction in ***HA index*** after taking clonidine. Investigators did not report the reductions, if any, associated with the placebo treatment. A mean reduction in ***HA index*** of 27% was also brought about by clonidine (compared with placebo). This reduction was significantly better than that of placebo ($p<0.025$). Clonidine reduced ***HA frequency*** 26% better than did placebo. Investigators did not report having analyzed this comparison for statistically significant differences.	Dropouts: 4 (13%), for "unknown reasons"
Sjaastad and Stensrud, 1972	CrOv QS: 4 (r, db+, dd)	N = 28 Age: N/S (range: 18-62) 79% female Classical or common migraine; ≥ 2 attacks/mo Chron: N/S Rec: N/S	***Placebo:*** n = 24* ***Pindolol:*** 2.5 mg or 5 mg, 3x/day; n = 24* 3-wk baseline period (no prophylactic med); two 4-wk treatment periods; 3-wk washout; no follow-up Acute meds permitted	***HA index:*** No. of HA days times severity; severity of each attack graded on scale of 1-3 ***HA frequency:*** No. of HA days	There were no significant differences between pindolol and placebo for ***HA index*** or ***HA frequency*** (no p-values reported). However, 3 patients were markedly improved on pindolol, showing a greater than 50% reduction in HA index.	Dropouts: 4 (14%), 3 due to AEs (pindolol)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Smits, van der Meer, Pfeil, et al., 1993	CrOv QS: 3 (r, ndb+, dd)	N = 20 Age: 40 (range 30-48) 100% female "Pure" menstrual migraine = attacks of migraine w/o aura (IHS), regularly occurring no earlier than 2 days before menstruation and no later than last day of menses; HAs during previous 12 cycles; no HAs during rest of cycle Chron: N/S Rec: N/S	***Placebo:*** n = 19* ***Estradiol (Estraderm TTS 50® patch):*** 50 µg/day, via 10-cm patch; one patch applied 48 hrs before expected onset of menstruation; another patch applied 4 days later; n = 19* No baseline period described; three 1-cyle treatment periods (two sequences: P-E-P and E-P-E); no washout; no follow-up Acute meds (aspirin, acetaminophen, or ergotamine) permitted Prophylactic meds permitted, provided taken for at least 3 mos prior to trial and not changed during trial	***HA frequency:*** No. of menstrual cycles accompanied by migraine attack ***HA severity:*** Not defined; each attack graded on scale of 1-3 (mild, moderate, severe) ***HA duration:*** Mean duration per attack (in hrs)	***HA frequency:*** Of the cycles occurring during Estraderm TTS® and placebo treatment, 17 (59%) and 20 (69%), respectively, were accompanied by migraine attacks. There was no significant difference between the two treatments during the first two periods (95% CI, -0.19 to 0.40) or during the last two periods (95% CI, -0.10 to 0.54). There were also no significant differences between the two treatment groups for ***HA severity*** or ***duration***.	Dropouts: No patients withdrew from the trial, but one (5%) did not provide data for the main efficacy analysis
Solomon, 1986	CrOv QS: 2 (nr, db, dd)	N = 20 Age: N/S % female N/S Classic or common migraine; ≥ 2 HAs/mo for > 1 yr Chron: N/S Rec: N/S	***Placebo:*** n = 15* ***Propranolol (long-acting):*** 120 mg, 1x/day; n = 15* ***Verapamil:*** 80 mg, 3x/day; n = 15* No baseline period described; three 2-mo treatment periods; no washout; no follow-up Nothing on acute meds	***HA frequency:*** No. of attacks/mo ***HA severity:*** Mean per attack; severity of each attack graded on scale of 1-4 (not described) ***HA duration:*** Mean per attack (hrs)	Propranolol, but not verapamil, was significantly ($p<0.05$) better than placebo for ***HA frequency;*** there was no significant difference between the two active treatments (no p-value reported). Mean HA frequency was 6.0 with placebo, 5.0 with verapamil, and 4.5 with propranolol (no variance data reported). Both verapamil and propranolol were significantly better than placebo for ***HA intensity*** ($p<0.05$), but there was no significant difference between the two active drugs (no p-value reported). There were no significant differences among the three treatments for ***HA duration***.	Dropouts: Abstract reports only no. of patients who completed trial and no. who withdrew due to AEs (5 -- 3 verapamil, 2 placebo) Abstract reporting limited information

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Solomon and Kunkel, 1993	CrOv QS: 3 (r, db, dd)	N = 31 Age: 36 (range: 19-49) 83% female Migraine w/ or w/o aura (IHS); history ≥ 2 yrs; 2-8 HAs in previous month; no cluster HA; no frequent TTHs Chron: 17 yrs (range: 4-35) Rec: N/S	***Placebo:*** n = 23* ***Flurbiprofen:*** 100 mg, 2x/day; n = 23* 2-wk baseline period (placebo); two 8-wk treatment periods; 2-wk washout; no follow-up Patients permitted to take a hydrocodone-acetaminophen compound or an isometheptene-acetaminophen compound for relief of acute attacks; ergotamine + caffeine could be used if other two agents ineffective	***HA frequency:*** No. of attacks per 8 wks ***HA severity:*** Mean per attack; each attack graded on scale of 1-5 ***HA duration:*** Total hrs with migraine per 8 wks	There was no significant difference between flurbiprofen and placebo for ***HA frequency*** ($0.05<p<0.10$). Overall mean HA frequencies were 4.39 with flurbiprofen and 5.73 with placebo (no variance data reported). 10/23 patients (43%) reported a ≥ 50% reduction in frequency with flurbiprofen compared to placebo. Flurbiprofen was significantly better than placebo for ***HA severity*** ($p<0.05$) and ***duration*** ($p<0.015$).	Dropouts: 8 (26%), 2 due to AEs (flurbiprofen) No carry-over effect
Solomon, Steel, and Spaccavento, 1983	CrOv QS: 4 (r, db+, dd)	N = 23 Age: 39 75% female Classic or common migraine (Ad Hoc); ≥ 2 attacks/mo Chron: N/S Rec: N/S	***Placebo:*** n = 12* ***Verapamil:*** 80 mg, 4x/day; n = 12* No baseline period described; two 3-mo treatment periods; 5-day washout; no follow-up Acute meds permitted	***HA index:*** Sum of severity scores divided by no. of days observed; severity of each attack graded on scale of 1-3 (mild TTH that responds to simple analgesics and does not interfere with activity, no nausea or vomiting; moderate unilateral vascular HA associated with nausea, responds to ergots or more potent analgesics, may interfere with activity; severe unilateral HA, with vomiting or severe incapacitation) ***Migraine frequency:*** No. of migraines per month	Mean ***HA index*** scores were significantly lower with verapamil (0.44) than with placebo (0.61) (no variance data reported; $p<0.05$). Mean ***migraine frequency*** was also significantly ($p<0.05$) lower with verapamil (3.8) than with placebo (6.7) (no variance data reported).	Dropouts: 11 (48%), 2 due to AEs (both with placebo) High dropout rate No baseline period No carry-over effect was observed 5/12 patients included in the efficacy analysis had been unsuccessfully treated with propranolol in the past

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Somerville and Herrmann, 1978	SPPG QS: 4 (r, db+, dd)	N = 150 Age: N/S (range: N/S) % female N/S Common or classical migraine; ≥ 2, but ≤ 15 HAs/mo in 1 mo prior to trial; migraine defined as "recurrent paroxysmal HA lasting ≥ 1 hr, associated with ≥ 1 of 5 symptoms, including nausea, vomiting, & photophobia" Excl: Pts with HAs caused by head trauma or pts with cervical spondylosis Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 52 ***Lisuride:*** Dose gradually increased to 0.025 mg, 3x/day, on Day 5 and used thereafter; n = 58 No baseline period described; 3-mo treatment period; successful pts from either treatment were treated for an additional 3 mos; no other follow-up described No mention of acute migraine meds	***HA frequency:*** Derived from pts' recordings of dates & duration of HAs ***HA intensity:*** Rating scale N/S, but recorded at onset by pts	Results were provided in a graph from which we could not obtain results for an analysis. Success was defined as a reduction in ***HA frequency*** from > 2 HAs/mo before treatment to 0-2 HAs/mo after treatment. Using this criterion, investigators reported that pts treated with lisuride reduced ***HA frequency*** better than did pts treated with placebo ($p < 0.05$).	Dropouts: 40 pts (27%) withdrew early, none due to AEs, and were not included in efficacy analyses; an additional 17 (11%), included in efficacy analyses, withdrew due to AEs (lisuride 12, placebo 5) Of the 40 pts described above, some withdrew early "due to lack of effect" (placebo 17, lisuride 8)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sørensen, Hansen, and Olesen, 1986	CrOv QS: 3 (r, db, dd)	N = 29 Age: 40 (median) (range: 19-63) 79% female Common migraine (Ad Hoc); ≥ 1-yr history; 2-6 attacks/mo; HA severity usually grade 2-3; no daily HA Chron: 17 yrs (median) (range: 2-30) Rec: HA clinic out-patients	***Placebo:*** n = 29* ***Flunarizine:*** 10 mg, 1x/day (at night); n = 29* 1-mo baseline period (no medication); two 4-mo treatment periods; 1-mo washout (placebo); no follow-up Acute meds permitted	***HA index:*** Duration times severity (migraine attacks only) ***HA frequency:*** No. of attacks/mo ***HA severity:*** Mean severity per attack; severity of each attack graded on scale of 1-3 (working capacity not affected, unable to work, bed rest required) ***HA duration:*** Total no. of hrs with migraine; mean duration of attacks (in hrs)	Investigators analyzed data from the last 3 months of each treatment period only. Flunarizine was significantly better than placebo at reducing ***HA index*** (p = 0.01). Compared with baseline values, HA index was reduced by 36% during treatment with flunarizine (by 56% in the last month of treatment) and by 6% during treatment with placebo (13% in the last month of treatment). Similar results were reported for ***HA frequency*** (p = 0.001) and for ***total HA duration*** (p = 0.02). There were no significant differences between flunarizine and placebo for mean ***severity*** or ***duration*** of individual attacks.	Dropouts: 2 (7%), 1 due to AEs (flunari-zine); data from both patients were included in the efficacy analysis No carry-over effect detected 19 patients had tried prophy-lactic med before, only 2 successfully
Sørensen, Larsen, Rasmus-sen, et al., 1991	SPPG QS: 4 (r, db+, dd)	N = 149 Age: 42 (median) (range: 20-64) 79% female Migraine w/ or w/o aura (IHS); ≥ 1-yr history; 2-8 migraine days/mo in past 3 mos Chron: 17 yrs (median) (range: 1-50) Rec: Neuro dept out-patients	***Metoprolol (slow-release):*** 200 mg, 1x/day (at night); n = 69 ***Flunarizine:*** 10 mg, 1x/day (at night); n = 58 1-mo baseline period (placebo); 5-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of migraine days/mo ***HA severity:*** Each attack graded on scale of 1-3 (not described) ***HA duration:*** Hrs with migraine per migraine day (attacks lasting overnight considered to be two migraine days with individual durations)	Both drugs significantly reduced ***HA frequency*** compared with baseline values (p<0.001 for both drugs for all months). The reduction was significant already in the first month for both drugs; thereafter, flunarizine was increasingly efficacious over time, whereas metoprolol reached maximum effect already during the first month. The mean change in HA frequency (± SEM) from baseline to month 5 was -2.2 (± 0.4) in the flunarizine group and -1.5 (± 0.4) in the metoprolol group; the difference between the two treatments was not statistically significant (p=0.25). Similar results were reported for ***HA severity*** and ***HA duration***.	Dropouts: 22 (15%), 11 due to AEs (10 flunari-zine, 1 meto-prolol)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sovak, Kunzel, Sternbach, et al., 1981	SPPG QS: 2 (r, ndb, dd)	N = 58 Age: N/S (range: 30-57) 100% female Common or classical migraine; no HAs between attacks; severe, "vascular-type" pain; no meds for BF group Chron: N/S Rec: Pain treatment center; U.S.	***Drug therapy (propranolol + analgesics):*** n = 20; dosages and treatment regimen not described ***Thermal BF + relax. (AT phrases):*** n = 28; eight to ten 45-min sessions (2 x /wk for first 2 wks, then at intervals increasing until there were 4 wks between the last two sessions); home practice: 2 x/ day with equipment + 10-min tape	***HA index:*** Composed of HA incidence, intensity (scale N/S), & duration Both groups monitored HAs daily by diary during treatment (length of time N/S).	Authors did not report results for comparisons between the two treatment groups for ***HA index***. Changes from pre- to posttreat. for each group were reported only on figures from which it was difficult to determine precise results. Fifty-four percent (15/28) and 45% (9/20) of pts in the thermal BF and drug therapy groups, respectively, improved with treatment. Authors did not report the cutoff percentage used to determine "improvement."	Dropouts: 10

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Steardo, Bonuso, Di Stasio, et al., 1982	SPPG QS: 1 (nr, ndb, dd)	N = 99 Age: N/S % female N/S Common or classic migraine (Ad Hoc); no previous experience with migraine-preventive meds Chron: N/S Rec: N/S	***Methysergide:*** 6-10 mg/day, according to body weight; n = 25 ***Propranolol:*** 40 mg, 3x/day (full dose achieved gradually); n = 24 ***Metoprolol:*** 100 mg, 3x/day (full dose achieved gradually); n = 16 No baseline period described; 6-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks per 6-mo period	All three drugs significantly reduced mean ***HA frequency*** compared with pre-treatment values ($p<0.001$ for methysergide and propranolol; $p<0.05$ for metoprolol). During the 6-mo treatment period, mean HA frequency (± SEM) was 10.92 (± 1.46) in the methysergide group, 7.67 (± 1.25) in the propranolol group, and 16.13 (± 1.31) in the metoprolol group. Investigators did not directly compare the treatments for this outcome. A reduction in ***HA frequency*** of 50% or greater was reported by 14/25 patients (56%) in the methysergide group, 16/24 patients (67%) in the propranolol group, and 1/16 (6%) in the metoprolol group. Investigators did not analyze these results.	Dropouts: 34 (34%), 18 due to AEs (6 methysergide, 4 propranolol, 8 metoprolol) Not clear how baseline values established High dropout rate (34%) Low quality score (1); not randomized, not double-blind None of the included patients had used migraine-preventive medication before; the trial also included a group of patients unresponsive to previous preventive treatment, who were nonrandomly assigned to treatment with propranolol; we have excluded this treatment group from consideration

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Steardo, Marano, Barone, et al., 1986	SPPG QS: 4 (r, db+, dd)	N = 104 Age: 30 (range: 16-51) 59% female Common or classical migraine (Ad Hoc); ≥ 2 attacks/mo in previous 8 mos; no prior prophylactic treatment Chron: 11 yrs Rec: Neuro dept out-patients	***Methysergide:*** Dose gradually increased over first wk to 2 mg, 3x/day; n = 51 (randomized; n's for later months N/S) ***Flunarizine:*** 10 mg, 1x/day (at night); n = 53 (randomized; n's for later months N/S) 1-mo baseline period; 5-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/mo ***HA severity:*** Severity of each attack graded on scale of 1-4 (mild, no reduction in activity; moderate, < 50% reduction in activity; severe, > 50% reduction in activity, but bed rest not required; disabling, bed rest required) ***HA duration:*** Hrs per attack	Both drugs significantly reduced mean ***HA frequency*** compared with baseline values ($p<0.001$ for each drug for every month of treatment). The effect was significant after only one month, leveled off after the second month, and remained approximately constant for the remainder of the trial. Analysis of covariance showed no significant differences between the two drugs for any month studied (no p-values reported). Mean HA frequencies were reported only in graphic form and could not be accurately read off the graph. Among patients reporting at least one HA during treatment month 5 (n's N/S), flunarizine reduced ***HA intensity*** by an estimated average of 0.28 ($p=0.0030$ vs. baseline), while methysergide resulted in an estimated average *increase* in severity of 0.09 ($p=0.40$ vs. baseline). The investigators did not directly compare the two treatments for this outcome. Both treatments reduced ***HA duration*** to a degree that was statistically significant for most months; there were no significant differences between the two treatments (no p-values reported).	Dropouts: 19 (18%), 7 due to AEs (all methysergide) Patients had never undergone migraine prophylactic treatment
Steiner, Joseph, Hedman, et al., 1988 AND Steiner, Cook, Joseph, et al., 1985	SPPG QS: 4 (r, db+, dd)	N = 59 Age: 38 76% female Classical or common migraine; ≥ 2-yr history; 2-8 attacks/mo; co-existing TTH OK provided patient could distinguish from migraine; no preventive meds in 4 wks preceding trial Chron: N/S Rec: Migraine clinic	***Placebo:*** n = 31 ***Metoprolol:*** 50 mg, 2x/day; n = 28 4-wk baseline period (placebo); 8-wk treatment period; patients then given opportunity to continue in 12-wk follow-up, with responders continuing on same med, placebo nonresponders switching to metoprolol 50 mg, 2x/day, and metoprolol nonresponders switching to 100 mg, 2x/day Patients allowed to take their usual meds for acute attacks	***HA index:*** Sum of severity scores per 4 wks ***HA frequency:*** No. of attacks per 4 wks; no. of migraine days per 4 wks ***HA severity:*** Per attack; severity graded every day on scale of 0-3 (no HA, mild, moderate, severe/incapacitating)	We analyzed results from the initial, double-blind portion of the trial only. Mean ***HA index*** scores were significantly decreased compared with baseline values in the metoprolol group ($p=0.012$), but not in the placebo group ($p=0.074$); there was no significant difference between the two treatments for this outcome ($p=0.081$). Mean HA index scores (± SD) in the placebo group were 10.8 (± 5.4) during the baseline period and 9.4 (± 4.8) during treatment; in the metoprolol group, the corresponding figures were 11.2 (± 6.0) and 8.2 (± 5.7), respectively. ***HA frequency:*** Both treatments significantly reduced the mean no. of attacks per 4 wks and the mean no. or HA days per 4 wks compared with baseline values; there was no significant difference between them for no. of attacks ($p=0.13$), and metoprolol was significantly better than placebo for no. of migraine days ($p=0.05$). Neither treatment significantly affected ***HA severity.***	Dropouts: 5 (8%), 1 due to AEs (metoprolol); all 5 patients were included in the efficacy analysis

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Stellar, Ahrens, Meibohm, et al., 1984	CrOv QS: 5 (r+, db+, dd)	N = 107 Age: 43 (range: 18-66) 72% female Classic or common migraine (Ad Hoc); ≥ 3 attacks during baseline period; history of co-existing TTHs OK provided patient could distinguish from migraine attacks Chron: N/S Rec: N/S	***Placebo:*** n = 94* ***Timolol:*** 20-30 mg/day, taken in two doses; n = 94* 1-mo baseline period (placebo); two 2-mo treatment periods; no washout, but data from first 2 wks of each treatment period not incuded in efficacy analysis to minimize carry-over effects; no follow-up Acute meds permitted	***HA frequency:*** No. of HAs per month ***HA severity:*** Mean severity per attack (scale used to grade individual attacks not described) ***HA duration:*** Mean duration (in hrs) per attack	Mean ***HA frequency*** was reduced from 6.8 during the baseline period to 5.0 with placebo and 4.3 with timolol (no variance data reported). Timolol was significantly better than placebo for this outcome ($p<0.01$). A 50% or greater reduction in HA frequency compared with baseline values was reported by 25/94 patients (27%) with placebo and by 40/94 patients (43%) with timolol. Investigators did not state whether or not they found the difference between the two treatments for this outcome to be statistically significant. Neither intervention significantly affected ***HA severity*** or ***duration***.	Dropouts: 9 patients (8%) withdrew prematurely, 2 due to AEs (timolol); an additional 4 patients (4%) were excluded from the efficacy analysis for protocol violations
Stensrud and Sjaastad, 1974	CrOv QS: 4 (r, db+, dd)	N = 26 Age: N/S (range: 17-55) 88% female Classic or common migraine (Ad Hoc); ≥ 3 HAs/mo; most patients had "relatively intractable migraine" Chron: N/S Rec: N/S	***Placebo:*** n = 24* ***Ketoprofen:*** 50 mg, 3x/day; n = 24* No baseline period described; two 6-wk treatment periods; "approximately" one-wk washout; no follow-up Acute meds permitted, though patients encouraged to avoid using them	***HA index:*** Frequency times severity; severity of each attack graded on scale of 1-3 (not described) ***HA frequency:*** No. of HA days	Ketoprofen was significantly better than placebo for ***HA index*** ($p<0.05$). 16/24 patients (67%) improved with ketoprofen compared to placebo, 3 were unchanged, and 5 were worse; improvement was > 50% in only 5/24 cases (21%). The mean percentage reduction in HA index with ketoprofen compared to placebo was 23%. Total HA index was reduced from 677 on placebo to 520 on ketoprofen. Ketoprofen was also significantly better than placebo for ***HA frequency*** ($p<0.02$). 19/24 patients (79%) improved with ketoprofen compared to placebo, 5/24 were worse; improvement was > 50% in only 3/24 cases (13%). The mean percentage reduction in HA frequency was 18%, and the total number of HA days was reduced from 344 on placebo to 274 on ketoprofen.	Dropouts: 2 (8%), for unspecified reasons

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Stensrud and Sjaastad, 1976a	CrOv QS: 3 (nr, db+, dd)	N = 29 Age: 45 (range: 25-61) 83% female Chron: N/S (range: N/S) Common or classical migraine; ≈ 50% of pts also had TTHs Rec: N/S	***Placebo:*** n = 27* ***Clonidine (Catapresan®):*** 75-150 µg/day; n = 27* 4- to 32-mo baseline (mean of 10 mos) treatment with clonidine (75-150 µg/day); two 7-wk treatment periods; no washout between treatment periods, but data from first 2 wks of each period excluded from analyses; no follow-up Nothing on acute meds	***HA index:*** Calculated as no. of HA days multiplied by intensity score (graded from 1 to 3) ***HA frequency:*** Defined as no. of HA days	The overall mean ***HA index*** score *increased* from 10.3 at baseline to 11.1 and 14.1 after treatment with clonidine or placebo, respectively. Clonidine was significantly more effective than placebo ($p<0.02$), although both interventions increased, rather than decreased, ***HA index*** from pre- to post-treatment.	Dropouts: 2 (7%), not specified if 1 was due to AEs; 1 was not Pts were treated during baseline with clonidine because investigators wished to determine whether the clonidine effect would be maintained over a lengthy period
Stensrud and Sjaastad, 1976b	CrOv QS: 4 (r, db+, dd)	N = 20 Age: 44 (range: 15-60) 70% female Common or classical migraine (Ad Hoc); frequency N/S Chron: N/S (range: N/S) Rec: N/S, but "outpatients"	***Placebo:*** n = 19* ***Propranolol (Inderal®):*** 40 mg, 4x/day; n = 19* No baseline period described; two 4-wk treatment periods; 1-wk washout between treatment periods; no follow-up Analgesics or ergotamines permitted for acute migraine attacks	***HA index:*** Calculated as HA days multiplied by HA intensity score ***HA frequency:*** Defined as "HA days," and recorded on forms by pts ***HA intensity:*** Rated on 3-point scale by pts	The post-treatment mean scores for ***HA index*** were 7.47 and 12.32 for propranolol and placebo, respectively. No baseline mean scores were provided. For reductions in HA index, propranolol was significantly better than placebo ($p < 0.001$). Investigators did not report pre- to post-treatment results.	Dropouts: 1 (5%), due to AEs (propranolol) Not clear if baseline data gathered

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Stensrud and Sjaastad, 1979	CrOv QS: 3 (r, db, dd)	N = 38 Age: N/S (range: 20-60) 71% female Migraine (Ad Hoc); ≥ 3-4 attacks/mo Chron: N/S Rec: N/S	**Placebo:** n = 38* ***Clonazepam (Rivotril®):*** 0.5 mg 2x/day; n = 38* 4-wk baseline period (drug-free); two 4-wk treatment periods; no washout; patients not experiencing side-effects with clonazepam 1 mg/day given option of continuing in open trial of 1-3 mg/day for up to a year Patients permitted to use analgesics or ergotamine to treat acute attacks	***HA index:*** Sum of HA severity scores; each attack graded on scale of 1-3 (not described) ***HA frequency:*** No. of HA days/treatment period	***HA index*** scores were reduced by 24% during treatment with clonazepam compared with baseline levels; this was not a statistically significant reduction (no p-value reported); treatment with placebo resulted in an 8% reduction vis-à-vis baseline. On average, HA index scores were 2.0 points lower with clonazepam than with placebo, but this difference was not significant (p=0.20). ***HA frequency*** was reduced by 50% during treatment with clonazepam compared with baseline levels (p<0.05); treatment with placebo resulted in only an 8% reduction vis-à-vis baseline. On average, patients reported 3.6 fewer days with HA with clonazepam than with placebo (p=0.055). This result may have been significant if investigators had corrected for the carry-over effect, which was found to be significant.	Dropouts: 1 (3%) during controlled portion of trial; reason for withdrawal N/S More than half of the patients suffered from interval HAs in addition to their migraines
Stensrud and Sjaastad, 1980a	CrOv QS: 4 (r, db+, dd)	N = 35 Age: N/S (range: 25-60) 69% female Classic or common migraine (Ad Hoc); approx 50% of patients also had "more continuous" HA Chron: N/S Rec: N/S	***Placebo:*** n = 28* ***Propranolol:*** 80 mg, 2x/day; n = 28* ***Atenolol:*** 50 mg, 2x/day; n = 28* No baseline period described; two 6-wk treatment periods; 1-wk washout; no follow-up Patients allowed to use analgesics or ergotamine to treat acute attacks	***HA index:*** Frequency times severity; severity of each attack graded on scale of 1-3 ***HA frequency:*** No. of HA days	Significantly lower ***HA index*** scores were recorded with atenolol than with placebo (p<0.05); the differences between propranolol and placebo and between propranolol and atenolol were not statistically significant (no p-values reported). Total HA index scores were 498 for the placebo period, 410 for the atenolol period, and 437 for the propranolol period. When 7 high-frequency outlier patients (suspected of recording data on interval HAs) were excluded from the analysis, both atenolol and propranolol were significantly better than placebo for HA index (p<0.05); there was still no significant difference between the two active treatments (no p-value reported). Total HA index scores for this reduced group were 320 during the placebo period, 187 during the atenolol period, and 190 during the propranolol period. Very similar results were reported for ***HA frequency***.	Dropouts: 7 (20%), 1 due to AEs (propranolol) "Most" patients had previously tried preventive meds, with little or moderate success

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sternieri, Bussone, Manzoni, et al., 1991	SPPG QS: 3 (r, db, dd)	N = 100 Age: N/S 73% female Migraine w/o aura (IHS); 3-12 HA days/mo for previous 3 mos; no other types of HA Chron: N/S Rec: N/S	***Placebo:*** n = 50 ***Lornoxicam:*** 4 mg, 3x/day; n = 46 1-mo baseline period (placebo); 2-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of HA days/mo	Lornoxicam significantly reduced ***HA frequency*** in comparison with baseline values ($p<0.05$) and was significantly better than placebo for this outcome ($p<0.05$). Mean HA frequency (± SEM) during the baseline period was 7.8 ± 0.6 for both treatment groups. After 2 mos of treatment, mean HA frequency in the lornoxicam group was 5.3 ± 0.5, compared with 7.3 ± 0.6 in the placebo group.	Dropouts: 8 patients (8%) withdrew before completing the trial, 6 due to AEs (4 lornoxicam, 2 placebo), but appear to have been included in the efficacy analysis. Four other patients (4%) were excluded from the efficacy analysis due to poor compliance. Abstract reporting limited interim results
Sudilovsky, Elkind, Ryan, et al., 1987	SPPG QS: 4 (r, db+, dd)	N = 140 Age: 39 76% female Classic or common migraine (Ad Hoc); ≥ 3 attacks/mo in previous year Chron: 21 yrs Rec: N/S	***Propranolol:*** 80 mg, 2x/day; n = 27 ***Nadolol, 160 mg/day:*** 1x/day; n = 33 ***Nadolol, 80 mg/day:*** 1x/day; n = 33 1- to 2-mo baseline period (placebo); 2-mo treatment period; no follow-up Acute meds permitted	***HA index:*** Defined as [4(no. of disabling HAs) + 3(no. of severe HAs) + 2(no. of moderate HAs) + 1(no. of mild HAs)], divided by the number of days for which patient evaluated ***HA frequency:*** No. of HA days divided by the number of days for which patient evaluated; no. of HAs the number of days for which patient evaluated	Nadolol, 160 mg, 1x/day was significantly more effective than nadolol 80 mg, 1x/day ($p<0.05$) and propranolol 80 mg, 2x/day ($p<0.05$) at reducing ***HA index*** from baseline to month 2; there was no significant difference between the lower dose of nadolol and propranolol for this outcome (no p-value reported). A reduction in HA index scores of 50% or greater was reported by 21/33 patients (64%) in the nadolol 160 mg group, 11/33 patients (33%) in the nadolol 80 mg group, and 10/27 patients (37%) in the propranolol group. Similar results were reported for ***HA frequency***.	Dropouts: 47 patients (34%) were excluded from the analysis of the primary 2-mo efficacy outcomes; 8 of these had withdrawn due to AEs (80 mg nadolol, 2; 160 mg nadolol, 4; propranolol, 4)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Sudilovsky, Stern, and Meyer, 1986b	SPPG QS: 2 (r, db, dnd)	N = 154 Age: N/S % female N/S Migraine Chron: N/S Rec: N/S	***Placebo:*** n = N/S ***Nadolol, 240 mg/day:*** Dosing schedule not described; n = N/S ***Nadolol, 160 mg/day:*** Dosing schedule not described; n = N/S ***Nadolol, 80 mg/day:*** Dosing schedule not described; n = N/S 2-mo baseline period (placebo); 2-mo treatment period; no follow-up Acute meds permitted	***HA frequency index:*** Not defined ***HA intensity index:*** Not defined ***HA pain index:*** Not defined	Results were not reported separately for the various doses of nadolol. Investigators analyzed the number of patients reporting a 50% or greater reduction (compared with baseline) in the ***HA indexes*** listed at left. Nadolol was significantly better than placebo for all three indexes ($p<0.05$).	Dropouts: Not described Abstract reporting limited results
Szekely, Merryman, Croft, et al., 1989	CrOv QS: 3 (r, db, dd)	N = 30 Age: N/S 100% female "Peri-menstrual exacerbations of HA"; efficacy analysis included patients with common (n=16) and classical (n=1) migraine, mixed HA (n=3), muscle-contraction HA (n=1), and cluster-like HA (n=1) (all Ad Hoc) Chron: N/S Rec: N/S	***Placebo:*** n = 22* ***Naproxen sodium:*** 550 mg, 2x/day; n = 22* 2-menstrual-cycle baseline period (HA recording); two 2-cycle treatment periods; study meds taken from 8th day after ovulatory rise in temperature through the 8th day of menstrual week; no washout; no follow-up No other meds taken during attacks	***HA index:*** Not defined, but combined frequency, severity, and duration ***HA frequency:*** Not defined ***HA severity:*** Not defined ***HA duration:*** Not defined	Naproxen sodium significantly reduced ***HA index*** in comparison to baseline ($p<0.001$) and was significantly better than placebo for this outcome ($p=0.03$). HA index scores were not reported. ***HA frequency*** was significantly reduced in comparison with baseline values in both treatment groups ($p<0.00001$). Naproxen sodium was significantly better than placebo for this outcome ($p=0.2$). There were no significant differences between naproxen sodium and placebo for ***HA severity*** or ***duration*** ($p=0.4$ for both outcomes).	Dropouts: 8 (27%), 2 due to AEs (intervention N/S) Abstract with limited information High dropout rate (27%) Efficacy analysis included 1 patient with TTH and 1 with "cluster-like" HA

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Tfelt-Hansen, Standnes, Kangas-niemi, et al.	CrOv QS: 4 (r, db+, dd)	N = 96 Age: 40 74% female Common migraine (Ad Hoc); 2-6 attacks/mo; patients with other types of HA excluded Chron: 21 yrs Rec: HA clinics and neuro depts	***Placebo:*** n = 80* ***Propranolol:*** 80 mg, 2x/day; n = 80* ***Timolol:*** 10 mg, 2x/day; n = 80* 4-wk baseline period (no prophylactic med); three 12-wk treatment periods; no washout, but only last 10 wks of each treatment period analyzed to minimize carry-over effects; no follow-up Acute meds permitted	***HA index (freq x sev):*** Frequency times severity ***HA index (freq x sev x dur):*** Frequency times severity times duration ***HA frequency:*** No. of attacks per 4 wks ***HA severity:*** Each attack graded on scale of 1-3 (bothering, cannot work, must go to bed); mean HA severity per month reported ***HA duration:*** Mean duration of attacks/mo	We analyzed continuous data on HA index (freq x sev) and dichotomous data on HA frequency. Both timolol and propranolol were significantly better than placebo for ***HA index (freq x sev)*** ($p<0.01$ for both comparisons); the difference between the two active drugs (0.95) was not significant (95% CI, -0.43 to 1.97). Mean HA index scores (± SD) were 9.03 (± 7.28) for placebo, 6.66 (± 5.87) for propranolol, and 5.71 (± 5.14) for timolol. A 50% or greater reduction in ***HA frequency*** was reported by 44/80 patients on timolol (55%), 48/80 patients on propranolol (60%), and 24/80 patients (30%) on placebo. Both treatments were significantly better than placebo for this outcome ($p<0.01$); investigators did not directly compare the two active treatments.	Dropouts: 16 patients (17%) did not provide enough data to be included in the efficacy analysis; not clear how many of these were due to AEs No carry-over effect
Thomas, Behari, and Ahuja, 1991	CrOv QS: 3 (nr, db+, dd)	N = 29 Age: 30 (range: 20-43) 87% female Common migraine (Ad Hoc); history > 2 yrs; ≥ 3 HAs/mo in previous 3 mos; patients with daily attacks of TTH excluded Chron: N/S Rec: N/S	***Placebo:*** n = 15* ***Flunarizine:*** 10 mg, 1x/day (bedtime); n = 15* No baseline period described; two 12-wk treatment periods; 2-wk washout; no follow-up Acute meds permitted	Severity of each HA graded on scale of 1-3 (mild, moderate, severe); duration graded on scale of 1-3 (2-8 hrs, 8-12 hrs, > 12 hrs) Clinic visits approx every 4 wks; following outcomes calculated at each visit: ***HA index:*** No. of HAs multiplied by severity, divided by no. of days in visit period ***Corrected HA unit index:*** Severity of attacks multiplied by duration, divided by no. of days in visit period ***HA frequency:*** No. of HAs divided by no. of days in visit period	Flunarizine significantly reduced median ***HA index*** scores compared with baseline values ($p<0.01$) and compared with placebo ($p<0.05$). Median scores were 6.7 (range: 3-16) pre-treatment, 6.0 (range: 0-16) on placebo, and 3.0 (range: 0-8.6) on flunarizine. Similar results were reported when group median scores were compared for ***corrected HA unit index*** and ***HA frequency.*** We used individual patient data reported by investigators to calculate group mean ***HA index*** scores (± SD) for pre-treatment (8.10 ± 3.84) and post-treatment with flunarizine (2.84 ± 2.17) and placebo (6.3 ± 5.22). We then used these means to calculate an ES comparing flunarizine and placebo for reduction in mean HA index from pre- to post-treatment. Using the same individual patient data, we established that 12/15 patients (80%) experienced a ***50% or more reduction in HA index*** from pre- to post-treatment on flunarizine, compared with 6 of the same 15 patients (40%) on placebo. Investigators did not compare the two treatments for this outcome.	Dropouts: 14 (48%), 1 due to AEs, 1 due to pregnancy, 10 for unknown reasons High dropout rate Not randomized Not clear how baseline values established (no baseline period described)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Titus, Dávalos, Alom, et al., 1986	SPPG QS: 2 (r, ndb, dd)	N = 124 Age: 31 (range: 12-56) 62% female Migraine; "tension" and "tension-vascular" HAs not included Chron: N/S Rec: N/S	***Methysergide:*** 3 mg/day (dosing schedule not described); n = 40 ***Oxitriptan (5-Hydroxytryptophan [5-HTP]):*** 600 mg/day (dosing schedule not described); n = 45 6-mo baseline period (no anti-migraine drugs); 6-mo treatment period; follow-up mentioned, but not described Nothing on acute meds	***HA frequency:*** No. of attacks; no. of attacks of severe intensity (scale used to grade severity not described)	***HA frequency:*** 30/40 patients (75%) in the methysergide group and 32/45 (71%) in the oxitriptan group and showed a 50% or greater reduction in the number of attacks or the number of severe attacks compared to baseline values. There was no significant difference between the two treatments for this outcome (p = 0.68).	Dropouts: 39 patients (31%) "lost to follow-up"; not clear whether any of these withdrew due to AEs Low quality score (2); not double-blind High dropout rate (31%)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Vilming, Standnes, and Hedman, 1985	CrOv QS: 4 (r, db+, dd)	N = 35 Age: 38 (range: 18-60) 83% female Common or classical migraine; 3-10 HAs/mo of > 2-hr duration + 4 other migraine-related symptoms, including prodromas with or without aura, phono- or photophobia Excl: Other types of vascular HAs, nonseparable TTHs and migraine, contraindica-tions of study meds Chron: 20 (range: 2-43) Rec: N/S	***Metoprolol:*** 50 mg, 2x/day; n = 30* ***Pizotifen:*** 0.5 mg, 1x/day on Days 1 & 2; 0.5 mg, 2x/day on Days 3 & 4; 0.5 mg, 3x/day on Day 5 and thereafter; n = 30* 4-wk run-in with placebo prior to treatment; two 8-wk treatment periods; 4-wk washout period with placebo between treatment periods; no follow-up Ergotamine and analgesic meds permitted	***HA index:*** Calculated as sum of intensity scores multiplied by no. of HA days ***HA frequency:*** Defined as "no. of migraine days" ***HA intensity:*** Recorded daily by pt on 3-point scale	Investigators found no significant difference between pizotifen and metoprolol for reductions in ***HA index*** ($p > 0.05$). ***HA index*** was reduced from a median baseline value of 13.0 to median values of 7.1 and 8.6 after treatment with pizotifen and metoprolol, respectively. The pre- to post-treatment reductions were statistically significant for both drugs ($p < 0.01$, each case). Fourteen of 33 pts (42%) taking pizotifen and 10/34 (29%) taking metoprolol reduced ***HA index*** ≥ 50% from baseline to post-treatment. The difference between the two treatments was not significant ($p > 0.05$).	Dropouts: 5 (14%), 4 due to AES (3 pizotifen, 1 metoprolol); all 5 included in efficacy analyses until they withdrew
Weber and Reinmuth, 1972	CrOv QS: 3 (r, db, dd)	N = 25 Age: 41 (range: 19-61) 52% female Migraine; frequency N/S Chron: N/S (range: N/S) Rec: N/S	***Placebo:*** n = 19* ***Propranolol:*** 20 mg, 4x/day; n = 19* No baseline described; two 3-mo treatment periods; no washout; no follow-up Acute migraine meds (salicylates, ergotamines) permitted, but not prophylactic use of ergotamines or methysergide	***HA frequency:*** Not defined; not clear how data gathered	Fifteen of 19 pts (79%) receiving propranolol improved on ***HA frequency*** (achieved ≥ 50% improvement from pre- to post-treatment); 2/19 pts (11%) receiving placebo improved on this outcome. Investigators did not report having analyzed the between-group or pre- to post-treatment results for statistical significance.	Dropouts: 6 (24%), none due to AEs Not clear how data obtained; no mention of HA diaries; HA frequency assessed at 4-wk intervals by investigators

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Welch, Ellis, and Keenan, 1985	CrOv QS: 3 (r, db, dd)	N = 46 Age: 39 (range: 22-71) 88% female Common or classic migraine (Ad Hoc); ≥ 1-yr history; ≥ 2 HAs/mo in last 3 mos Chron: N/S Rec: N/S	***Placebo:*** n = 31* ***Naproxen sodium (Anaprox®):*** 550 mg, 2x/day; n = 31* 2-wk baseline period (placebo); two 8-wk treatment periods; 2-wk washout (placebo); no follow-up Acetaminophen, a narcotic preparation (usually codeine), or ergotamine permitted for treatment of acute attacks	***HA index:*** Computed on average weekly basis; $7[1(F_1) + 2(F_2) + 3(F_3)]$/no. of days in period, where F_1=no. of days with mild HA, F_2=no. of days with moderate HA, F_3=no. of days with severe HA ***HA frequency:*** Days per wk with HA ***HA duration:*** Hrs per wk with HA	Naproxen sodium was significantly better than placebo for ***HA index*** (p=0.02). Mean HA index scores (± SD) were 2.61 (± 2.01) with naproxen sodium and 3.47 (± 2.16) with placebo. 10/31 patients (32%) reported a > 50% improvement in HA index score on naproxen sodium compared with placebo. There was no significant difference between the two treatments for ***HA frequency*** (p=0.11). Mean HA frequency (± SD) was 1.57 (± 1.14) with naproxen sodium and 1.88 (± 1.08) with placebo.	Dropouts: 15 (33%), 5 due to AEs (4 naproxen sodium, 1 placebo) No carry-over effects
Wessely, Baumgartner, Klingler, et al., 1987	SPPG QS: 2 (nr, db, dd)	N = 45 Age: 43 89% female Classical or common migraine Chron: N/S Rec: N/S	***Placebo:*** n = 19 ***Gabapentin:*** 300 mg, 3x/day; n = 14 3-mo baseline period; 3-mo treatment period; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks/month	***HA frequency*** was reduced from 6.5 attacks per month (baseline) to 4.1 attacks per month (during treatment period) in the gapapentin group; corresponding figures in the placebo group were 4.3 and 4.0, respectively (no variance data reported). Investigators did not report whether they found the difference between the two treatments to be statitistically significant.	Dropouts: 12 (27%), 3 due to AEs (2 gabapentin, 1 placebo) Abstract reporting limited interim results

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Widerøe and Vigander, 1974	CrOv QS: 3 (r, db, dd)	N = 30 Age: 38 (average) (range: 18-55) 87% female Common or classical migraine (Ad Hoc); average of 3 HAs/mo in 1 mo prior to trial Chron: N/S (range: N/S) Rec: Pts who had achieved ≥ 50% reduction in HA frequency in previous uncontrolled pilot study by same authors; all had been taking prophylactics (propranolol) for ≈ 6 mos	***Placebo:*** n = 26* ***Propranolol:*** 40 mg, 4x/day; n = 26* No baseline described; two 3-mo treatment periods; no washout; no follow-up Patients' usual medications for acute migraine attacks apparently permitted, but this is not clear	***HA frequency:*** Not defined, but recorded daily by pts and reported as "average monthly number of attacks"	***HA frequency*** was reduced from an average of 3 HAs/mo at baseline to an average of 0.4 and 1.7 HAs/mo after treatment with propranolol or placebo, respectively. Investigators did not report having analyzed the differences between treatments for statistical significance.	Dropouts: 4 (13%), none due to AEs

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Wilkinson, 1970	CrOv QS: 3 (r, db, dd)	N = 27 Age: 38 (range: 22-63) 89% female Chron: N/S (range: N/S) Common or classical migraine; hist. of ≥ 1 classical M/mo; "many" pts had classical Ms Excl: Current use of antimigraine prophylactics; previous use of clonidine Rec: Inpatients of 3 hospitals	***Placebo (lactose):*** n = 23* ***Clonidine:*** 25 μg, 2x/day; n = 23* ***Clonidine:*** 50 μg, 2x/day; n = 23* 2-wk baseline; three 6-wk treatment periods; no washout between treatment periods, but data from first 2 wks of second and third treatment periods excluded from analyses; no follow-up Nothing on acute meds	***HA frequency:*** Definition N/S, but obtained from pts' diaries ***HA intensity:*** Rating scale N/S, but obtained from pts' diaries	Results were reported only as pts' "preferences" (not defined). Fourteen of 23 (61%) and 7/23 pts (30%) preferred clonidine or placebo, respectively. Two of 23 (9%) had no preference. Investigators did not report whether or not they analyzed these results for statistically significant differences. No within-group results were provided for comparisons of ***HA frequency*** or ***intensity*** before and after treatment with each intervention.	Dropouts: 4 (15%), 2 for unspecified reasons; 2 because they "were worse" This study reports preliminary results from 23 pts who had completed treatment (from a trial with 82 pts)
Wilkinson, Agnoli, Gerber, et al., 1989	SPPG QS: 3 (r, db, dd)	N = 127 Age: N/S (range: N/S) % female N/S Common or classical migraine; 2-8 HAs/mo Excl: Use of concomitant migraine prophylactic meds Chron: N/S (range: N/S) Rec: N/S	***Lisuride (Cuyalit®):*** 0.025 mg, 3x/day; n = 43 ***Lisuride (Cuyalit®):*** 0.05 mg, 3x/day; n = 49 1-mo baseline; 3-mo treatment period, followed by 1-mo washout without meds; no follow-up Ergotamine apparently permitted, but this is not clear	***HA index:*** Calculated as the sum of severe HAs times 4, moderate HAs times 2, and mild HAs times 1 ***HA frequency:*** Defined as "no of attacks" ***HA intensity:*** Recorded by pt on 3-point scale	Investigators did not provide specific results for ***HA index***, but reported that both lisuride groups improved from pre- to post-treatment. There were no statistically significant differences between the two dosages ($p > 0.05$). From baseline to the end of 3 mos, 16/43 pts (37%) treated with lisuride 0.025 mg, 3x/day, reduced ***HA frequency*** ≥ 50%. Over the same period, 18/49 pts (37%) treated with lisuride 0.05 mg, 3x/day, reduced ***HA frequency*** ≥ 50%. Investigators stated that there were no major differences between the two treatments, but did not report whether or not they analyzed the results for statistical significance.	Dropouts: 35 pts (28%) withdrew, 15 due to AEs (lower dose 9, higher dose 6) Trial was multi-center study in 5 European cities

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Wörz, Reinhardt-Benmalek, Foeh, et al., 1992	CrOv QS: 3 (r, db, dd)	N = 125 Age: 39 78% female Migraine w/ or w/o aura (IHS); ≥ 2-yr history; ≥ 3 attacks/mo; no other types of HA; no migraine-preventive med in month prior to trial Chron: 20 yrs Rec: Neuro clinics and pain centers	***Metoprolol:*** 50 mg, 2x/day; n = 78* ***Bisoprolol:*** 5 mg, 1x/day (a.m.); n = 78* 1-mo baseline period (HA recording); two 3-mo treatment periods; no washout, but data from first month of each treatment period excluded from analysis to minimize carry-over effects; no follow-up Acute meds permitted	***HA frequency:*** No. of attacks per month ***HA severity:*** Severity of each attack graded on scale of 1-4 (mild, moderate, severe, very severe) ***HA duration:*** Per attack, in hrs	There were no significant differences between the two treatments for ***HA frequency*** (p>0.05). Mean HA frequency (± SD) was 4.0 (± 1.56) during the baseline period, 2.05 (± 1.84) during treatment with bisoprolol, and 1.99 (± 1.51) during treatment with metoprolol. A reduction of 50% or more in HA frequency was reported by 41/78 patients (53%) with bisoprolol and 40/78 patients (51%) with metoprolol. Neither drug significantly reduced mean ***HA severity*** or ***duration***.	Dropouts: 32 (26%), 14 due to AEs (not broken down by intervention); an additional 15 patients were excluded from the efficacy analysis due to protocol violations No carry-over effect Dose was doubled in a few patients (approx 10%) after 4 wks
Zeeberg, Orholm, Dalsgaard Nielsen, et al., 1981	SPPG QS: 3 (r, db, dd)	N = 59 Age: N/S 87% female Classic or common migraine (Ad Hoc); history ≥ 3 yrs; ≥ 6 attacks in previous 2 mos; avg duration ≥ 4 hrs; not using prophylactic med Chron: N/S Rec: GP referrals	***Placebo:*** n = 25 ***Femoxetine:*** 200 mg/day for first wk, 300 mg/day therafter; n = 20 No baseline period described; 12-wk treatment period; no follow-up Patients allowed to take meds for acute attacks	***HA index:*** No. of HA days/two-wk period x severity (severity graded on scale of 1-3); medians/two-wk period reported (in graphic form only) ***HA frequency:*** Number of attacks; medians/two-wk period reported (in graphic form only) ***HA duration:*** In hrs; median duration/two-wk period reported (in graphic form only)	Median values for the principal efficacy outcomes were reported in graphic form only and could not be reliably read off the graphs. Investigators employed a nonparametric type of ANOVA analysis, assessing treatments, time course, and interaction between treatment and time course simultaneously. ***HA index***, ***frequency***, and ***duration*** were all significantly reduced over time in both groups. Direct comparison between femoxetine and placebo showed no significant differences (p-values between 0.7-0.17 for the three outcomes). Differences between treatments disregarding time-course were never significant (all p-values > 0.10).	Dropouts: 14 (24%), 3 due to AEs (all with femoxetine)

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruitment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Ziegler and Ellis, 1985	CrOv QS: 3 (r, db, dd)	N = 40 Age: 40 82% female Common or classic migraine; ≥ 2 HAs/mo for ≥ 1 yr Chron: N/S Rec: N/S	***Placebo:*** n = 34* ***Naproxen sodium (Anaprox®):*** 550 mg, 2x/day; n = 34* 2-wk baseline period (placebo); two 8-wk treatment periods; 2-wk washout (placebo); no follow-up Acute meds permitted, but patients instructed to avoid all other drugs with anti-platelet or prostaglandin synthesis-inhibiting effect, especially aspirin	***HA index:*** Computed on average weekly basis; $7[1(F_1) + 2(F_2) + 3(F_3)]$/no. of days in period, where F_1=no. of days with mild HA, F_2=no. of days with moderate HA, F_3=no. of days with severe HA ***HA duration:*** Hrs per wk with HA	Naproxen sodium was significantly better than placebo for ***HA index*** (p=0.004). Mean HA index scores (± SD) were 2.79 (± 2.47) with naproxen sodium and 3.82 (± 2.73) with placebo. 13/34 patients (38%) reported a > 50% improvement in HA index score on naproxen sodium compared with placebo. Naproxen sodium was also significantly better than placebo for ***HA duration*** (p=0.02).	Dropouts: 6 (15%), 1 due to AEs (naproxen sodium)
Ziegler, Hurwitz, Hassanein, et al., 1987 *and* Ziegler, Hurwitz, Preskorn, et al., 1993 (study of predictors of response in the same study population)	CrOv QS: 3 (r, db, dd)	N = 54 Age: 38 (range: 22-57) 73% female Migraine; > 50% of HAs "disabling" or "severe"; > 50% of HAs of duration ≥ 2 hrs; ≥ 2 HAs/mo in last 3 mos; ≤ 3 HAs/wk in last 3 mos; pain not confined to neck or posterior head regions Chron: N/S Rec: N/S	***Placebo:*** n= 30* ***Propranolol:*** Initially 80 mg/day; could be increased after 4 wks to maximum of 240 mg/day; n = 30* ***Amitriptyline:*** Initially 50 mg/day; could be increased after 4 wks to maximum of 150 mg/day; n = 30* 4-wk baseline period; three treatment periods; these of 8 wks' duration each, except in the following cases: (a) if no response to placebo after 4 wks, then patient proceeded to next treatment; (b) if "toxic reaction" experienced in first 4 wks of treatment, then patient proceeded to next treatment after 4 wks; 4-wk "crossover" periods after baseline period and each of first two treatment periods (taper prior agent, 1 wk; placebo washout, 1 wk; start next agent, 2 wks); no follow-up Acetaminophen or codeine permitted for acute attacks	***Weekly HA index:*** Total of daily HA index scores for 7 days; daily score = HA severity (scale of 1-10) multiplied by duration (hrs) for all HAs of severity ≥ 4; investigators reported both continuous (mean weekly HA index scores) and categorical data (no. of patients with ≥50%, 11-49%, and ≤ 10% reduction in mean weekly HA index scores)	Both active treatments produced significantly lower ***mean weekly HA index*** scores than did placebo (p<0.05 for both comparisons). There was no significant difference between the two active treatments (p>0.05). Mean weekly scores were 404.6 for propranolol, 429.4 for amitriptyline, and 510.8 for placebo (no variance data reported). A good response with propranolol or amitriptyline was defined as a ***reduction of 50% or more in mean weekly HA index score*** vis-á-vis the score achieved on placebo. Ten of 30 patients (33%) had a good response with propranolol, as did 12/30 (40%) with amitriptyline. Five of 30 (17%) and 12/30 (40%) patients reported a "moderate" response (reduction of 11-49%) with propranolol and amitriptyline, respectively, and 13/30 (43%) and 8/30 (27%) recorded a "poor" response (≤ 10% reduction) with propranolol and amitriptyline, respectively. There was no significant difference between the two active treatments for this outcome (p=0.29). Ziegler, Hurwitz, Preskorn, et al. (1993) studied predictors of response to treatment in this study population. They reported that specific response to amitriptyline was correlated with female sex and with baseline HAs of shortest duration and highest frequency. Response to propranolol was correlated with attacks of greatest duration at baseline and with low pulse rise with exercise at baseline. Nonspecific response was associated with male sex, most frequent HAs by history, and least frequent HAs during baseline period.	Dropouts: 24 (44%), 3 due to "toxic reactions" (not clear to which intervention); 3 of the 24 dropouts were excluded before treatment began due to a low rate of HAs during the baseline period

1 See last page of table for key to abbreviations.
2 An asterisk denotes a crossover trial.

Study	Design/ Method	Patients/ Recruit-ment	Interventions	Principal Outcomes Analyzed	Results	Dropouts/ Notes
Zuddas, Mulas, Del Zompo, et al., 1985	SPPG QS: 3 (r, db+, dnd)	N = 30 Age: 32 (range: 19-39) 100% female Migraine associated with menstrual cycle, defined as from 2 days before until 3 days after first day of cycle; half of pts experienced photophobia; HA duration range: 5-72 hrs Chron: 17 (range: 12-28) Rec: N/S	***Placebo:*** n = 15 ***Lisuride:*** Dose gradually increased until it was 0.025 mg, 3x/day on Day 7 and thereafter; n = 15 No baseline described; 3-mo treatment period; no follow-up No mention of acute migraine meds	***HA index:*** Not defined, but reported for 3 mos ***HA frequency:*** Defined as "no. of HAs in 3 mos" ***HA intensity:*** Rated on 3-point scale for 3 mos	Investigators defined success as (1) an improvement of > 40% for each outcome and (2) the disappearance of or marked improvement of menstruation-related HAs, with improvement defined as "a reduction in ***HA intensity*** rating from 3 to 1." Investigators reported that lisuride was significantly better than placebo, but did not specify the outcome being measured or a p-value. In the lisuride group, > 65% of patients improved significantly, but investigators did not specify the outcome being measured (no p-value given). In the placebo group, < 40% of pts improved on the same outcome.	Dropouts: N/S Information obtained from abstract Not clear how data obtained

[1] Key to abbreviations: ad = advertisement; AE = adverse events; a.m. = ante meridiem; ANOVA = analysis of variance; approx = approximately; ARIMA = autoregressive integrated moving average; Assoc = Association; AT = autogenic; av or avg = average; bef. = before; BF = biofeedback; CDH = chronic daily headache; Chron = chronicity; cog.-beh. = cognitive-behavioral; CrOv = crossover; db = double-blind; db+ = double-blinding described; db- = double-blinding inadequate; dd = dropouts described; DEK = dihydroergokryptine; DHE = dihydroergotamine; dnd = dropouts not described; ea. = each; ES = effect size; Excl = exclusion criteria; Fed = Federation; GP = general practice; Grp = Group; HA = headache; HCl = hydrochloride; HI = headache index; hist. = history; hr = hour; IHS = International Headache Society; in = intranasal; kg = kilogram; L = liter; L-5-HTP = oxitriptan; LA = long-acting; M = migraine; MAOI = monoamine oxidase inhibitor; max = maximum; mcg = microgram; MD = medical doctor; meds = medications; mg = milligram; MINES = Migraine-Nimodipine European Study Group; mo = month; mod = moderate; N/S = not specified; N = population size (n = sample size); N/S = not specified; n.s. = not (statistically) significant; ndb = not double-blinded; neuro. = neurology; no. = number; nr = not randomized; NSAID = nonsteroidal anti-inflammatory drug; OK = okay; OTC = over-the-counter; p.o. = per os (orally); pt = patient (or "points"); QS = quality score; r = randomized; r+ = randomization described; r- = randomization inadequate; Rec = recruitment setting; relax. = relaxation; SD = standard deviation; SEM = standard error of the mean; SPPG = single-period parallel-group; tab = tablet; tot. = total; TTH = tension-type headache; TTS = transdermal therapeutic system; U.K. = United Kingdom; Univ. = University; U.S. = United States; vs. = versus; w/ = with; w/o = without; wk = week; yr = year; µg = microgram; 5-HTP = oxitriptan

Evidence Table 2: Efficacy of Alpha-2 Agonists [1, 2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO (AND DOSING STUDIES)							
Clonidine							
Adam, Gore, and Price, 1978	Clonidine (Dixarit®), 0.075-0.150 mg/day for 6 mos	-	-	70*	-	-	n.s. (no p-value reported) HF
	Placebo	-		70*	-	-	
Boisen, Deth, Hübbe, et al., 1978	Clonidine, 0.1 mg/day for 8 wks	-	-	49*	-	13.1	n.s. (no p-value reported) HF
	Placebo	-		49*	-	13.3	
Bredfeldt, Sutherland, and Kruse, 1989,	Clonidine (Dixarit®), ≈ 0.2 mg/day via 1 transdermal (Catapres TTS-2®) patch/wk for 6 wks	-	-	30*	-	10.0	n.s. (no p-value reported) HF
	Placebo	-		30*	-	11.2	
Das, Ahuja, and Narainaswamy, 1979	Clonidine, 50 µg/day for 6 wks	-	-	20*	-	8.2	n.s. ($p > 0.05$) HF
	Placebo	-		20*	-	8.0	
Kallanranta, Hakka-rainen, Hokkanen, et al., 1977 (Study 1)	Clonidine, 75 µg/day for 4 wks	-	-	50*	3.94	2.26	0.45 (0.05 to 0.85) HF
	Placebo	-		50*	3.94	2.98	
Mondrup and Møller, 1977	Clonidine, 100 µg/day for 1 wk; dose then increased to 150 µg/day for 11 wks	-	-	21*	24.4 (median)	20.5 (median)	n.s. (no p-value reported) HF
	Placebo	-		21*	24.4 (median)	17.1 (median)	
Ryan, Diamond, and Ryan, 1975	Clonidine, 0.05-0.15 mg/day for 8 wks	-	-	133*	-	-	n.s. (no p-value reported) HI
	Placebo	-		133*	-	-	
Shafar, Tallett, and Knowlson, 1972	Clonidine, 100 µg/day for 16 wks	-	-	42*	15.07	11.12	n.s. ($p < 0.1$) HI
(Data are from group with less frequent HAs)	Placebo	-		42*	15.07	13.23	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Sjaastad and Stensrud, 1971	Clonidine (Catapresan®), 75 µg/day for 3 wks	-	-	26*	-	-	p < 0.025 (clonidine better) HI
	Placebo	-		26*	-	-	
Stensrud and Sjaastad, 1976a	Clonidine (Catapresan®), 75-150 µg/day for 7 wks	-	-	27*	10.3	11.1	p < 0.02 (clonidine better, though both *increased*) HI
	Placebo	-		27*	10.3	14.1	
Wilkinson, 1970	Clonidine, 100 µg/day for 6 wks	-	-	23*	-	-	-
	Placebo (lactose)	-		23*	-	-	
Wilkinson, 1970	Clonidine, 50 µg/day for 6 wks	-	-	23*	-	-	-
	Placebo	-		23*	-	-	
Wilkinson, 1970	Clonidine, 100 µg/day for 6 wks	-	-	23*	-	-	-
	Clonidine, 50 µg/day for 6 wks	-		23*	-	-	
Guanfacine							
Elkind, Webster, Herbertson, et al., 1989a	Guanfacine, 1.0 mg/day for 12 wks	-	-	12	-	-	p = 0.005 (guanfacine better) HF
	Placebo	-		12	-	-	
Elkind, Webster, Herbertson, et al., 1989a	Guanfacine, 0.5 mg/day for 12 wks	-	-	13	-	-	n.s. (p = 0.62) HF
	Placebo	-		12	-	-	
Elkind, Webster, Herbertson, et al., 1989a	Guanfacine, 1.0 mg/day for 12 wks	-	-	12	-	-	-
	Guanfacine, 0.5 mg/day for 12 wks	-		13	-	-	

[1]See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH ANTICONVULSANTS							
Clonidine vs. carbamazepine							
Anthony, Lance, and Somerville, 1972	Clonidine, 225 µg/day for 1 mo	16/30 (53%)	2.3 (0.80 to 6.5) ≥ 50% reduction in HF	30	-	-	n.s. (0.1 < p < 0.2) HF
	Carbamazepine, 600 mg/day for 1 mo	10/30 (33%)		30	-	-	
COMPARISONS WITH BETA-BLOCKERS							
Clonidine vs. metoprolol							
Louis, Schoenen, and Hedman, 1985a	Clonidine, 100 µg/day for 8 wks	8/29* (28%)	0.65 (0.21 to 2.0) > 50% reduction in HF	31*	11.2 (median)	10.2 (median)	p < 0.05 (metoprolol better) HI
	Metoprolol, 100 mg/day for 8 wks	10/27* (37%)		31*	11.2 (median)	8.4 (median)	
Clonidine vs. practolol							
Kallanranta, Hakka-rainen, Hokkanen, et al., 1977 (Study 2)	Clonidine, 150 µg/day for 8 wks	-	-	50*	4.0	1.88	0.21 (-0.19 to 0.60) HF
	Practolol, 150 mg/day for 8 wks	-		50*	4.0	2.49	
Clonidine vs. prindolol							
Anthony, Lance, and Somerville, 1972	Clonidine, 225 µg/day for 1 mo	16/30 (53%)	0.65 (0.24 to 1.8) ≥ 50% reduction in HF	-	-	-	-
	Prindolol, 10 mg/day for 1 mo	21/33 (64%)		-	-	-	
Clonidine vs. propranolol							
Kåss and Nestvold, 1980	Clonidine (Catapresan®), 100 µg/day for 16 wks	8/21* (38%)	0.38 (0.11 to 1.32) > 50% reduction in HF	21*	-	-	n.s. (no p-value reported) HF
	Propranolol (Inderal®), 160 mg/day for 16 wks	13/21* (62%)		21*	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH SEROTONIN ANTAGONISTS							
Clonidine vs. pizotifen							
Behan, 1985	Clonidine (Dixarit®), 100 µg/day for 1 mo; 100-150 µg/day for 2d mo	-	-	26	-	-	-
	Pizotifen (Sanomigran®), 1.5 mg/night for 1 mo; 1.5 - 3.0 mg/night for 2d mo	-		18	-	-	

[1] Key to abbreviations: HA = headache; HF = headache frequency; HI = headache index; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not significant (statistically); TTS = transdermal therapeutic system; wk = week; µg = microgram

Evidence Table 3: Efficacy of Anticonvulsants[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO (AND DOSING STUDIES)							
Divalproex sodium							
Klapper, 1996	Divalproex sodium, 1500 mg/day for 3 mos	20/44 (45%)	3.1 (1.2 to 7.9) ≥ 50% reduction in HF	44	-	1.7 (reduction from baseline)	p≤0.05 (divalproex sodium better) HF
	Placebo	9/42 (21%)		42	-	0.5 (reduction from baseline)	
Klapper, 1996	Divalproex sodium, 1000 mg/day for 3 mos	17/40 (43%)	2.7 (1.03 to 7.1) ≥ 50% reduction in HF	40	-	2.0 (reduction from baseline)	p≤0.05 (divalproex sodium better) HF
	Placebo	9/42 (21%)		42	-	0.5 (reduction from baseline)	
Klapper, 1996	Divalproex sodium, 500 mg/day for 3 mos	20/45 (44%)	2.9 (1.1 to 7.5) ≥ 50% reduction in HF	45	-	1.7 (reduction from baseline)	p≤0.05 (divalproex sodium better) HF
	Placebo	9/42 (21%)		42	-	0.5 (reduction from baseline)	
Mathew, Saper, Silberstein, et al., 1995	Divalproex sodium, 1087 mg/day (average) for 3 mos	33/69 (48%)	5.7 (1.98 to 16) ≥ 50% reduction in HF	69	6.0	3.5	p≤0.001 (divalproex sodium better) HF
	Placebo	5/36 (14%)		36	6.4	5.7	
Sodium valproate							
Hering and Kuritzky, 1992	Sodium valproate, 800 mg/day for 2 mos	-	-	29*	-	8.826	0.93 (0.39 to 1.5) HF
	Placebo	-		29*	-	15.586	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Jensen, Brinck, and Olesen, 1994	Sodium valproate (slow-release), 1000-1500 mg/day for 3 mos	22/34 (65%)	7.1 (2.4 to 21) ≥ 50% reduction in HF	34*	6.1	3.5	p=0.0018 (sodium valproate better) HF
	Placebo	7/34 (21%)		34*	6.1	6.1	
Carbamazepine							
Rompel and Bauermeister, 1970	Carbamazepine, 600 mg/day for 6 wks	26/45 (58%)	12 (3.9 to 35) Marked or complete improvement in HI	45*	-	0.67	- HF
	Placebo	5/48 (10%)		48*	-	3.87	
Clonazepam							
Stensrud and Sjaastad, 1979	Clonazepam, 1 mg/day for 1 mo	-	-	38*	-	-	p=0.20 (n.s.) HI
	Placebo	-		38*	-	-	
Gabapentin							
Wessely, Baumgartner, Klingler, et al., 1987	Gabapentin, 900 mg/day for 3 mos	-	-	14	6.5	4.1	- HF
	Placebo	-		19	4.3	4.0	
COMPARISONS WITH BETA-BLOCKERS							
Divalproex sodium vs. propranolol							
Klapper, 1994	Divalproex sodium, 1100 mg/day (average) for 2 mos	-	-	12*	-	10.9	- HF
	Propranolol, 140 mg/day (average) for 2 mos	-		12*	-	20.4	
Carbamazepine vs. prindolol							
Anthony, Lance, and Somerville, 1972	Carbamazepine, 600 mg/day for 1 mo	10/30 (33%)	0.29 (0.10 to 0.81) ≥ 50% reduction in HF	-	-	-	-
	Prindolol, 10 mg/day for 1 mo	21/33 (64%)		-	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH ALPHA-2 AGONISTS							
Carbamazepine vs. clonidine							
Anthony, Lance, and Somerville, 1972	Carbamazepine, 600 mg/day for 1 mo	10/30 (33%)	0.44 (0.15 to 1.2)	-	-	-	-
	Clonidine, 225 µg/day for 1 mo	16/30 (53%)	≥ 50% reduction in HF	-	-	-	

[1]Key to abbreviations: HF = headache frequency; HI = headache index; HS = headache severity;mg = milligram; mo = month or months; N = population studied (n = sample size); n.s. = not (statistically) significant; µg = microgram

Evidence Table 4: Efficacy of Antidepressants[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO							
Amitriptyline							
Couch and Hassanein, 1976 and 1979	Amitriptyline, 50-100 mg/day for 1 mo	26/47 (55%)	2.4 (1.1 to 5.4) ≥ 50% reduction in HI	37	112.1	68.5	0.62 (0.15 to 1.1) HI
	Placebo	18/53 (34%)		36	67.7	104.1	
Gomersall and Stuart, 1973	Amitriptyline, 30-60 mg/day for 6.5 mos (26 wks)	-	-	20*	-	207	p<0.001 (amitriptyline better) HF
	Placebo	-		20*	-	356	
Ziegler, Hurwitz, Hassanein, et al., 1987	Amitriptyline, 50-150 mg/day for 2 mos	-	-	30*	-	429.4	p<0.05 (amitriptyline better) HI
	Placebo	-		30*	-	510.8	
Clomipramine							
Langohr, Gerber, Koletzki, et al., 1985	Clomipramine, 100 mg/day (max) for 1 mo	5/20* (24%)	0.95 (0.25 to 3.6) > 50% reduction in HF	20*	-	-	n.s. (no p-value reported) HF
	Placebo	7/27* (26%)		27*	-	-	
Noone, 1980	Clomipramine, 30 mg/day for 2 mos	-	-	10*	6 (median)	3 (median)	p=0.46 (n.s) HF
	Placebo	-		10*	6 (median)	3.5 (median)	
Femoxetine							
Orholm, Honoré, and Zeeberg, 1986	Femoxetine, 200-600 mg/day for 4 mos	-	-	25	7.3 (median)	6.3 (median)	n.s. (no p-value reported) HI
	Placebo	-		28	6.8 (median)	4.5 (median)	
Zeeberg, Orholm, Dalsgaard Nielsen, et al., 1981	Femoxetine, 200-300 mg/day for 3 mos	-	-	20	-	-	p>0.10 (n.s.) HI
	Placebo	-		25	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Fluoxetine							
Adly, Straumanis, and Chesson, 1992	Fluoxetine, 20 mg every other day - 40 mg/day for 2 mos	-	-	9	32 (median)	6 (median)	p<0.05 (fluoxetine better) HI
	Placebo	-		9	35 (median)	24 (median)	
Saper, Silberstein, Lake, et al., 1994	Fluoxetine, 20 - 40 mg/day for 3 mos	-	-	31	-	-	n.s. (no p-value reported) HI
	Placebo	-		26	-	-	
Mianserin							
Monro, Swade, and Coppen, 1985	Mianserin, 30-60 mg/day for 4 mos	-	-	16	-	-	n.s. (no p-value reported) HI
	Placebo	-		18	-	-	
Opipramol							
Jacobs, 1972	Opipramol for 1.5 mos (6 wks)	-	-	13	-	2.8	0.05>p>0.02 (opipramol better) HF
	Placebo	-		12	-	-0.1	
COMPARISONS AMONG ANTIDEPRESSANTS							
Amitriptyline vs. fluvoxamine							
Bánk, 1994	Amitriptyline, 25 mg/day for 3 mos	–	-	20	0.41 (median)	0.24 (median)	- HS
	Fluvoxamine, 50 mg/day for 3 mos	–		24	0.43 (median)	0.18 (median)	
COMPARISONS WITH BETA-BLOCKERS							
Amitriptyline vs. propranolol							
Mathew, 1981 *(Migraine-only)*	Amitriptyline, 25-75 mg/day for 6 mos	-	-	32	3.93	2.28	-0.15 (-0.62 to 0.32) HI
	Propranolol, 60-160 mg/day for 6 mos	-		38	4.12	1.57	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Mathew, 1981 *(Mixed HA)*	Amitriptyline, 25-75 mg/day for 6 mos	-	-	31	7.78	3.12	0.02 (-0.46 to 0.49) HI
	Propranolol, 60-160 mg/day for 6 mos	-		38	6.70	3.24	
Ziegler, Hurwitz, Hassanein, et al., 1987 (See ET 1)	Amitriptyline, 50-150 mg/day for 2 mos	12/30* (40%)	1.33 (0.47 to 3.8) ≥ 50% reduction in HI vis-à-vis placebo	30*	-	429.4	p>0.05 (n.s) HI
	Propranolol, 80-240 mg/day for 2 mos (See ET 1)	10/30* (33%)		30*	-	404.6	
Femoxetine vs. propranolol							
Andersson and Petersen, 1981	Femoxetine, 200-400 mg/day for 3 mos	6/28* (21%)	0.49 (0.15 to 1.6) > 50% reduction in HI	28*	24.5	17.9	-0.17 (-0.70 to 0.35) HI
	Propranolol, 80-160 mg/day for 3 mos	10/28* (36%)		28*	24.5	16.0	
Kangasniemi, Nyrke, Lang, et al., 1983	Femoxetine, 200-400 mg/day for 3 mos	-	-	24*	10.30	9.68	-0.34 (-0.91 to 0.23) HI
	Propranolol, 80-160 mg/day for 3 mos	-		24*	10.30	7.07	
Clomipramine vs. metoprolol							
Langohr, Gerber, Koletzki, et al., 1985	Clomipramine, 100 mg/day (max) for 2 mos	5/20* (24%)	0.45 (0.12 to 1.7) > 50% reduction in HF	20*	-	-	p<0.05 (metoprolol better) HF
	Metoprolol, 100 mg/day (max) for 2 mos	9/21* (44%)		21*	-	-	
COMPARISONS WITH OTHER AGENTS							
Amitriptyline vs. timed-release DHE							
Bonuso, Di Stasio, Barone, et al., 1983	Amitriptyline, 75 mg/day for 2 mos	-	-	15	17.0	5.4	0.82 (0.08 to 1.6) HS
	DHE (timed-release), 10 mg/day for 2 mos	-		15	18.7	10.7	

[1] Key to abbreviations: DHE = dihydroergotamine; ET = Evidence Table; HA = headache; HF = headache frequency; HI = headache index; HS = headache severity; max. = maximum; mg = milligram; N = population studied (n = sample size); n.s. = not (statistically) significant

Evidence Table 5: Efficacy of Beta-Blockers[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO							
Propranolol							
Ahuja and Verma, 1985	Propranolol, 120 mg/day for 2 mos	-	-	26*	-	20.69	0.58 (0.02 to 1.1) HI
	Placebo	-		26*	-	38.00	
Al-Qassab and Findley, 1993	Propranolol (long-acting), 160 mg/day for 2 mos	-	-	30*	-	3.8 (median)	n.s. ($p > 0.96$) HF
	Placebo	-		30*	-	3.2 (median)	
Al-Qassab and Findley, 1993	Propranolol (long-acting), 80 mg/day for 2 mos	-	-	30*	-	3.8 (median)	n.s. ($p > 0.63$) HF
	Placebo	-		30*	-	3.2 (median)	
Børgesen, Nielsen, and Møller, 1974	Propranolol, 120 mg/day for 8 wks	15/30 (50%)	2.3 (0.81 to 6.7) ≥ 50% reduction in HF	30*	1.77	1.03	0.44 (0.09 to 0.80) HF
	Placebo	9/30 (30%)		30*	1.77	1.33	
Dahlöf, 1987	Propranolol, 120 mg/day for 1 mo	-	-	28*	-	3.2	0.52 (-0.01 to 1.1) HF †
	Placebo	-		28*	-	4.3	
Diamond and Medina, 1976	Propranolol, 80- 160 mg/day for 4 - 8 wks (patient's preference)	-	-	62*	-	-	-
	Placebo	-		62*	-	-	
Forssman, Henriksson, Johannsson, et al., 1976	Propranolol, 240 mg/day (dosage gradually increased to this level) for 10 wks	-	-	32*	5.14	3.00	0.56 (0.06 to 1.1) HI
	Placebo	-		32*	5.14	4.77	
Johnson, Hornabrook, and Lambie, 1986	Propranolol, 240 mg/day for 3 mos	-	-	17*	-	13.8	0.45 (-0.23 to 1.1) HF
	Placebo	-		17*	-	20.1	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

† Effect size calculations are based on the assumption that the data reported in the article (unlabeled) represent mean ± standard error of the mean. Under the assumption that the reported figures are standard deviations, the resulting effect size of 2.75 (95% CI: 2.1 to 3.4) makes this study an outlier.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Kuritzky and Hering, 1987	Propranolol (long-acting), 160 mg/day for 1 mo	-	-	31*	-	3.23	p=0.014 (propranolol better) HF
	Placebo	-		31*	-	5.56	
Malvea, Gwon, and Graham, 1973	Propranolol, dose N/S, for 6 wks	-	-	29*	25.4	18.6	- HI
	Placebo	-		29*	25.4	23.3	
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986	Propranolol, 120 mg/day for 3 mos	-	-	31*	-	-	0.52 (0.17 to 0.88) HF
	Placebo	-		31*	-	-	
Palferman, Gibberd, and Simmonds, 1983	Propranolol, 120 mg/day for 2 mos	-	-	10*	-	47	n.s. (p>0.05) HI
	Placebo	-		10*	-	52	
Pita, Higueras, Bolaños, et al., 1977	Propranolol, 160 mg/day for 2 mos	-	-	8*	-	2.25	1.1 (0.33 to 1.8) HF
	Placebo	-		8*	-	7.5	
Pradalier, Serratrice, Collard, et al., 1989b	Propranolol (long-acting), 160 mg/day for 12 wks	-	-	31	6.11	3.15	0.38 (-0.16 to 0.91) HF ‡
	Placebo	-		24	6.00	6.41	
Sargent, Solbach, Damasio, et al., 1985	Propranolol, 120 mg/day for 3 mos	-	-	44	-	0.21 (difference from baseline)	0.25 (-0.17 to 0.67) HF
	Placebo	-		43	-	-0.25 (difference from baseline)	
Solomon, 1986	Propranolol (long-acting), 120 mg/day for 2 mos	-	-	15*	-	4.5	p<0.05 (propranolol better) HF
	Placebo	-		15*	-	6.0	
Stensrud and Sjaastad, 1976b	Propranolol (Inderal®), 160 mg/day for 4 wks	-	-	19*	-	7.47	0.61 (0.17 to 1.05) HF
	Placebo	-		19*	-	12.32	
Stensrud and Sjaastad, 1980a	Propranolol, 160 mg/day for 6 wks	-	-	28*	-	-	n.s. (no p-value reported) HI
	Placebo	-		28*	-	-	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

‡ Effect size calculations are based upon the assumption that the data reported as standard deviations actually represent mean ± standard error of the mean. Under the assumption that the reported figures are standard deviations, the resulting effect size of 1.9 (1.2 to 2.55) makes this study an outlier.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984	Propranolol, 160 mg/day for 12 wks	48/80* (60%)	3.5 (1.8 to 6.7) ≥ 50% reduction in HF	80*	-	6.66	0.38 (0.07 to 0.70) HI
	Placebo	24/80* (30%)		80*	-	9.03	
Weber and Reinmuth, 1972	Propranolol, 80 mg/day for 3 mos	15/19 (79%)	31.5 (5.1 to 195) ≥ 50% reduction in HF	19*	-	-	-
	Placebo	2/19 (11%)		19*	-	-	
Widerøe and Vigander, 1974	Propranolol, 160 mg/day for 3 mos	-	-	26*	3.0	0.4	1.1 (0.68 to 1.4) HF
	Placebo	-		26*	3.0	1.7	
Ziegler, Hurwitz, Hassanein, et al., 1987	Propranolol, 80-240 mg/day for 2 mos	-	-	30*	-	404.6	p<0.05 (propranolol better) HI
	Placebo	-		30*	-	510.8	
Combined	***Test for homogeneity: Chi-square = 6.5, d.f.=2, p=0.04***			***Test for homogeneity: Chi-square = 15.0, d.f.=11, p=0.18***			***0.55 (0.43 to 0.68)***
Metoprolol							
Andersson, Dahl, Hansen, et al., 1983	Metoprolol, 200 mg/day (controlled release) for 2 mos	10/30 (33%)	3.9 (1.1 to 14) ≥ 50% reduction in HI	30	17.63	11.95	0.58 (0.08 to 1.1) HI
	Placebo	4/35 (11%)		35	16.33	16.51	
Kangasniemi, Andersen, Andersson, et al., 1987	Metoprolol, 200 mg/day (slow-release tabs) for 2 mos	-	-	73*	3.8 (median)	1.8 (median)	p = 0.004 (metoprolol better) HF
	Placebo	-		73*	3.8 (median)	2.5 (median)	
Langohr, Gerber, Koletzki, et al., 1985	Metoprolol, 100 mg/day (max) for 1 mo	9/21* (44%)	2.1 (0.63 to 7.2) >50% reduction in HF	21*	-	-	n.s. (no p-value reported) HF
	Placebo	7/27* (26%)		27*	-	-	
Steiner, Joseph, Hedman, et al., 1988	Metoprolol, 100 mg/day for 2 mos	-	-	28	11.2	8.2	0.16 (-0.36 to 0.67) HI
	Placebo	-		31	10.8	9.4	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Atenolol							
Forssman, Lindblad, and Zbornikova, 1983	Atenolol, 100 mg/day for 3 mos	-	-	20*	-	0.17	- HF
	Placebo	-		20*	-	0.23	
Johannsson, Nilsson, Widelius, et al., 1987	Atenolol, 100 mg/day for 3 mos	-	-	63*	-	-	p=0.004 (atenolol better) HI
	Placebo	-		63*	-	-	
Stensrud and Sjaastad, 1980a	Atenolol, 100 mg/day for 6 wks	-	-	28*	-	-	p<0.05 (atenolol better) HI
	Placebo	-		28*	-	-	
Nadolol							
Freitag and Diamond, 1984	Nadolol, 80, 160, or 240 mg/day for 4 mos (3 groups combined)	7/22 (32%)	26.6 (0.30 to 2395.0) ≥ 50% reduction in HI	24	-	-	-
	Placebo	0/8 (0%)		8	-	-	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 240 mg/day for 3 mos	-	-	20	8.45	3.28	- HF
	Placebo	-		20	6.9	4.25	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 160 mg/day for 3 mos	-	-	20	6.8	2.10	- HF
	Placebo	-		20	6.9	4.25	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 80 mg/day for 3 mos	-	-	20	6.73	4.05	- HF
	Placebo	-		20	6.9	4.25	
Sudilovsky, Stern, and Meyer, 1986b	Nadolol, 240 mg/day or 160 mg/day or 80 mg/day (results not reported separately by dose)	-	-	(Total n=154)	-	-	p<0.05 (nadolol better) HI
	Placebo	-			-	-	
Timolol							
Briggs and Millac, 1979	Timolol, 20 mg/day for 3 mos	-	-	13*	-	4.4	0.93 (0.39 to 1.5) HF
	Placebo	-		13*	-	6.8	
Stellar, Ahrens, Meibohm, et al., 1984	Timolol, 20-30 mg/day for 2 mos	40/94* (43%)	2.0 (1.1 to 3.8) ≥ 50% reduction in HF	94*	6.8	4.3	p<0.01 (timolol better) HF
	Placebo	25/94* (27%)		94*	6.8	5.0	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984	Timolol, 20 mg/day for 12 wks	44/80* (55%)	2.9 (1.5 to 5.5) ≥ 50% reduction in HF	80*	-	5.71	0.54 (0.22 to 0.85) HI
	Placebo	24/80* (30%)		80*	-	9.03	
Pindolol							
Ekbom and Lundberg, 1972	Pindolol, 15 mg/day for 1 mo	-	-	9	-	-	n.s. (no p-value reported) HI
	Placebo	-		10	-	-	
Ekbom and Lundberg, 1972	Pindolol, 7.5 mg/day for 1 mo	-	-	7	-	-	n.s. (no p-value reported) HI
	Placebo	-		10	-	-	
Sjaastad and Stensrud, 1972	Pindolol, 7.5 or 15 mg/day for 1 mo (results not reported separately by dose)	-	-	24*	-	-	0.024 (-0.38 to 0.43) HI
	Placebo	-		24*	-	-	
Other beta-blockers							
Nanda, Johnson, Gray, et al., 1978	Acebutolol, 800 mg/day for 3 mos	-	-	33*	-	-	n.s. (no p-value reported) HF
	Placebo	-		33*	-	-	
Ekbom, 1975	Alprenolol, 400 mg/day for 6 wks	-	-	28*	-	4.0	-0.05 (-0.58 to 0.47) HI
	Placebo	-		28*	-	3.8	
Ekbom and Zetterman, 1977	Oxprenolol, 240 mg/day for 2 mos	-	-	30*	-	30.9	0.15 (-0.36 to 0.65) HI
	Placebo	-		30*	-	33.9	
DOSING STUDIES							
Propranolol							
Al-Qassab and Findley, 1993	Propranolol, 160 mg/day for 2 mos	-	-	30*	-	3.8 (median)	n.s. (p > 0.75) HF
	Propranolol, 80 mg/day for 2 mos	-		30*	-	3.8 (median)	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Carroll, Reidy, Savundra, et al., 1990	Propranolol (long-acting), 160 mg/day for 12 wks	-	-	37*	6.10 (median)	3.4 (median)	p = 0.03 (propranolol LA 160 mg better) HF
	Propranolol (long-acting), 80 mg/day for 12 wks	-		37*	6.10 (median)	3.70 (median)	
Havanka-Kanniainen, Hokkanen, and Myllylä, 1988	Propranolol (long-acting), 160 mg/day for 3 mos	17/21 (81%)	0.71 (0.14 to 3.6) ≥ 50% reduction in HF (no. of attacks)	21	5.4	4.4	-0.16 (-0.76 to 0.45) HF (no. of HA days)
	Propranolol (long-acting), 80 mg/day for 3 mos	18/21 (86%)		21	6.2	5.2	
Nadolol							
Ryan, 1984	Nadolol, 160 mg/day for 3 mos	-	-	16	10.43	5.83	- HI
	Nadolol, 80 mg/day for 3 mos	-		15	12.73	4.84	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 240 mg/day for 3 mos	-	-	20	8.45	3.28	- HF
	Nadolol, 160 mg/day for 3 mos	-		20	6.8	2.10	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 240 mg/day for 3 mos	-	-	20	8.45	3.28	- HF
	Nadolol, 80 mg/day for 3 mos	-		20	6.73	4.05	
Ryan, Ryan, and Sudilovsky, 1983	Nadolol, 160 mg/day for 3 mos	-	-	20	6.8	2.10	- HF
	Nadolol, 80 mg/day for 3 mos	-		20	6.73	4.05	
Sudilovsky, Elkind, Ryan, et al., 1987	Nadolol, 160 mg/day for 2 mos	21/33 (64%)	3.5 (1.3 to 9.6) ≥ 50% reduction in HI	-	-	-	-
	Nadolol, 80 mg/day for 2 mos	11/33 (33%)		-	-	-	
Pindolol							
Ekbom and Lundberg, 1972	Pindolol, 15 mg/day for 1 mo	-	-	9	-	-	n.s. (no p-value reported) HI
	Pindolol, 7.5 mg/day for 1 mo	-		7	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS AMONG BETA-BLOCKERS							
Nadolol vs. propranolol							
Olerud, Gustavsson, and Furberg, 1986	Nadolol, 40-160 mg/day for 6 mos	5/13 (38%)	0.47 (0.10 to 2.2) HF	13	5.6 (median)	2.7 (median)	- HF
	Propranolol, 80-160 mg/day for 6 mos	8/14 (57%)		14	3.6 (median)	1.9 (median)	
Ryan, 1984	Nadolol, 160 mg/day for 3 mos	-	-	16	10.43	5.83	- HI
	Propranolol, 160 mg/day for 3 mos	-		14	14.71	8.01	
Ryan, 1984	Nadolol, 80 mg/day for 3 mos	-	-	15	12.73	4.84	- HI
	Propranolol, 160 mg/day for mos	-		14	14.71	8.01	
Sudilovsky, Elkind, Ryan, et al., 1987	Nadolol, 160 mg/day for 2 mos	21/33 (64%)	3.0 (1.04 to 8.5) ≥ 50% reduction in HI	-	-	-	-
	Propranolol, 160 mg/day for 2 mos	10/27 (37%)		-	-	-	
Sudilovsky, Elkind, Ryan, et al., 1987	Nadolol, 80 mg/day for 2 mos	11/33 (33%)	0.85 (0.29 to 2.5) ≥ 50% reduction in HI	-	-	-	-
	Propranolol, 160 mg/day for 2 mos	10/27 (37%)		-	-	-	
Metoprolol vs. propranolol							
Gerber, Diener, Scholz, et al., 1991	Metoprolol, 50-200 mg/day (see ET 1) for 6 mos	-	-	22?	-	-	p>0.05 (n.s) HF
	Propranolol, 40-160 mg/day (see ET 1) for 6 mos	-		19?	-	-	
Kangasniemi and Hedman, 1984	Metoprolol (controlled-release), 200 mg/day for 8 wks	17/34* (50%)	1.2 (0.46 to 3.1) HI	34*	9.7	4.9	0.15 (-0.33 to 0.63) HI
	Propranolol, 160 mg/day for 8 wks	15/33* (45%)		33*	9.7	5.4	
Olsson, Behring, Forssman, et al., 1984	Metoprolol, 100 mg/day for 8 wks	21/56* (37%)	1.4 (0.62 to 3.1) HI	56*	-	-	-
	Propranolol, 80mg/day for 8 wks	16/53* (30%)		53*	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Steardo, Bonuso, Di Stasio, et al., 1982	Metoprolol, 300 mg/day for 6 mos	1/16 (6%)	0.03 (0.004 to 0.29) ≥ 50% reduction in HF	16	-	16.13	-1.3 (-2.0 to 0.62) HF
	Propranolol, 120 mg/day for 6 mos	16/24 (67%)		24	-	7.67	
Atenolol vs. propranolol							
Stensrud and Sjaastad, 1980a	Atenolol, 100 mg/day for 6 wks	-	-	28*	-	-	n.s. (no p-value reported) HI
	Propranolol, 160 mg/day for 6 wks	-		28*	-	-	
Timolol vs. propranolol							
Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984	Timolol, 20 mg/day for 12 wks	44/80* (55%)	0.81 (0.43 to 1.5) ≥ 50% reduction in HF	80*	-	5.71	0.15 (-0.16 to 0.46) HI
	Propranolol, 160 mg/day for 12 wks	48/80* (60%)		80*	-	6.66	
Bisoprolol vs. metoprolol							
Wörz, Reinhardt-Benmalek, Foeh, et al., 1992	Bisoprolol, 5 mg/day for 3 mos	41/78* (53%)	1.05 (0.56 to 2.0) ≥ 50% reduction in HF	78*	4.0	2.05	-0.04 (-0.35 to 0.28) HF
	Metoprolol, 100 mg/day for 3 mos	40/78* (51%)		78*	4.0	1.99	
COMPARISONS WITH CALCIUM ANTAGONISTS							
Propranolol vs. flunarizine							
Gawel, Kreeft, Nelson, et al., 1992	Propranolol, 160 mg/day (max) for 4 mos	-	-	45	-	-0.20 (difference from baseline)	0.064 (-0.35 to 0.48) HS
	Flunarizine, 10 mg/day for 4 mos	-		44	-	-0.02 (difference from baseline)	
Lücking, Oestreich, Schmidt, et al., 1988 (Study 1)	Propranolol, 120 mg/day for 4 mos	-	-	170	6	4	0 (-0.21 to 0.21) HF
	Flunarizine, 10 mg/day for 4 mos	-		166	6	4	
Lücking, Oestreich, Schmidt, et al., 1988 (Study 2)	Propranolol, 120 mg/day for 4 mos	-	-	34	5	3	-0.13 (-0.60 to 0.34) HF
	Flunarizine, 10 mg/day for 4 mos	-		35	6	4	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Ludin, 1989	Propranolol, 120 mg/day for 4 mos	-	-	32	121.4	66.9	0.16 (-0.68 to 1.0) HI
	Flunarizine, 10 mg/day for 4 mos	-		27	92.9	93.0	
Shimell, Fritz, and Levien, 1990	Propranolol, 180 mg/day for 4 mos	-	-	29	5.71	1.17	n.s. (no p-value reported) HF
	Flunarizine, 10 mg/day for 4 mos	-		28	4.57	1.35	
Propranolol vs. nifedipine							
Albers, Simon, Hamik, et al., 1989	Propranolol, 120-180 mg/day for 6 mos	-	-	12	6.1	2.2	0.68 (-0.27 to 1.64) HF
	Nifedipine, 60-90 mg/day for 6 mos	-		7	3.6	1.5	
Gerber, Diener, Scholz, et al., 1991	Propranolol, 40-160 mg/day (see ET 1) for 6 mos	-	-	19?	-	-	p>0.05 (n.s.) HF
	Nifedipine, 10-40 mg/day (see ET 1) for 6 mos	-		17?	-	-	
Propranolol vs. cyclandelate							
Gerber, Schellenberg, Thom, et al., 1995	Propranolol, 120-160 mg/day (see ET 1) for 4 mos	18/34 (53%)	0.45 (0.16 to 1.3) ≥ 50% reduction in HF	34	5.7	3.1	n.s. (no p-value reported) HF
	Cyclandelate, 1200-1600 mg/day (see ET 1) for 4 mos	20/28 (71%)		28	6.3	2.7	
Propranolol vs. nimodipine							
Formisano, Falaschi, Cerbo, et al., 1991	Propranolol, 120 mg/day for 4 mos	-	-	8	5.0	2.6	0.13 (-0.78 to 1.0) HF
	Nimodipine, 120 mg/day for 4 mos	-		11	4.0	2.9	
Propranolol vs. verapamil							
Solomon, 1986	Propranolol (long-acting), 120 mg/day for 2 mos	-	-	15*	-	4.5	n.s. (no p-value reported) HF
	Verapamil, 240 mg/day for 2 mos	-		15*	-	5.0	
Metoprolol vs. flunarizine							
Grotemeyer, Schlake, Husstedt, et al., 1987	Metoprolol, 200 mg/day for 3 mos	12/24* (50%)	2.4 (0.74 to 8.0) ≥ 50% reduction in HF	-	-	-	-
	Flunarizine, 10 mg/day for 3 mos	7/24* (29%)		-	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Sørensen, Larsen, Rasmussen, et al., 1991	Metoprolol, 200 mg/day for 5 mos	-	-	69	-	-1.5 (change from baseline)	-0.22 (-0.57 to 0.13) HF
	Flunarizine, 10 mg/day for 5 mos	-		58	-	-2.2 (change from baseline)	
Metoprolol vs. nifedipine							
Gerber, Diener, Scholz, et al., 1991	Metoprolol, 50-200 mg/day (see ET 1) for 6 mos	-	-	22?	-	-	p<0.05 (metoprolol better) HF
	Nifedipine, 10-40 mg/day (see ET 1) for 6 mos	-		17?	-	-	
COMPARISONS WITH ANTIDEPRESSANTS							
Propranolol vs. amitriptyline							
Mathew, 1981 *(Migraine-only)*	Propranolol, 60-160 mg/day for 6 mos	-	-	38	4.12	1.57	0.15 (-0.32 to 0.62) HI
	Amitriptyline, 25-75 mg/day for 6 mos	-		32	3.93	2.28	
Mathew, 1981 *(Mixed HA)*	Propranolol, 60-160 mg/day for 6 mos	-	-	38	6.70	3.24	-0.0016 (-0.49 to 0.46) HI
	Amitriptyline, 25-75 mg/day for 6 mos	-		31	7.78	3.12	
Ziegler, Hurwitz, Hassanein, et al., 1987	Propranolol, 80-240 mg/day for 2 mos	10/30* (33%)	0.75 (0.26 to 2.2) ≥ 50% reduction in HI compared to placebo	30*	-	404.6	p>0.05 (n.s.) HI
	Amitriptyline, 50-150 mg/day for 2 mos	12/30* (40%)		30*	-	429.4	
Propranolol vs. femoxetine							
Andersson and Petersen, 1981	Propranolol, 80-160 mg/day for 3 mos	10/28* (36%)	2.0 (0.62 to 6.7) > 50% reduction in HI	28*	24.5	16.0	0.17 (-0.35 to 0.70) HI
	Femoxetine, 200-400 mg/day for 3 mos	6/28* (21%)		28*	24.5	17.9	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Kangasniemi, Nyrke, Lang, et al., 1983	Propranolol, 80-160 mg/day for 3 mos	-	-	24*	10.30	7.07	0.34 (-0.23 to 0.91) HI
	Femoxetine, 200-400 mg/day for 3 mos	-		24*	10.30	9.68	
Metoprolol vs. clomipramine							
Langohr, Gerber, Koletzki, et al., 1985	Metoprolol, 100 mg/day (max) for 1 mo	9/21* (44%)	2.2 (0.59 to 8.5) >50% reduction in HF	21*	-	-	p<0.05 (metoprolol better) HF
	Clomipramine, 100 mg/day (max) for 1 mo	5/20* (24%)		20*	-	-	
COMPARISONS WITH NSAIDs							
Metoprolol vs. aspirin							
Grotemeyer, Scharafinski, Schlake, et al., 1990	Metoprolol, 200 mg/day for 3 mos	14/21* (67%)	12 (2.6 to 54) > 50% reduction in HF	21*	2.0	1.6	-0.33 (-0.94 to 0.28) HS
	Aspirin, 1500 mg/day	3/21* (14%)		21*	2.0	1.4	
Propranolol vs. tolfenamic acid							
Kjærsgård-Rasmussen, Holt-Larsen, Borg, et al., 1994	Propranolol, 120 mg/day for 3 mos	-	-	29	-	-6.9 (difference from baseline)	0.24 (-0.76 to 0.29) HI
	Tolfenamic acid, 300 mg/day for 3 mos	-		27	-	-15.7 (difference from baseline)	
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986	Propranolol, 120 mg/day for 3 mos	-	-	31*	-	-	0.05 (-0.30 to 0.40) HF
	Tolfenamic acid, 300 mg/day for 3 mos	-		31*	-	-	
Propranolol vs. aspirin							
Baldrati, Cortelli, Procaccianti, et al., 1983	Propranolol, approx. 120 mg/day (avg) for 3 mos	9/12* (75%)	1.0 (0.16 to 6.3) > 50% reduction in HI	12*	-	-	0.01 (-0.55 to 0.58) HI
	Aspirin, approx. 975 mg/day (avg) for 3 mos	9/12* (75%)		12*	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Propranolol vs. mefenamic acid							
Johnson, Hornabrook, and Lambie, 1986	Propranolol, 240 mg/day for 3 mos	-	-	17*	-	13.8	-0.06 (-0.74 to 0.61) HF
	Mefenamic acid, 1500 mg/day for 3 mos	-		17*	-	12.9	
Propranolol vs. naproxen sodium							
Sargent, Solbach, Damasio, et al., 1985	Propranolol, 120 mg/day for 3 mos	-	-	44	-	0.21 (difference from baseline)	0.37 (-0.05 to 0.80) HF
	Naproxen sodium, 1100 mg/day for 3 mos	-		42	-	-0.48 (difference from baseline)	
COMPARISONS WITH ANTICONVULSANTS							
Propranolol vs. divalproex sodium							
Klapper, 1994	Propranolol, 140 mg/day (avg) for 2 mos	-	-	12*	-	20.4	- HF
	Divalproex sodium, 1100 mg/day (avg) for 2 mos	-		12*	-	10.9	
Prindolol vs. carbamazepine							
Anthony, Lance, and Somerville, 1972	Prindolol, 10 mg/day for 1 mo	21/33 (64%)	3.5 (1.2 to 9.9) ≥ 50% reduction in HF	-	-	-	-
	Carbamazepine, 600 mg/day for 1 mo	10/30 (33%)		-	-	-	
COMPARISONS WITH METHYSERGIDE							
Propranolol vs. methysergide							
Behan and Reid, 1980	Propranolol, 120 mg/day for 3 mos	19/36* (53%)	1.7 (0.68 to 4.3) ≥ 50% reduction in HF	-	-	-	-
	Methysergide, 3 mg/day for 3 mos	15/38* (39%)		-	-	-	
Steardo, Bonuso, Di Stasio, et al., 1982	Propranolol, 120 mg/day for 6 mos	16/24 (67%)	1.6 (0.49 to 5.0) ≥ 50% reduction in HF	24	-	7.67	0.51 (-0.06 to 1.1) HF
	Methysergide, 6-10 mg/day for 6 mos	14/25 (56%)		25	-	10.92	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Metoprolol vs. methysergide							
Steardo, Bonuso, Di Stasio, et al., 1982	Metoprolol, 300 mg/day for 6 mos	1/16 (6%)	0.05 (0.01 to 0.45) ≥ 50% reduction in HF	16	-	16.13	-0.81 (-1.5 to -0.16) HF
	Methysergide, 6-10 mg/day for 6 mos	14/25 (56%)		25	-	10.92	
COMPARISONS WITH ALPHA-2 AGONISTS							
Metoprolol vs. clonidine							
Louis, Schoenen, and Hedman, 1985a	Metoprolol, 100 mg/day for 8 wks	10/27* (37%)	1.5 (0.50 to 4.8) >50% reduction in HF	31*	11.2 (median)	8.4 (median)	p<0.05 (metoprolol better) HI
	Clonidine, 100 µg/day for 8 wks	8/29* (28%)		31*	11.2 (median)	10.2 (median)	
Practolol vs. clonidine							
Kallanranta, Hakkarainen, Hokkanen, et al., 1977 (Study 2)	Practolol, 150 mg/day for 8 wks	-	-	50*	4.0	2.49	-0.21 (-0.60 to 0.19) HF
	Clonidine, 150 µg/day for 8 wks	-		50*	4.0	1.88	
Prindolol vs. clonidine							
Anthony, Lance, and Somerville, 1972	Prindolol, 10 mg/day for 1 mo	21/33 (64%)	1.5 (0.56 to 4.2) ≥ 50% reduction in HF	-	-	-	-
	Clonidine, 225 µg/day for 1 mo	16/30 (53%)		-	-	-	
Propranolol vs. clonidine							
Kåss and Nestvold, 1980	Propranolol (Inderal®), 160 mg/day for 4 mos	13/21* (62%)	2.6 (0.76 to 9.2) >50% reduction in HF	21*	-	-	n.s. (no p-value reported) HF
	Clonidine (Catapresan®), 100 mg/day for 4 mos	8/21* (38%)		21*	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH SEROTONIN ANTAGONISTS							
Metoprolol vs. pizotifen							
Vilming, Standnes, and Hedman, 1985	Metoprolol, 100 mg/day for 8 wks	10/34* (29%)	0.57 (0.21 to 1.6) ≥ 50% reduction in HI	30*	13.0 (median)	8.6 (median)	n.s. (p>0.05) HI
	Pizotifen, 0.5 mg/day, gradually increased to 1.5 mg/day for 8 wks	14/33* (42%)		30*	13.0 (median)	7.1 (median)	

[1] Key to abbreviations: avg = average; d.f. = degrees of freedom; ET = Evidence Table; HA = headache; HF = headache frequency; HI = headache index; HS = headache severity; LA = long-acting; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not (statistically) significant; N/S = not specified; wk = week; µg = microgram

Evidence Table 6: Efficacy of Calcium Antagonists[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO (AND DOSING STUDIES)							
Flunarizine							
Al Deeb, Biary, Bahou, et al., 1992	Flunarizine, 10 mg/day for 3 mos	6/21 (29%)	1.3 (0.32 to 5.1) ≥ 50% reduction in HS	21	13.75	9.9	0.24 (-0.37 to 0.84) HF
	Placebo	5/21 (24%)		21	9.83	7.86	
Diamond and Freitag, 1993	Flunarizine, 10 mg/day for 5 mos	20/50 (40%)	1.3 (0.59 to 3.0) ≥ 50% reduction in HF or HS	50	-	-2.083 (change from baseline)	0.37 (-0.02 to 0.77) HI
	Placebo	17/51 (33%)		51	-	-0.640 (change from baseline)	
Frenken and Nuijten, 1984	Flunarizine, 10 mg/day for 3 mos	-	-	17	3.3	0.8	n.s. (p=0.029) HF
	Placebo	-		18	3.8	2.6	
Louis, 1981	Flunarizine, 10 mg/day for 3 mos	-	-	29	-	-	1.2 (0.69 to 1.7) HF
	Placebo	-		29	-	-	
Mendenopoulos, Manafi, Logothetis, et al., 1985	Flunarizine, 10 mg/day for 3 mos	-	-	9	34.7	6.2	0.99 (0.05 to 1.92) HI
	Placebo	-		11	37.0	61.6	
Pini, Ferrari, Guidetti, et al., 1985	Flunarizine, 20 mg/day for 2 wks; then 10 mg/day for "up to 120 days"	-	-	14	0.54	0.31	0.02 (-0.72 to 0.76) HI
	Placebo	-		14	0.33	0.30	
Sørensen, Hansen, and Olesen, 1986	Flunarizine, 10 mg/day for 5 mos	-	-	29*	-	-	0.26 (-0.11 to 0.63) HI
	Placebo	-		29*	-	-	
Thomas, Behari, and Ahuja, 1991	Flunarizine, 10 mg/day for 3 mos	12/15* (80%)	6.0 (1.2 to 30) ≥ 50% reduction in HI	15*	8.10	2.84	0.87 (0.12 to 1.61) HI
	Placebo	6/15* (40%)		15*	8.10	6.30	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Bassi, Brunati, Rapuzzi, et al., 1992	Flunarizine, 10 mg/day for 4 mos	-	-	14	-	-	n.s. (no p-value reported) HI
	Flunarizine, 10 mg/day for 1 wk, then 3 mg/day for 4 mos	-		15	-	-	
Nimodipine							
Ansell, Fazzone, Festenstein, et al., 1988	Nimodipine, 120 mg/day for 4 mos	-	-	30	-	-	n.s. (no p-value reported) HI
	Placebo	-		27	-	-	
Gelmers, 1983	Nimodipine, 120 mg/day for 3 mos	-	-	28	56	19	0.78 (0.20 to 1.4) HI
	Placebo	-		22	72	53	
Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b	Nimodipine, 120 mg/day for 2 mos	-	-	29*	-	10.3	0.85 (0.31 to 1.4) HI
	Placebo	-		29*	-	13.7	
Migraine-Nimodipine European Study Group (MINES), 1989a	Nimodipine, 120 mg/day for 3 mos	-	-	43	7.7	2.1	n.s. (no p-value reported) HI
	Placebo	-		46	8.1	0.9	
Migraine-Nimodipine European Study Group (MINES), 1989b	Nimodipine, 120 mg/day for 3 mos	-	-	94	9.27	4.19	p=0.91 (n.s.) HI
	Placebo	-		98	8.78	3.87	
Meyer and Hardenberg, 1983	Nimodipine, 120 mg/day for 2 mos	-	-	27*	-	-	n.s. (no p-value reported) HF
	Nimodipine, 60 mg/day for 2 mos	-		27*	-	-	
Verapamil							
Markley, Cheronis, and Piepho, 1984	Verapamil, 240 mg/day for 2 mos	-	-	14*	-	72.6	1.14 (0.34 to 1.94) HI
	Placebo	-		14*	-	116.4	
Solomon, Steel, and Spaccavento, 1983	Verapamil, 320 mg/day for 3 mos	-	-	12*	-	0.44	0.38 (-0.43 to 1.18) HI
	Placebo	-		12*	-	0.61	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Solomon, 1986	Verapamil, 240 mg/day for 2 mos	-	-	15*	-	5.0	n.s. (p>0.05) HF
	Placebo	-		15*	-	6.0	
Nifedipine							
McArthur, Marek, Pestronk, et al., 1989	Nifedipine, 60-90 mg/day for 3 mos	-	-	14*	-	1.9	0.12 (-0.62 to 0.86) HF
	Placebo	-		14*	-	2.1	
Shukla, Garg, Nag, et al., 1995	Nifedipine, 15 mg/day for 2 mos	-	-	28*	808.6	616.4	0.17 (-0.35 to 0.70) HI
	Placebo	-		28*	808.6	750.6	
Nicardipine							
Leandri, Rigardo, Schizzi, et al., 1990	Nicardipine, 40 mg/day for 2 mos	-	-	30*	12.61	2.35	0.47 (-0.05 to 0.98) HI
	Placebo	-		30*	12.61	8.09	
COMPARISONS AMONG CALCIUM ANTAGONISTS							
Nimodipine vs. flunarizine							
Bussone, Baldini, D'Andrea, et al., 1987	Nimodipine, 120 mg/day for 3 mos	6/14 (43%)	1.3 (0.29 to 5.4) ≥ 50% reduction in HI	12	258.4	116.9	0.22 (-0.56 to 1.01) HI
	Flunarizine, 10 mg/day for 3 mos	6/16 (38%)		13	286.6	200.4	
Nifedipine vs. flunarizine							
Lamsudin and Sadjimin, 1993	Nifedipine, 20 mg/day for 3 mos	-	-	38	26.28	9.07	-0.082 (-0.66 to 0.50) HI
	Flunarizine, 10 mg/day for 3 mos	-		40	26.41	6.69	
Cyclandelate vs. flunarizine							
Nappi, Sandrini, Savoini, et al., 1987	Cyclandelate, 1600 mg/day for 3 mos	-	-	19	-	-	p<0.02 (flunarizine better) HI
	Flunarizine, 5 mg/day for 3 mos	-		18	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH BETA-BLOCKERS							
Flunarizine vs. propranolol							
Gawel, Kreeft, Nelson, et al., 1992	Flunarizine, 10 mg/day for 4 mos	-	-	44	-	-0.02 (difference from baseline)	-0.064 (-0.48 to 0.35) HS
	Propranolol, 160 mg/day (max) for 4 mos	-		45	-	-0.20 (difference from baseline)	
Lücking, Oestreich, Schmidt, et al., 1988 (Study 1)	Flunarizine, 10 mg/day for 4 mos	-	-	166	6	4	0 (-0.21 to 0.21) HF
	Propranolol, 120 mg/day for 4 mos	-		170	6	4	
Lücking, Oestreich, Schmidt, et al., 1988 (Study 2)	Flunarizine, 10 mg/day for 4 mos	-	-	35	6	4	0.13 (-0.34 to 0.60) HF
	Propranolol, 120 mg/day for 4 mos	-		34	5	3	
Ludin, 1989	Flunarizine, 10 mg/day for 4 mos	-	-	27	92.9	93.0	-0.16 (-1.0 to 0.68) HI
	Propranolol, 120 mg/day for 4 mos	-		32	121.4	66.9	
Shimell, Fritz, and Levien, 1990	Flunarizine, 10 mg/day for 4 mos	-	-	28	4.57	1.35	n.s. (no p-value reported) HF
	Propranolol, 180 mg/day for 4 mos	-		29	5.71	1.17	
Flunarizine vs. metoprolol							
Grotemeyer, Schlake, Husstedt, et al., 1987	Flunarizine, 10 mg/day for 3 mos	7/24* (29%)	0.41 (0.13 to 1.4) ≥ 50% reduction in HF	-	-	-	-
	Metoprolol, 200 mg/day for 3 mos	12/24* (50%)		-	-	-	
Sørensen, Larsen, Rasmussen, et al., 1991	Flunarizine, 10 mg/day for 5 mos	-	-	58	-	-2.2 (change from baseline)	0.22 (-0.13 to 0.57) HF
	Metoprolol, 200 mg/day for 5 mos	-		69	-	-1.5 (change from baseline)	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Nifedipine vs. propranolol							
Albers, Simon, Hamik, et al., 1989	Nifedipine, 60-90 mg/day for 6 mos	-	-	7	3.6	1.5	-0.68 (-1.64 to 0.27) HF
	Propranolol, 120-180 mg/day for 6 mos	-		12	6.1	2.2	
Gerber, Diener, Scholz, et al., 1991	Nifedipine, 10-40 mg/day for 6 mos (See ET 1)	-	-	17?	-	-	p>0.05 (n.s.) HF
	Propranolol, 40-160 mg/day for 6 mos (See ET 1)	-		19?	-	-	
Nifedipine vs. metoprolol							
Gerber, Diener, Scholz, et al., 1991	Nifedipine, 10-40 mg/day for 6 mos (See ET 1)	-	-	17?	-	-	p<0.05 (metoprolol better) HF
	Metoprolol, 50-200 mg/day for 6 mos (See ET 1)	-		22?	-	-	
Nimodipine vs. propranolol							
Formisano, Falaschi, Cerbo, et al., 1991	Nimodipine, 120 mg/day for 4 mos	-	-	11	4.0	2.9	-0.13 (-1.0 to 0.78) HF
	Propranolol, 120 mg/day for 4 mos	-		8	5.0	2.6	
Verapamil vs. propranolol							
Solomon, 1986	Verapamil, 240 mg/day for 2 mos	-	-	15*	-	5.0	n.s. (no p-value reported) HF
	Propranolol, 120 mg/day for 2 mos	-		15*	-	4.5	
Cyclandelate vs. propranolol							
Gerber, Schellenberg, Thom, et al., 1995	Cyclandelate, 1200-1600 mg/day for 2 mos (See ET 1)	20/28 (71%)	2.2 (0.77 to 6.4) ≥ 50% reduction in HF	28	6.3	2.7	n.s. (no p-value reported) HF
	Propranolol, 120-160 mg/day for 2 mos (See ET 1)	18/34 (53%)		34	5.7	3.1	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH SEROTONIN ANTAGONISTS							
Flunarizine vs. pizotifen							
Cerbo, Casacchia, Formisano, et al., 1986	Flunarizine, 15 mg/day for 2 mos	-	-	21*	-	-	n.s. (no p-value reported) HI
	Pizotifen, 1.5 mg/day for 2 mos	-		21*	-	-	
Louis and Spierings, 1982	Flunarizine, 10 mg/day for 4 mos	-	-	36	-	-	n.s. (no p-value reported) HF
	Pizotifen, 2-3 mg/day for 4 mos	-		30	-	-	
Rascol, Montastruc, and Rascol, 1986	Flunarizine, 10 mg/day for 4 mos	-	-	21	-	-	n.s. (no p-value reported) HF
	Pizotifen, 2.19 mg/day for 4 mos	-		14	-	-	
Nimodipine vs. pizotifen							
Gawel, 1987	Nimodipine, 120 mg/day for 3 mos	-	-	25	7.56	6.04	-0.11 (-0.64 to 0.42) HF
	Pizotifen, 3 mg/day for 3 mos	-		29	7.55	6.65	
Havanka-Kanniainen, Hokkanen, and Myllyiä, 1987	Nimodipine, 120 mg/day for 3 mos	-	-	43*	6.2	2.3	0.11 (-0.31 to 0.54) HF
	Pizotifen, 1.5 mg/day for 3 mos	-		43*	6.2	2.6	
Micieli, Trucco, Agostinis, et al., 1985	Nimodipine, 120 mg/day for 3 mos	-	-	20*	-	-	n.s. (no p-value reported) HI
	Pizotifen, 1.5 mg/day for 3 mos	-		20*	-	-	
Cyclandelate vs. pizotifen							
Mastrosimone, Iaccarino, and de Caterina, 1992	Cyclandelate, 1600 mg/day for 3 mos	-	-	35	-	-	p<0.001 (cyclandelate better) HI
	Pizotifen, 1.5 mg/day for 3 mos	-		26	-	-	
COMPARISONS WITH OTHER (MISCELLANEOUS) AGENTS							
Flunarizine vs. dihydroergokryptine (DEK)							
Agnoli, Bussone, Mailland, et al., 1991	Flunarizine, 5 mg/day for 6 mos	4/41 (10%)	1.4 (0.30 to 6.7) ≥ 50% reduction in HF	41	6.4	-	p=0.025 (DEK better) HF
	DEK, 20 mg/day for 6 mos	3/42 (7%)		42	6.4	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio or p-value	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Flunarizine vs. methysergide							
Steardo, Marano, Barone, et al., 1986	Flunarizine, 10 mg/day for 5 mos	-	-	53?	-	-	n.s. (no p-value reported) HF
	Methysergide, 6 mg/day for 5 mos	-		51?	-	-	
Flunarizine vs. etilefrine pivalate							
Grotemeyer, Schlake, and Husstedt, 1989	Flunarizine, 5 mg/day for 2 mos; then for 3 mos both treatments are compared (See ET 1)	-	-	?	-	-	-
	Etilefrine pivalate, 20 mg/day for 3 mos, during which both treatments are compared (See ET 1)	-		?	-	-	

[1] Key to abbreviations: DEK = dihydroergokryptine; ET = Evidence Table; HF = headache frequency; HI = headache index; HS = headache severity; max. = maximum; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not (statistically) significant; N/S = not specified; wk = week; µg = microgram

Evidence Table 7: Efficacy of Ergots[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO							
Cafergot comp.® (1 cap = ergotamine 1 mg + caffeine 100 mg + butalbital 50 mg + belladonna alkaloids 0.125 mg):							
Kallos and Kallos-Deffner, 1971	Cafergot comp.®, 2 caps/day, perimenstrually, for 2 menstrual cycles (see Evidence Table 1 for details)	-	-	20*	-	0.35	- HF
	Placebo	-		20*	-	1.55	
Dihydroergotamine (DHE)							
Autret and de Chasteigner, 1987	DHE (timed-release), 10 mg/day for 2 mos	-	-	58	-	1.98 (reduction from baseline)	0.60 (0.23 to 0.98) HI
	Placebo	-		57	-	0.058 (reduction from baseline)	
Martucci, Manna, Mattesi, et al., 1983	DHE (timed-release), 10 mg/day for 45 days	-	-	79*	-	-	- HI
	Placebo	-		79*	-	-	
Neuman, Demarez, Harmey, et al., 1986	DHE (timed-release), 10 mg/day for 1 mo	-	-	20	3.3	1.3	2.1 (1.3 to 2.8) HF
	Placebo	-		20	3.3	3.0	
DHE + aspirin							
Bousser, Chick, Fuseau, et al., 1988	DHE + aspirin (timed-release), 10 mg + 80 mg/day for 2 mos	-	-	38*	-	11.5	0.62 (0.16 to 1.1) HF
	Placebo	-		38*	-	16.6	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Preceding page blank

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Dihydroergokryptine (DEK)							
Canonico, Scapagnini, Genazzani, et al., 1989	DEK, 20 mg/day for 2 mos	-	-	102*	-	-	- HI
	Placebo	-		102*	-	-	
Fiorini, Sances, Martignoni, et al., 1991	DEK, 20 mg/day for 2 menstrual cycles	-	-	10	-	32.9	0.93 (-0.02 to 1.9) HI
	Placebo	-		9	-	60.8	
DOSING STUDIES							
DHE							
Buscaino, Sorge, Bussone, et al., 1991	DHE, 10 mg/day (1 x 10 mg) for 2 mos	-	-	45	-	-	n.s. (no p-value reported) HI
	DHE, 10 mg/day (2 x 5 mg) for 2 mos	-		45	-	-	
Ergotamine							
Barrie, Fox, Weatherall, et al., 1968	Ergotamine, 1 mg/day for 1 mo	-	-	15	-	-	-
	Ergotamine, 0.5 mg/day for 1 mo	-		17	-	-	
COMPARISONS AMONG ERGOTS							
DEK vs. DHE							
Frediani, Grazzi, Zanotti, et al., 1991	DEK, 20 mg/day for 4 mos	-	-	-	-	-	- HI
	DHE (timed-release), 10 mg/day for 4 mos	-		-	-	-	
COMPARISONS WITH ANTIDEPRESSANTS							
DHE vs. amitriptyline							
Bonuso, Di Stasio, Barone, et al., 1983	DHE (timed-release), 10 mg/day for 2 mos	-	-	15	18.7	10.7	-0.82 (-1.6 to -0.08) HS
	Amitriptyline, 75 mg/day for 2 mos	-		15	17.0	5.4	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH CALCIUM ANTAGONISTS							
DEK vs. flunarizine							
Agnoli, Bussone, Mailland, et al., 1991	DEK, 20 mg/day for 6 mos	3/42 (7%)	0.71 (0.15 to 3.4) ≥ 50% reduction in HF	42	-	-	p=0.025 (DEK better) HF
	Flunarizine, 5 mg/day for 6 mos	4/41 (10%)		41	-	-	
COMPARISONS WITH METHYSERGIDE							
DEK vs. methysergide							
Cangi, Boccuni, Zanotti, et al., 1989	DEK, 20 mg/day for 2 mos	-	-	11	9.8	6.8	-0.22 (-1.1 to 0.61) HF
	Methysergide, 2 mg/day for 2 mos	-		11	8.6	6.0	
Ergotamine vs. methysergide							
Barrie, Fox, Weatherall, et al., 1968	Ergotamine, 0.5 mg/day or 1 mg/day for 1 mo	-	-	17 or 15	-	-	-
	Methysergide, 3 mg/day or 6 mg/day for 1 mo	-		16 or 11	-	-	

Key to abbreviations: cap = capsule; caps = capsules; DEK = dihydroergokryptine; DHE = dihydroergotamine; HF = headache frequency; HI = headache index; HS = headache severity;mg = milligram; mo = month; mos = months; N or n = sample size; n.s. = not (statistically) significant

Evidence Table 8: Efficacy of Methysergide[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO							
Lance, Fine, and Curran, 1963	Methysergide, 6 mg/day for 4 wks	38/56 (68%)	8.1 (3.0 to 22) ≥ 50% reduction in HF	-	-	-	-
	Placebo	7/34 (21%)		-	-	-	
Pedersen and Møller, 1966	Methysergide (prolonged-action), 6 mg/day for 6 wks	34/60* (57%)	3.6 (1.7 to 7.7) ≥ 50% reduction in HF	60*	-	-	0.22 (-0.04 to 0.47) Mean within-patient difference in HF
	Placebo	16/60* (27%)		60*	-	-	
Ryan, 1968	Methysergide, 4 mg/day for 4 wks	-	-	62*	-	11.3	- HI
	Placebo	-		62*	-	17.0	
Shekelle and Ostfeld, 1964	Methysergide, 6 mg/day for 5 wks	-	-	13*	-	-	1.02 (0.48 to 1.6) Mean within-patient difference in HF
	Placebo	-		13*	-	-	
Barrie, Fox, Weatherall, et al., 1968	Methysergide, 6 mg/day for 1 mo	-	-	-	-	-	-
	Methysergide, 3 mg/day for 1 mo	-		-	-	-	
COMPARISONS WITH SEROTONIN ANTAGONISTS							
Vs. pizotifen							
Andersson, 1973	Methysergide, 4 mg/day for 3 mos	15/48* (31%)	0.73 (0.31 to 1.7) > 50% reduction in HF	48*	5.9	4.1	-0.17 (-0.57 to 0.23) HF
	Pizotifen, 2 mg/day for 3 mos	18/47* (38%)		47*	5.9	3.5	
Forssman, Henriksson, and Kihlstrand, 1972	Methysergide, 4-6 mg/day for 10 wks	-	-	17*	3.5	1.8	n.s. (no p-value reported) HI
	Pizotifen, 2-3 mg/day for 10 wks	-		17*	3.5	2.1	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Presthus, 1971	Methysergide, 3 mg/day for 5 wks	-	-	19*	-	-	-0.29 (-0.76 to 0.17) Mean within-patient difference in HF
	Pizotifen, 1.5 mg/day for 5 wks	-		19*	-	-	
Ryan, 1968	Methysergide, 4 mg/day for 4 wks	-	-	62*	-	11.3	- HI
	Pizotifen, 4 mg/day for 4 wks	-		62*	-	8.9	
Vs. Oxitriptan							
Sicuteri, 1973	Methysergide, 2 mg/day for 40 days	-	-	20	-	5.9 (mean within-patient difference, pre- to post-treatment)	0.09 (-0.53 to 0.71) HI
	Oxitriptan, 200 mg/day for 40 days	-		20	-	5.6 (mean within-patient difference, pre- to post-treatment)	
Titus, Dávalos, Alom, et al., 1986	Methysergide, 3 mg/day for 6 mos	30/40 (75%)	1.2 (0.47 to 3.2) ≥ 50% reduction in HF or frequency of severe HAs	-	-	-	-
	Oxitriptan, 600 mg/day for 6 mos	32/45 (71%)		-	-	-	
Vs. lisuride							
Herrmann, Horowski, Dannehl, et al., 1977	Methysergide, 6 mg/day for 3 mos	27/53 (51%)	0.93 (0.46 to 1.9) ≥ 50% reduction in HF	-	-	-	-
	Lisuride, 75 mcg/day for 3 mos	38/72 (53%)		-	-	-	
COMPARISONS WITH BETA-BLOCKERS							
Vs. propranolol							
Behan and Reid, 1980	Methysergide, 3 mg/day for 3 mos	15/38* (39%)	0.58 (0.23 to 1.5) ≥ 50% reduction in HF	-	-	-	-
	Propranolol, 120 mg/day for 3 mos	19/36* (53%)		-	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Steardo, Bonuso, Di Stasio, et al., 1982	Methysergide, 6-10 mg/day for 6 mos	14/25 (56%)	0.64 (0.20 to 2.0) ≥ 50% reduction in HF	25	-	10.92	-0.51 (-1.1 to 0.06) HF
	Propranolol, 120 mg/day for 6 mos	16/24 (67%)		24	-	7.67	
Vs. metoprolol							
Steardo, Bonuso, Di Stasio, et al., 1982	Methysergide, 6-10 mg/day for 6 mos	14/25 (56%)	18 (2.2 to 153) ≥ 50% reduction in HF	25	-	10.92	0.81 (0.16 to 1.5) HF
	Metoprolol, 300 mg/day for 6 mos	1/16 (6%)		16	-	16.13	
COMPARISONS WITH OTHER AGENTS							
Vs. flumedroxone (Demigran®)							
Hudgson, Foster, and Newell, 1967	Methysergide, 3 mg/day for 4 mos	-	-	33*	-	2.8	- HF
	Flumedroxone (Demigran®), 15 mg/day for 4 mos	-		33*	-	4.3	
Vs. dihydroergokryptine (DEK)							
Cangi, Boccuni, Zanotti, et al., 1989	Methysergide, 2 mg/day for 2 mos	-	-	11	8.6	6.0	0.22 (-0.61 to 1.1) HF
	DEK, 20 mg/day for 2 mos	-		11	9.8	6.8	
Vs. ergotamine							
Barrie, Fox, Weatherall, et al., 1968	Methysergide, 3 mg/day or 6 mg/day for 1 mo	-	-	-	-	-	-
	Ergotamine, 0.5 mg/day or 1 mg/day for 1 mo	-		-	-	-	
Vs. flunarizine							
Steardo, Marano, Barone, et al., 1986	Methysergide, 6 mg/day for 5 mos	-	-	51?	-	-	n.s. (no p-value reported) HF
	Flunarizine, 10 mg/day for 5 mos	-		53?	-	-	

[1] Key to abbreviations: DEK = dihydroergokryptine; HF = headache frequency; HI = headache index; mcg = microgram; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not (statistically) significant; N/S = not specified; wk = week

Evidence Table 9: Efficacy of NSAIDs[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO (AND DOSING STUDIES)							
Naproxen or naproxen sodium							
Bellavance and Meloche, 1990	Naproxen sodium, 1100 mg/day for 3 mos	-	-	56	5.32	2.85	p<0.0166 (naproxen better) HI
	Placebo	-		52	5.56	5.08	
Lindegaard, Övrelid, and Sjaastad, 1980	Naproxen, 500 mg/day for 6 wks	-	-	15	-	3.4	0.20 (-0.54 to 0.95) HI
	Placebo	-		13	-	4.0	
Sances, Martignoni, Fioroni, et al., 1990	Naproxen sodium, 1100 mg/day for 3 mos	6/18 (33%)	7.7 (0.87 to 69) ≥ 50% improvement in HI	18	75.1	49.4	0.35 (-0.32 to 1.0) HI
	Placebo	1/17 (6%)		17	78.6	69.1	
Sargent, Solbach, Damasio, et al., 1985	Naproxen sodium, 1100 mg/day for 3 mos	-	-	42	-	-0.48 (difference from baseline)	-0.13 (-0.55 to 0.30) HF
	Placebo	-		43	-	-0.25 (difference from baseline)	
Szekely, Merryman, Croft, et al., 1989	Naproxen sodium, 1100 mg/day for 2 mos	-	-	22*	-	-	p=0.03 (naproxen better) HI
	Placebo	-		22*	-	-	
Welch, Ellis, and Keenan, 1985	Naproxen sodium, 1100 mg/day for 2 mos	-	-	31*	-	2.61	0.41 (-0.09 to 0.91) HI
	Placebo	-		31*	-	3.47	
Ziegler and Ellis, 1985	Naproxen sodium, 1100 mg/day for 2 mos	-	-	34*	-	2.79	0.40 (-0.08 to 0.88) HI
	Placebo	-		34*	-	3.82	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Aspirin							
O'Neill and Mann, 1978	Aspirin, 1300 mg/day for 3 mos	-	-	12*	-	-	1.7 (1.1 to 2.2) HF
	Placebo	-		12*	-	-	
Ryan and Ryan, 1981	Aspirin, 1300 mg/day for 2 mos	-	-	40	8.15	7.13	- HF
	Placebo	-		40	7.79	7.64	
Aspirin + dipyridamole							
Masel, Chesson, Peters, et al., 1980	Aspirin + dipyridamole, 975 + 75 mg/day for 3 mos	-	-	25*	2.00 (median)	1.33 (median)	p<0.01 (aspirin + dipyridamole better) HF
	Placebo	-		25*	2.00 (median)	2.33 (median)	
Ryan and Ryan, 1981	Aspirin + dipyridamole, 1300 + 75 mg/day for 2 mos	-	-	40	9.15	7.15	- HF
	Placebo	-		40	7.79	7.64	
Ryan and Ryan, 1981	Aspirin + dipyridamole, 1300 + 75 mg/day for 2 mos	-	-	40	9.15	7.15	- HF
	Aspirin, 1300 mg/day for 2 mos	-		40	8.15	7.13	
Fenoprofen							
Couch, Bearss, and Verhulst, 1987	Fenoprofen, 1800 mg/day for 3 mos	-	-	24	216	161	n.s. (no p-value reported) HI
	Placebo	-		26	222	168	
Couch, Bearss, and Verhulst, 1987	Fenoprofen, 600 mg/day for 3 mos	-	-	23	140	95	n.s. (no p-value reported) HI
	Placebo	-		26	222	168	
Couch, Bearss, and Verhulst, 1987	Fenoprofen, 1800 mg/day for 3 mos	-	-	24	216	161	n.s. (no p-value reported) HI
	Fenoprofen, 600 mg/day for 3 mos	-		23	140	95	
Diamond, Solomon, Freitag, et al., 1987	Fenoprofen, 1800 mg/day for 3 mos	16/27 (59%)	3.2 (1.1 to 9.0) > 50% reduction in HI	27	-	-	-
	Placebo	11/35 (31%)		35	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Diamond, Solomon, Freitag, et al., 1987	Fenoprofen, 600 mg/day for 3 mos	11/34 (32%)	1.0 (0.38 to 2.9) > 50% reduction in HI	34	-	-	-
	Placebo	11/35 (31%)		35	-	-	
Diamond, Solomon, Freitag, et al., 1987	Fenoprofen, 1800 mg/day for 3 mos	16/27 (59%)	3.0 (1.1 to 8.8)	27	-	-	-
	Fenoprofen, 600 mg/day for 3 mos	11/34 (32%)		34	-	-	
Tolfenamic acid							
Mikkelsen and Falk, 1982	Tolfenamic acid, 300 mg/day for 10 wks	-	-	31*	-	-	0.38 (-0.12 to 0.88) HF
	Placebo	-		31*	-	-	
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986	Tolfenamic acid, 300 mg/day for 12 wks	-	-	31*	-	-	0.44 (0.17 to 0.79) HF
	Placebo	-		31*	-	-	
Flurbiprofen							
Solomon and Kunkel, 1993	Flurbiprofen, 200 mg/day for 2 mos	-	-	23*	-	4.39	0.70 (-0.12 to 1.5) HF
	Placebo	-		23*	-	5.73	
Indobufen							
Carrieri, Orefice, and Sorge, 1988	Indobufen, 400 mg/day for 3 mos	-	-	18	10.4	6.1	0.66 (-0.02 to 1.3) HI
	Placebo	-		17	10.6	10.4	
Indomethacin							
Anthony and Lance, 1968	Indomethacin, 75 mg/day for 1 mo	7/19 (37%)	1.0 (0.27 to 3.7) > 50% reduction in HF *or* HS	-	-	-	-
	Placebo	7/19 (37%)		-	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Ketoprofen							
Stensrud and Sjaastad, 1974	Ketoprofen, 150 mg/day for 6 wks	-	-	24*	-	-	p<0.05 (ketoprofen better) HI
	Placebo	-		24*	-	-	
Lornoxicam							
Sternieri, Bussone, Manzoni, et al., 1991	Lornoxicam, 12 mg/day for 2 mos	-	-	46	7.8	5.3	0.52 (0.11 to 0.93) HF
	Placebo	-		50	7.8	7.3	
Mefenamic acid							
Johnson, Hornabrook, and Lambie, 1986	Mefenamic acid, 1500 mg/day for 3 mos	-	-	17*	-	12.9	0.52 (-0.17 to 1.2) HF
	Placebo	-		17*	-	20.1	
COMPARISONS WITH BETA-BLOCKERS							
Aspirin vs. metoprolol							
Grotemeyer, Scharafinski, Schlake, et al., 1990	Aspirin, 1500 mg/day for 3 mos	3/21* (14%)	0.084 (0.018 to 0.38) > 50% reduction in HF	21*	2.0	1.4	0.33 (-0.28 to 0.94) HS
	Metoprolol, 200 mg/day for 3 mos	14/21* (67%)		21*	2.0	1.6	
Aspirin vs. propranolol							
Baldrati, Cortelli, Procaccianti, et al., 1983	Aspirin, approx. 975 mg/day (avg) for 3 mos	9/12* (75%)	1.0 (0.16 to 6.3) > 50% reduction in HI	12*	-	-	-0.01 (-0.58 to 0.55) HI
	Propranolol, approx. 120 mg/day (avg) for 3 mos	9/12* (75%)		12*	-	-	
Mefenamic acid vs. propranolol							
Johnson, Hornabrook, and Lambie, 1986	Mefenamic acid, 1500 mg/day for 3 mos	-	-	17*	-	12.9	0.06 (-0.61 to 0.74) HF
	Propranolol, 240 mg/day for 3 mos	-		17*	-	13.8	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Naproxen sodium vs. propranolol							
Sargent, Solbach, Damasio, et al., 1985	Naproxen sodium, 1100 mg/day for 3 mos	-	-	42	-	-0.48 (difference from baseline)	-0.37 (-0.80 to 0.05) HF
	Propranolol, 120 mg/day for 3 mos	-		44	-	0.21 (difference from baseline)	
Tolfenamic acid vs. propranolol							
Kjærsgård-Rasmussen, Holt-Larsen, Borg, et al., 1994	Tolfenamic acid, 300 mg/day for 3 mos	-	-	27	-	-15.7 (difference from baseline)	-0.24 (-0.76 to 0.29) HI
	Propranolol, 120 mg/day for 3 mos	-		29	-	-6.9 (difference from baseline)	
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986	Tolfenamic acid, 300 mg/day for 3 mos	-	-	31*	-	-	-0.05 (-0.40 to 0.30) HF
	Propranolol, 120 mg/day for 3 mos	-		31*	-	-	
COMPARISONS WITH SEROTONIN ANTAGONISTS							
Naproxen sodium vs. pizotifen							
Bellavance and Meloche, 1990	Naproxen sodium, 1100 mg/day for 3 mos	-	-	56	5.32	2.85	n.s. (no p-value reported) HI
	Pizotifen, 1.5 mg/day for 3 mos	-		58	5.77	3.27	

[1] Key to abbreviations: avg = average; HF = headache frequency; HI = headache index; HS = headache severity; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not (statistically) significant; N/S = not specified; wk = week

Evidence Table 10: Efficacy of Other Serotoninergic Agents[1, 2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS WITH PLACEBO (AND DOSING STUDIES)							
Pizotifen							
Arthur and Hornabrook, 1971	Pizotifen, 3 mg/day for 1 mo	21/52 (40%)	5.2 (1.9 to 14.3) ≥ 50% reduction in HF	52*	-	-	p < 0.005 (pizotifen better) HF
	Placebo	6/52 (12%)		52*	-	-	
Bellavance and Meloche, 1990	Pizotifen, 1.5 mg/day for 3 mos	-	-	58	5.77	3.27	n.s. (no p-value reported) HI
	Placebo	-		52	5.56	5.08	
Carroll and Maclay, 1975	Pizotifen, 1.5 to 3 mg/day for 2 mos	-	-	14*	-	-	-
	Placebo	-		14*	-	-	
Hughes and Foster, 1971	Pizotifen, 3 mg/day for 6 wks	-	-	26*	18.1	18.5	n.s. (no p-value reported) HF
	Placebo (lactose)	-		26*	18.1	20.3	
Krakowski and Engisch, 1973	Pizotifen, 6 mg/day for 12 wks	-	-	13	31.8	16.8	0.90 (0.01 to 1.8) HI
	Placebo	-		9	36.2	32.8	
Lance and Anthony, 1968	Pizotifen, 3 mg/day for 1 mo	12/25 (48%)	1.6 (0.53 to 5.1) ≥ 50% reduction in *either* HF *or* HA intensity	25	-	-	n.s. (p = 0.4) HF *or* HA intensity
	Placebo	9/25 (36%)		25	-	-	
Lawrence, Hossain, and Littlestone, 1977	Pizotifen, 3 mg/day for 10 wks	-	-	14	-	8.6	0.62 (-0.14 to 1.4) HI
	Placebo	-		14	-	14.9	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Osterman, 1977	Pizotifen, 3 mg/day for 8 wks	12/27 (44%)	-	27*	-	1.6	0.95 (0.38 to 1.5) HI
	Placebo	-		27*	-	2.4	
Ryan, 1968	Pizotifen, 4 mg/day	-	-	62*	-	8.9	- HI
	Placebo	-		62*	-	17.0	
Ryan, 1971	Pizotifen, dose increased from 0.5 mg/day to 3 mg/day for 2 wks; after 2 wks, and at 4-wk intervals, dosage adjusted according to a protocol for 10 wks	-	-	25	21.53	15.68	- HI
	Placebo	-		20	10.00	6.65	
Sjaastad and Stensrud, 1969	Pizotifen, 4 mg/day for 8 wks	9/20 (45%)	-	20*	-	5.6	1.1 (0.36 to 1.7) HF
	Placebo	-		20*	-	9.9	
Tropisetron							
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 1**	Tropisetron, 50 mg/day for 3 mos	13/45 (29%)	0.60 (0.25 to 1.4) ≥ 50% reduction in *either* HF *or* HI	45	-	-	n.s. (p > 0.05) HF
	Placebo	19/47 (40%)		47	-	-	
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 1**	Tropisetron, 25 mg/day for 3 mos	16/43 (37%)	0.87 (0.37 to 2.0) ≥ 50% reduction in *either* HF *or* HI	43	-	-	n.s. (p > 0.05) HF
	Placebo	19/47 (40%)		47	-	-	
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 2**	Tropisetron, 15 mg/day for 3 mos	17/30 (57%)	2.4 (0.70 to 8.2) ≥ 50% reduction in *either* HF *or* HI	30	-	-	n.s. (p > 0.05) HF
	Placebo	6/17 (35%)		17	-	-	
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 1**	Tropisetron, 50 mg/day for 3 mos	13/45 (29%)	0.69 (0.28 to 1.7) ≥ 50% reduction in *either* HF *or* HI	45	-	-	-
	Tropisetron, 25 mg/day for 3 mos	16/43 (37%)		43	-	-	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Lisuride							
Herrmann, Krištof, and Sastre y Hernandez, 1978	Lisuride, 0.075 mg/day for 6 mos	-	-	103	-	-	p = 0.05 (lisuride better) HF
	Placebo	-		111	-	-	
Sances, Martignoni, Rosettino, et al., 1989	Lisuride, 0.15 mg/day for 3 mos	-	-	20	81.7	47.3	0.76 (0.12 to 1.4) HI
	Placebo	-		20	102	95.8	
Somerville and Herrmann, 1978	Lisuride, 0.075 mg/day for 3 mos	-	-	58	-	-	p < 0.05 (lisuride better) HF
	Placebo	-		52	-	-	
Zuddas, Mulas, Del Zompo, et al., 1985	Lisuride, 0.075 mg/day for 3 mos	-	-	15	-	-	-
	Placebo	-		15	-	-	
Wilkinson, Agnoli, Gerber, et al., 1989	Lisuride, 0.15 mg/day for 3 mos	18/49 (37%)	0.98 (0.42 to 2.3) ≥ 50% reduction in HF	49	-	-	n.s. (p > 0.05) HI
	Lisuride, 0.075 mg/day for 3 mos	16/43 (37%)		43	-	-	
Oxitriptan							
De Benedittis and Massei, 1986	Oxitriptan, 400 mg/day for 2 mos	-	-	31*	43.8	25.1	0.08 (-0.42 to 0.58) HI
	Placebo	-		31*	43.8	26.5	
Kangasniemi, Falck, Långvik, et al., 1978	Oxitriptan, 2000 mg/day for 3 mos	-	-	8*	-	16.0	-0.45 (-0.54 to 1.4) HI
	Placebo (levoleucine), 1280 mg/day for 3 mos	-		8*	-	23.8	
Mathew, 1978	Oxitriptan, 300 mg/day for 8 wks	-	-	12*	-	-	-
	Placebo	-		12*	-	-	
Iprazochrome							
Osterman, 1977	Iprazochrome, 15 mg/day for 8 wks	6/27 (22%)	-	27*	-	2.1	n.s. (no p-value reported) HI
	Placebo	-		27*	-	2.4	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISONS AMONG SEROTONIN ANTAGONISTS							
Pizotifen vs. iprazochrome							
Osterman, 1977	Pizotifen, 3 mg/day for 8 wks	12/27 (44%)	2.8 (0.86 to 9.1) ≥ 50% reduction in HF	27*	-	1.6	0.73 (0.18 to 1.3) HI
	Iprazochrome, 15 mg/day for 8 wks	6/27 (22%)		27*	-	2.1	
Kangasniemi, 1979	Pizotifen, 1.5 mg/day for 3 mos	-	-	34*	-	2.7	0.26 (-0.22 to 0.73) HI
	Iprazochrome, 15 mg/day for 3 mos	-		34*	-	3.2	
Pizotifen vs. lisuride							
Nattero, Biale, Savi, et al., 1991	Pizotifen, 4.5 mg/day for 16 wks	10/43 (23%)	0.57 (0.22 to 1.5) ≥ 50% reduction in HF	43*	-	-	- HF
	Lisuride, 0.225 mg/day for 16 wks	15/43 (35%)		43*	-	-	
Pizotifen vs. oxitriptan							
Bono, Criscuoli, Martignoni, et al., 1982	Pizotifen, 1.40 mg/day for 2 mos	-	-	34	-	-	$p < 0.02$ (pizotifen better) HI
	Oxitriptan, 400 mg/day for 2 mos	-		33	-	-	
COMPARISONS WITH CALCIUM ANTAGONISTS							
Pizotifen vs. flunarizine							
Cerbo, Casacchia, Formisano, et al., 1986	Pizotifen, 1.5 mg/day for 2 mos	-	-	21*	-	-	n.s. (no p-value reported) HF
	Flunarizine, 15 mg/day for 2 mos	-		21*	-	-	
Louis and Spierings, 1982	Pizotifen, 2-3 mg/day for 4 mos	-	-	30	-	-	n.s. (no p-value reported) HF
	Flunarizine, 10 mg/day for 4 mos	-		36	-	-	
Rascol, Montastruc, and Rascol, 1986	Pizotifen, 2.19 mg/day for 4 mos	-	-	14	-	-	n.s. (no p-value reported) HF
	Flunarizine, 10 mg/day for 4 mos	-		21	-	-	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Pizotifen vs. nimodipine							
Gawel, 1987	Pizotifen, 3 mg/day for 3 mos	-	-	54*	7.55	6.65	0.11 (-0.42 to 0.64) HF
	Nimodipine, 120 mg/day for 3 mos	-		54*	7.56	6.04	
Havanka-Kanniainen, Hokkanen, and Myllylä, 1987	Pizotifen, 1.5 mg/day for 3 mos	-	-	43*	6.2	2.6	-0.11 (-0.54 to 0.31) HF
	Nimodipine, 120 mg/day for 3 mos	-		43*	6.2	2.3	
Micieli, Trucco, Agostinis, et al., 1985	Pizotifen, 1.5 mg/day for 3 mos	-	-	20*	-	-	n.s. (no p-value reported) HI
	Nimodipine, 120 mg/day for 3 mos	-		20*	-	-	
Pizotifen vs. cyclandelate							
Mastrosimone, Iaccarino, and de Caterina, 1992	Pizotifen, 1.5 mg/day for 3 mos	-	-	26	-	-	p < 0.001 (cyclandelate better) Total pain index
	Cyclandelate, 1600 mg/day for 3 mos	-		35	-	-	
COMPARISONS WITH METHYSERGIDE							
Pizotifen vs. methysergide							
Andersson, 1973	Pizotifen, 2.0 mg/day for 3 mos	18/47 (38%)	1.4 (0.59 to 3.2) > 50% reduction in HF	49*	5.9	3.5	0.17 (-0.23 to 0.57) HF
	Methysergide, 4 mg/day for 3 mos	15/48 (31%)		49*	5.9	4.1	
Forssman, Henriksson, and Kihlstrand, 1972	Pizotifen, 2-3 mg/day for 10 wks	-	-	17*	3.5	2.1	n.s. (no p-value reported) HI
	Methysergide, 4-6 mg/day for 10 wks	-		17*	3.5	1.8	
Presthus, 1971	Pizotifen, 1.5 mg/day for 5 wks	-	-	19*	-	-	0.29 (-0.17 to 0.76) HF
	Methysergide, 3 mg/day for 5 wks	-		19*	-	-	
Ryan, 1968	Pizotifen, 4 mg/day for 4 wks	-	-	62*	-	8.9	- HI
	Methysergide, 4 mg/day for 4 wks	-		62*	-	11.3	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Oxitriptan vs. methysergide							
Sicuteri, 1973	Oxitriptan, 200 mg/day for 40 days	-	-	20	-	5.6 (mean within-patient, pre- to -post-treatment)	-0.09 (-0.71 to 0.53) HI
	Methysergide, 2 mg/day for 40 days	-		20	-	5.9 (mean within-patient, pre- to -post-treatment)	
Titus, Dávalos, Alom, et al., 1986	Oxitriptan, 600 mg/day for 6 mos	32/45 (71%)	0.82 (0.31 to 2.2) ≥ 50% reduction in HF or frequency of severe HAs	45	-	-	-
	Methysergide, 3 mg/day for 6 mos	30/40 (75%)		40	-	-	
Lisuride vs. methysergide							
Herrmann, Horowski, Dannehl, et al., 1977	Lisuride, 75 mcg/day for 3 mos	38/72 (53%)	1.1 (0.53 to 2.2) ≥ 50% reduction in HF	72	-	-	-
	Methysergide, 6 mg/day for 3 mos	27/53 (51%)		53	-	-	
COMPARISON WITH ALPHA-2 AGONIST							
Pizotifen vs. clonidine							
Behan, 1985	Pizotifen (Sanomigran®), 1.5 mg/night for 1 mo; 1.5 - 3.0 mg/night for 2d mo	-	-	18	-	-	-
	Clonidine (Dixarit®), 100 µg/day for 1 mo; 100-150 µg/day for 2d mo	-		26	-	-	
COMPARISON WITH ANTINAUSEANT							
Pizotifen vs. prochlorperazine							
Hübbe, 1973	Pizotifen, 3 mg/day for 2 mos	-	-	40*	-	-	n.s. (no p-value reported) HF
	Prochlorperazine, 15 mg/day for 2 mos	-		40*	-	-	

[1]See last page of this table for key to abbreviations.
[2]An asterisk denotes a cross-over trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
COMPARISON WITH BETA-BLOCKER							
Pizotifen vs. metoprolol							
Vilming, Standnes, and Hedman, 1985	Pizotifen, 0.5 mg/day, gradually increased to 1.5 mg/day for 8 wks	14/33 (42%)	1.8 (0.64 to 4.9) ≥ 50% reduction in HI	30*	13.0 (median)	7.1 (median)	n.s. ($p > 0.05$) HI
	Metoprolol, 100 mg/day for 8 wks	10/34 (29%)		30*	13.0 (median)	8.6 (median)	
COMPARISON WITH NSAID							
Pizotyline vs. naproxen sodium							
Bellavance and Meloche, 1990	Pizotyline, 1.5 mg/day for 3 mos	-	-	58	5.77	3.27	n.s. (no p-value reported) HI
	Naproxen sodium, 1100 mg/day for 3 mos	-		56	5.32	2.85	

[1] Key to abbreviations: HA = headache; HF = headache frequency; HI = headache index; mcg = microgram; mg = milligram; mo = month; N = population studied (n = sample size); n.s. = not (statistically) significant; N/S = not specified; wk = week; µg = microgram

Evidence Table 11: Efficacy of Other Treatments[1,2]

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
HORMONAL TREATMENTS							
Estradiol vs. placebo							
Dennerstein, Morse, Burrows, et al., 1988	Estradiol (percutaneous gel), 1.5 mg/day, 7 days, for 2 menstrual cycles	-	-	19*	-	-	0.71 (0.26 to 1.2) HF (within-patient difference)
	Placebo	-		19*	-	-	
Smits, van der Meer, Pfeil, et al., 1993	Estradiol (Estraderm TTS® patch), 50 µg/day for 8 days during 1-2 menstrual cycles (see Evidence Table 1)	-	-	19*	-	-	n.s. (no p-value reported) HF
	Placebo	-		19*	-	-	
Flumedroxone vs. placebo							
Bradley, Hudgson, Foster, et al., 1968	Flumedroxone, 30 mg/day for 3 mos	-	-	14*	-	-	n.s. (no p-value reported) HI (within-patient difference)
(Men)	Placebo	-		14*	-	-	
Bradley, Hudgson, Foster, et al., 1968	Flumedroxone, 30 mg/day for 3 mos	-	-	7*	-	-	n.s. (no p-value reported) HI (within-patient difference)
(Women w/o menstrual exacerbation of HA)	Placebo	-		7*	-	-	
Bradley, Hudgson, Foster, et al., 1968	Flumedroxone, 30 mg/day for 3 mos	-	-	18*	-	-	p<0.05 (flumedroxone better) HI (within-patient difference)
(Women with menstrual exacerbation of HA)	Placebo	-		18*	-	-	
Lundberg, 1969	Flumedroxone, 10 mg/day for 1 mo	-	-	21	-	-	p<0.0005 (flumedroxone better) HF
	Placebo	-		23	-	-	

[1] See last page of this table for key to abbreviations.
[2] An asterisk denotes a crossover trial.

Study	Treatment	# of patients improved/N (%)	Odds ratio	Mean Values			Effect size or p-value
				N	Before Treatment	After Treatment	
Flumedroxone vs. methysergide							
Hudgson, Foster, and Newell, 1967	Flumedroxone, 15 mg/day for 4 mos	-	-	33*	-	4.3	- HF
	Methysergide, 3 mg/day for 4 mos	-		33*	-	2.8	
Ovral® (norgestrel 0.5 mg + ethinyl estradiol 0.005 mg) vs. no treatment							
Ryan, 1978	Ovral®, as prescribed, for 2 mos	-	-	40*	-	48.70	- HI
	No treatment	-		40*	-	32.85	
FEVERFEW							
Johnson, Kadam, Hylands, et al., 1985	50 mg/day for 6 mos	-	-	8	-	1.50	2.3 (1.0 to 3.6) HF
	Placebo	-		7	-	3.43	
Murphy, Heptinstall, and Mitchell, 1988	Feverfew, ≈82 mg/day (mean dose) for 4 mos	-	-	59*	-	3.6	0.56 (0.19 to 0.93) HF
	Placebo	-		59*	-	4.7	

Key to abbreviations: ES = effect size; Freq = frequency; HA = headache; HF = headache frequency; HI = headache index; HS = headache severity; Imprv'd = improved; MD = medical doctor; med = medication; mo = month or months; N or n = number of patients; normo = normobaric; n.s. = not (statistically) significant; OC = outcome; OR = odds ratio

Evidence Table 12: Adverse events[1, 2]

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Adam, Gore, and Price, 1978		**Clonidine (Dixarit®)**, 0.025 mg, 3x/day for 6 mos (could be increased to max. of 0.050 mg, 3x/day for 6 mos)	**Placebo**	Information on AEs provided only on the 26 patients who withdrew from trial.
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	2 (palpitations & dyspnoea; nausea, epigastric discomfort, abdominal distension)	1 (nausea, vomiting, flatulence, skin irritation)	
Adly, Straumanis, and Chesson, 1992		**Fluoxetine**, doses ranged from 20 mg every other day to 40 mg/day	**Placebo**	Data at left are only for those patients who completed the trial (18/32). One patient in the fluoxetine group withdrew prematurely due to AEs (anxiety and insomnia). No patients withdrew from the placebo group due to AEs.
	Number of patients evaluable for AEs:	9	9	
	Number of patients reporting AEs:	3 (33%)	3 (33%)	
	Total number of AEs reported:	6	4	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Insomnia	2 (22%)	2 (22%)	
	Anxiety	1 (11%)	1 (11%)	
	Excitement	1 (11%)	0	
	Strange skin sensations	1 (11%)	0	
	Floating sensation	1 (11%)	0	
	Weakness/fatigue	0	1 (11%)	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Agnoli, Bussone, Mailland, et al., 1991		**Dihydroergokryptine (DEK)**, 10 mg/day for 6 mos	**Flunarizine**, 5 mg/day for 6 mos	Abstract reporting limited results. Investigators stated only that the overall rate of AEs was similar in the two groups.
	Number of patients evaluable for AEs:	54	48	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	4 (causative AEs N/S)	0	
Ahuja and Verma, 1985		**Propranolol** 40 mg, 3x/day for 8 wks	**Placebo**	Regarding AEs, investigators reported only that there were "no significant side effects of propranolol observed during the trial period." No information was provided on AEs that might have resulted from the placebo treatment.
	Number of patients evaluable for AEs:	26* (See note)	26* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Albers, Simon, Hamik, et al., 1989		**Nifedipine**, 60-90 mg/day for 6 mos	**Propranolol**, 120-180 mg/day for 6 mos	*Nifedipine vs. propranolol:* 0.16 (-0.025 to 0.34)
	Number of patients evaluable for AEs:	20	18	
	Number of patients reporting AEs:	20 (100%)	15 (83%)	
	Total number of AEs reported:	52	17	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Dizziness	13 (65%)	3 (17%)	
	Warm, swollen, red legs	9 (45%)	0	
	Fatigue	0	8 (44%)	
	Increased HA frequency	4 (20%)	3 (17%)	
	Tachycardia	6 (30%)	0	
	Facial flushing	6 (30%)	0	
	Nausea	6 (30%)	0	
	Decrease in concentration	4 (20%)	0	
	Shakiness	4 (20%)	0	
	Depression	0	3 (17%)	
	Withdrawals due to AEs:	13 (causative AEs N/S)	5 (causative AEs N/S)	
Al Deeb, Biary, Bahou, et al., 1992		**Flunarizine**, 10 mg/day for 3 mos	**Placebo**	Limited information provided on AEs. Four of 50 patients (8%) withdrew due to AEs "such as tiredness or weight-gain, depression or giddiness." The investigators did not report from which treatment group these withdrawals came.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Al-Qassab and Findley, 1993		**Propranolol (long-acting),** 160 mg, 1x/day for 2 mos	**Propranolol (long-acting),** 80 mg, 1x/day for 2 mos	**Placebo**	Of the 45 patients randomized to treatment, 1 was withdrawn due to AEs. Investigators did not describe the AE or report the treatment group from which the patient withdrew. Authors reported only that "reported side effects during the three treatment periods were similar and were not statistically significant." It was also reported that the incidence of side effects were similar on the active drug as on placebo.
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	N/S (See note)	
Andersson, 1973		**Methysergide,** 1 mg, 4x/day for 3 mos		**Pizotifen,** 0.5 mg, 4x/day for 3 mos	Limited information reported on AEs. Among patients who experienced AEs but did not withdraw from the trial, restlessness and pain in the legs were the most common AEs associated with methysergide; weight gain was the most common AE associated with pizotifen.
	Number of patients evaluable for AEs:	N/S		N/S	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	4 (muscle pain in legs [3], severe phlebitis [1])		9 (weight gain [4], drowsiness [2], vertigo and drowsiness [2], muscle pains in legs [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Andersson, Dahl, Hansen, et al., 1983		**Metoprolol**, 200 mg, 1x/day for 8 wks	**Placebo**	Data at left appear to concern only the 65/71 patients included in the efficacy analyses, but this is not clear.
	Number of patients evaluable for AEs:	30 (See note)	35 (See note)	
	Number of patients reporting AEs:	16 (53%)	10 (29%)	*Metoprolol vs. placebo:* 0.24 (0.0049 to 0.46)
	Total number of AEs reported:	31	32	
	Number *of AEs* reported:	*n (%)*	*n (%)*	
	Sleep disturbances	11 (35%)	9 (28%)	
	Fatigue	9 (29%)	1 (3%)	
	Gastrointestinal	3 (10%)	6 (19%)	
	Bradycardia	0	1 (3%)	
	Paraesthesia	2 (6%)	4 (13%)	
	Depression	2 (6%)	2 (6%)	
	Others	3 (10%)	10 (31%)	
	Withdrawals due to AEs:	1 (N/S)	1 (N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Andersson and Petersen, 1981		**Femoxetine**, 200 mg, 2x/day for 3 mos; dose reduced by half during first week	**Propranolol**, 80 mg, 2x/day for 3 mos; dose reduced by half during first week	The data reported at left appear to include only those patients who completed the trial (37/49 patients randomized to treatment), though this is not entirely clear. Two patients withdrew prematurely due to unspecified AEs associated with femoxetine; two withdrew due to unspecified AEs associated with propranolol.
	Number of patients evaluable for AEs:	37*	37*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	14	30	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Tiredness	4 (11%)	8 (22%)	
	Menstrual disorder	1 (3%)	10 (27%)	
	Depression	1 (3%)	3 (8%)	
	Nausea	1 (3%)	2 (5%)	
	Feeling unwell	2 (5%)	0	
	Insomnia	1 (3%)	1 (3%)	
	Dizziness	1 (3%)	1 (3%)	
	Exanthema	1 (3%)	1 (3%)	
	Precordial pain	1 (3%)	0	
	Gastric distress	1 (3%)	0	
	Palpitations	0	1 (3%)	
	Unrest of the legs	0	1 (3%)	
	Paresthesia	0	1 (3%)	
	Irritability	0	1 (3%)	
	Withdrawals due to AEs:	(See note)	(See note)	
Ansell, Fazzone, Festenstein, et al., 1988		**Nimodipine**, 120 mg/day for 4 mos	**Placebo**	Investigators reported only that no patients withdrew due to AEs and that no "serious" AEs were reported. AEs were recorded at monthly clinic visits.
	Number of patients evaluable for AEs:	34	34	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Anthony and Lance, 1968		**Indomethacin,** 25 mg, 3x/day for 1-9 mos	**Placebo,** 3x/day for 1 mo	See Evidence Table 1 on study design. Investigators stated that no patients withdrew due to AEs.
	Number of patients evaluable for AEs:	38 (See note)	19 (See note)	
	Number of patients reporting AEs:	15 (39%)	N/S	
	Total number of AEs reported:	35	7	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Full head	5 (13%)	4 (21%)	
	Indigestion	7 (18%)	1 (5%)	
	Lightheadedness	5 (13%)	0	
	Insomnia	5 (13%)	0	
	Dizziness	2 (5%)	2 (11%)	
	Poor concentration	3 (8%)	0	
	Bifrontal headache	2 (5%)	0	
	Depression	1 (3%)	0	
	Irritability	1 (3%)	0	
	Tiredness	1 (3%)	0	
	Unsteadiness	1 (3%)	0	
	Nausea	1 (3%)	0	
	Epigastric pain	1 (3%)	0	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Anthony, Lance, and Somerville, 1972		**Prindolol**, 2.5 mg, 4x/day for 1-20 mos	**Clonidine**, 75 μg, 3x/day for 1-18 mos	**Carbamaze-pine**, 200 mg, 3x/day for 1-4 mos	AEs reported for entire (partial crossover) trial (see Evidence Table 1 for details of trial design). Withdrawals from the prindolol group were due to increasing headache (2); and dizziness, nausea, vomiting, paraesthesiae, lassitude and exhaustion, and cramps (1 each).
	Number of patients evaluable for AEs:	79*	73*	51*	
	Number of patients reporting AEs:	15 (19%)	30 (41%)	27 (53%)	
	Total number of AEs reported:	21	41	40	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	*Carbamazepine vs. prindolol:* 0.34 (0.17 to 0.49)
	Drowsiness, tiredness, weakness	2 (3%)	15 (21%)	7 (14%)	
	Nausea	2 (3%)	5 (7%)	6 (12%)	
	Giddiness, ataxia	1 (1%)	0	10 (20%)	*Carbamazepine vs. clonidine:* 0.12 (-0.060 to 0.29)
	Faintness, dizziness	3 (4%)	5 (7%)	3 (6%)	
	Dry mouth, sore tongue, bad taste	0	10 (14%)	0	
	Cramps, limb pains	6 (8%)	1 (1%)	2 (4%)	*Clonidine vs. prindolol:* 0.22 (0.074 to 0.36)
	Irritability, agitation	4 (5%)	2 (3%)	2 (4%)	
	Epigastric discomfort	0	1 (1%)	1 (2%)	
	Insomnia, nightmares	0	1 (1%)	1 (2%)	
	Itching skin, rash	0	0	2 (4%)	
	Blurred vision	0	0	2 (4%)	
	Lack of concentration	0	0	2 (4%)	
	Vomiting	1 (1%)	0	0	
	Increased appetite	0	0	1 (2%)	
	Bruising, prominent veins	0	1 (1%)	0	
	Swelling of throat	0	0	1 (2%)	
	Paraesthesiae	1 (1%)	0	0	
	Jaundice	1 (1%)	0	0	
	Withdrawals due to AEs:	8 (See note)	8 (causative AEs N/S)	12 (causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Arthur and Hornabrook, 1971		**Pizotifen (BC 105),** 3 mg/day for 1 mo	**Placebo**	Information on AEs provided only on the 52/63 patients from whom efficacy data were obtained, which included the three patients who withdrew due to severe AEs.
	Number of patients evaluable for AEs:	52* (See note)	52* (See note)	
	Number of patients reporting AEs:	22 (42%)	6 (12%)	
	Total number of AEs reported:	22	6	
	Number of patients reporting:	*n (%)*	*n (%)*	Of patients treated with pizotifen, weight gain was reported by 26 of the 44 patients (59%) for whom data were available. Fifteen of 46 patients (33%) treated with placebo reported weight gain.
	Bizarre feelings in head	0	1 (2%)	
	"Dead" feelings in legs	0	1 (2%)	
	Depression	4 (8%)	N/S	
	Dizziness	1 (2%)	N/S	
	Drowsiness	11 (21%)	N/S	
	Enuresis	1 (2%)	N/S	*Pizotifen vs. placebo:* 0.30 (0.14 to 0.45)
	Faintness	0	1 (2%)	
	Fatigue	2 (4%)	2 (4%)	
	Increased appetite	1 (2%)	N/S	
	Nausea	0	1 (2%)	
	Wakefulness	2 (4%)	N/S	
	Withdrawals due to AEs:	3 (drowsiness [2 – 1 with diplopia & blurred vision], dizziness [1])	N/S	
Autret and de Chasteigner, 1987		**DHE (timed-release),** 5 mg, 2x/day for 2 mos	**Placebo**	Abstract providing limited information. Investigators stated that all 115 patients who started the treatment phase of the trial completed it. No information was provided on AEs reported during the trial.
	Number of patients evaluable for AEs:	58	57	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Baldrati, Cortelli, Procaccianti, et al., 1983		**Aspirin**, mean dose (± SD) 13.5 ± 1.2 mg/kg/day, for 3 mos	**Propranolol**, mean dose (± SD) 1.8 ± 0.1 mg/kg/day, for 3 mos	Overall AE rates were reported only for those patients who *completed* the trial (12/18). AEs associated with aspirin were gastric distress, palpitations, weight gain, and constipation (number of patients reporting these N/S). AEs associated with propranolol were palpitations, gastric distress, dizziness, insomnia, and constipation number of patients reporting these N/S). Three patients withdrew before completing the trial due to AEs associated with aspirin (gastric distress in all three cases); two withdrew due to AEs associated with propranolol (hypotension, worsening of HA). *Aspirin vs. propranolol*: 0.00 (-0.37 to 0.37)
	Number of patients evaluable for AEs:	12*	12*	
	Number of patients reporting AEs:	6 (50%)	6 (50%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bánk, 1994		**Amitriptyline**, 25 mg, 1x/day for 12 wks	**Fluvoxamine**, 50 mg, 1x/day for 12 wks	*Fluvoxamine vs. amitriptyline:* -0.18 (-0.40 to 0.060)
	Number of patients evaluable for AEs:	29	30	
	Number of patients reporting AEs:	12 (41%)	7 (23%)	
	Total number of AEs reported:	12	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	12 (41%)	N/S	
	Dry mouth	0	N/S	
	Nausea	0	N/S	
	General weakness	0	N/S	
	Withdrawals due to AEs:	7 (all due to drowsiness)	3 (drowsiness, severe constipation, feeling of pressure in abdomen)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions				Notes; Difference in proportion of patients reporting adverse events (95% CI)
Barrie, Fox, Weatherall, et al., 1968		**Ergotamine**, 0.17 mg, 3x/day for up to 2 mos	**Ergotamine**, 0.33 mg, 3x/day for up to 2 mos	**Methyser-gide**, 1 mg, 3x/day for up to 2 mos	**Methyser-gide**, 2 mg, 3x/day for up to 2 mos	Data on AEs were reported only for the four treatment arms at left (of six), and only for all four treatment periods combined.
	Number of patients evaluable for AEs:	73	68	76	54	
	Number of patients reporting AEs:	N/S	N/S	N/S	N/S	
	Total number of AEs reported:	23	25	53	61	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Drowsiness	6 (8%)	7 (10%)	9 (12%)	9 (17%)	
	Depression	3 (4%)	6 (9%)	7 (9%)	8 (15%)	
	Nausea, vomiting	1 (1%)	3 (4%)	11 (14%)	8 (15%)	
	Vertigo, "muzzy head"	3 (4%)	4 (6%)	4 (5%)	9 (17%)	
	Swollen joints, stiffness or cramps	6 (8%)	0	5 (7%)	7 (13%)	
	Digestive disturbance	0	2 (3%)	7 (9%)	7 (13%)	
	Swollen eyes, visual disturbance	0	1 (1%)	1 (1%)	4 (7%)	
	Other	4 (5%)	2 (3%)	9 (12%)	9 (17%)	
	Withdrawals due to AEs:	N/S	N/S	N/S	N/S	
Bassi, Brunati, Rapuzzi, et al., 1992		**Flunarizine**, 10 mg, 1x/day for 4 mos		**Flunarizine**, 10 mg, 1x/day for one wk, then 3 mg, 1x/day for total of 4 mos		The data reported at left are for those patients who completed the trial (29/40). Two patients, one from each treatment group, withdrew prematurely due to unspecified AEs.
	Number of patients evaluable for AEs:	15		14		
	Number of patients reporting AEs:	13 (86%)		5 (38%)		
	Total number of AEs reported:	13		5		*Flunarizine, 10 mg vs. 3 mg:* 0.49 (0.16 to 0.74)
	Number of patients reporting:	*n (%)*		*n (%)*		
	Sleepiness	5 (33%)		2 (14%)		
	Weight gain	5 (33%)		2 (14%)		
	Depression	2 (13%)		1 (7%)		
	Rash	1 (7%)		0		
	Withdrawals due to AEs:	(See note)		(See note)		

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Behan, 1985		**Clonidine (Dixarit®)**, 50 µg, 2x/day for 1 mo; 50-75 µg, 2x/day for 2d mo	**Pizotifen (Sanomigran®)**, 1.5 mg, 1x/night for 1 mo; 1.5-3.0 mg, 1x/night for 2d mo	Five patients taking pizotifen experienced weight gain, and one reported drowsiness. Four patients in the pizotifen group and 7 in the clonidine group withdrew from the study, but investigators did not state whether or not withdrawals resulted from AEs.
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	1 (weight gain)	
Behan and Reid, 1980		**Propranolol**, 40 mg, 3x/day for 3 mos	**Methysergide**, 1 mg, 3x/day for 3 mos	Data at left concern only the 36 patients who completed the trial. AEs reported by these patients in association with methysergide included nausea, vomiting, dizziness, nightmares, circumoral numbness, and abdominal cramps (number of patients reporting each of these symptoms not given). AEs associated with propranolol included generalized weakness and dizziness (9 patients), coldness of hands and circumoral paraesthesia (1), excessive tearing (1), and depression (1). 3 patients withdrew prematurely from the trial due to AEs associated with methysergide (severe chest pains and intermittent claudication [2], bilateral spasm of brachial arteries [1]). No patients withdrew due to AEs associated with propranolol *Propranolol vs. methysergide:* -0.11 (-0.32 to 0.11)
	Number of patients evaluable for AEs:	36*	36*	
	Number of patients reporting AEs:	12 (33%)	16 (44%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bellavance and Meloche, 1990		**Naproxen sodium**, 550 mg, 2x/day for 12 wks	**Pizotyline**, 0.5 mg, 3x/day for 12 wks	**Placebo**	Patients questioned about AEs at monthly clinic visits. *Naproxen sodium vs. placebo:* 0.061 (-0.092 to 0.21)
	Number of patients evaluable for AEs:	58	58	56	
	Number of patients reporting AEs:	15 (26%)	16 (28%)	11 (20%)	*Pizotyline vs. placebo:* 0.078 (-0.077 to 0.23)
	Total number of AEs reported:	N/S	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	*Naproxen sodium vs. pizotyline:* -0.017 (-0.18 to 0.14)
	Gastrointestinal symptoms	8 (14%)	7 (12%)	3 (5%)	
	Central nervous system symptoms	4 (7%)	4 (7%)	5 (9%)	
	Skin symptoms	2 (3%)	0	1 (2%)	
	Weight gain	0	6 (10%)	1 (2%)	
	Other AEs	4 (7%)	2 (3%)	4 (7%)	
	Withdrawals due to AEs:	3 (gastric ulcer [1], epigastric burning [2])	2 (weight gain [1], sleepiness [1])	2 (hematoma and epigastric pain [1], parasthesia [1])	
Boisen, Deth, Hübbe, et al., 1978		**Clonidine**, 0.05 mg (in 2 tabs), 2x/day for 8 wks		**Placebo**	Data at left concern only those 49 patients (of 71) who completed the crossover. In this group, the most common AEs reported were drowsiness, dizziness, and nausea. Two patients withdrew prematurely due to AEs associated with clonidine (fainting, severe vomiting). *Clonidine vs. placebo:* 0.14 (-0.02 to 0.29)
	Number of patients evaluable for AEs:	49* (See note)		49* (See note)	
	Number of patients reporting AEs:	13 (26%)		6 (12%)	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	(See note)		(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bono, Criscuoli, Martignoni, et al., 1982		**Pizotifen,** 1.40 mg/day for 2 mos	**Oxitriptan,** 400 mg/day for 2 mos	Limited data were provided on AEs, but appear to have been drawn from all 80 patients randomized to treatment. Figures at left are from the 13/80 patients (16%) who withdrew from the trial. Data from these patients were not included in the efficacy analyses. Of the 67 patients completing the trial and included in the efficacy analyses, weight gain was reported by 22/34 (65%) who took pizotifen and by 9/33 (27%) who took oxitriptan.
	Number of patients evaluable for AEs:	(See note)	(See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	5 (nausea, diarrhea, pyrosis, drowsiness)	
Bonuso, Di Stasio, Barone, et al., 1983		**DHE (timed-release)**, 5 mg, 2x/day for 2 mos	**Amitriptyline**, 75 mg/day (dosing schedule not described) for 2 mos	Investigators reported only that the most common AEs reported with DHE were nausea and stomach ache; the most common AEs associated with amitriptyline were drowsiness and dry mouth.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	2	3	
Børgesen, Nielsen, and Møller, 1974		**Propranolol**, 40 mg, 3x/day for 12 wks	**Placebo**	Little information was provided on AEs from the 45 patients randomized to treatment in this crossover trial. Investigators reported that patients had been informed before the trial began that they might experience AEs such as fatigue, drowsiness, and diarrhea. Many patients reported such side effects, both when receiving propranolol and when receiving placebo. Investigators reported that "none of the side effects were persistent or intolerable."
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	2 (N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bousser, Chick, Fuseau, et al., 1988		**DHE + aspirin (timed-release)**, 5 mg + 40 mg, 2x/day for 2 mos	**Placebo**	Data on AEs were reported only for those patients who completed the trial (38/45). Six patients treated with DHE + aspirin and one treated with placebo reported such symptoms as nausea, sleepiness, gastralgia, and abdominal discomfort (numbers reporting each symptom N/S). Four patients on placebo temporarily suspended treatment due to AEs (diarrhea, vomiting, gastralgia), as did one of the same patients on DHE + aspirin (diarrhea).
	Number of patients evaluable for AEs:	38*	38*	
	Number of patients reporting AEs:	7 (18%)	5 (13%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	
Bradley, Hudgson, Foster, et al., 1968		**Flumedroxone**, 10 mg, 3x/day for 3 mos	**Placebo**	Data at left concern only those patients who completed the trial (39/48). Two patients withdrew prematurely due to AEs associated with flumedroxone (severe polymenorrhagia and nausea; mastitis and glandular-fever-like syndrome). AEs reported by male patients in association with flumedroxone included drowsiness, dyspepsia, and decreased libido (no n's reported). Six of 14 women of reproductive age reported polymenorrhagia. One of these six also reported engorgement of the breasts and varicose veins. *Flumedroxone vs. placebo:* 0.28 (0.078 to 0.46)
	Number of patients evaluable for AEs:	39*	39*	
	Number of patients reporting AEs:	17 (44%)	6 (15%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bredfeldt, Sutherland, and Kruse, 1989		**Clonidine (Dixarit®),** ≈ 0.2 mg/day via 1 transdermal (Catapres TTS-2®) patch/wk for 6 wks	**Placebo**	Investigators reported that "[i]n general, both patches were well tolerated by study participants." Of patients completing the trial, 6 reported skin irritation under clonidine patch; 1 experienced fatigue (treatment N/S); and "several" experienced dry mouth (treatment N/S). No AEs were reported for patients taking placebo.
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	3 (overtired)	0	Some patients (number N/S) were also taking OTC meds containing acetaminophen or narcotic preparations prescribed by physicians.
Briggs and Millac, 1979		**Timolol,** 10 mg, 2x/day for 12 wks	**Placebo**	Limited data were provided on AEs. The data at left concern all 14 patients randomized to treatment in this crossover trial.
	Number of patients evaluable for AEs:	14* (See note)	14* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Cold extremities	1 (7%)	0	
	Visual disturbance	0	1 (7%)	
	Withdrawals due to AEs:	0	1 (constipation & fluid retention)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Buscaino, Sorge, Bussone, et al., 1991		**DHE (timed-release),** 10 mg, 1x/day for 2 mos	**DHE (timed-release),** 5 mg, 2x/day for 2 mos	*10 mg, 1x/day vs. 5 mg, 2x/day:* -0.022 (-0.17 to 0.12)
	Number of patients evaluable for AEs:	45	45	
	Number of patients reporting AEs:	6 (13%)	7 (16%)	
	Total number of AEs reported:	6		
	Number of patients reporting:	*n (%)*	*n (%)*	
	Epigastralgia	1 (2%)	4 (9%)	
	Heartburn	1 (2%)	1 (2%)	
	Nausea	1 (2%)	0	
	Increase in appetite	1 (2%)	1 (2%)	
	Auricular tinnitus	0	1 (2%)	
	Polyphagism	0	1 (2%)	
	Paresthesia	1 (2%)	0	
	Rise in diastolic BP	1 (2%)	0	
	Headache	0	1 (2%)	
	Withdrawals due to AEs:	1 (heartburn)	4 (epigastralgia [2]; epigastralgia, auricular tinnitus, and polyphagism [1]; heartburn [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Bussone, Baldini, D'Andrea, et al., 1987		**Nimodipine**, 120 mg/day for 12 wks	**Flunarizine**, 10 mg/day for 12 wks	*Nimodipine vs. flunarizine*: -0.28 (-0.55 to 0.030)
	Number of patients evaluable for AEs:	14	16	
	Number of patients reporting AEs:	2 (14%)	7 (44%)	
	Total number of AEs reported:	2	9	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight increase	0	5 (31%)	
	Erythema	0	2 (13%)	
	Abdominal discomfort	1 (7%)	0	
	Exacerbation of insomnia	1 (7%)	0	
	Drowsiness/daytime sedation	0	1 (6%)	
	Depression	0	1 (6%)	
	Withdrawals due to AEs:	1 (causative AEs N/S)	2 (causative AEs N/S)	
Cangi, Boccuni, Zanotti, et al., 1989		**Dihydroergokryptine (DEK)**, 10 mg, 2x/day for 2 mos	**Methysergide**, 1 mg, 2x/day for 2 mos	This was an abstract reporting interim results of a longer-term trial. Regarding AEs, investigators reported only that "both drugs have been well tolerated by patients" (p. 449).
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	
Canonico, Scapagnini, Genazzani, et al., 1989		**Dihydroergokryptine (DEK)**, 10 mg, 2x/day for 2 mos	**Placebo**	Abstract providing limited information. Dropouts were not described.
	Number of patients evaluable for AEs:	102*	102*	*DEK vs. placebo:* 0.039 (-0.0027 to 0.080)
	Number of patients reporting AEs:	4 (4%)	0	
	Total number of AEs reported:	N/S	0	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Carrieri, Orefice, and Sorge, 1988		**Indobufen**, 200 mg, 2x/day for 3 mos	**Placebo**	Data at left appears to be for those patients who completed 3 mos of treatment (35/40). None of the 5 patients who withdrew prematurely did so due to AEs.
	Number of patients evaluable for AEs:	18	17	
	Number of patients reporting AEs:	2 (11%)	1 (6%)	
	Total number of AEs reported:	2	1	
	Number of patients reporting:	*n (%)*	*n (%)*	*Indobufen vs. placebo:* 0.049 (-0.15 to 0.24)
	Transient heartburn	2 (11%)	1 (6%)	
	Withdrawals due to AEs:	0	0	
Carroll and Maclay, 1975		**Pizotifen (Sanomigran®)**, inc'd from 0.5 mg, 1x/day to 0.5 mg, 3x/day for 2 wks or until end of trial -- if relief insufficient, dose increased to 1 mg, 3x/day until end of 2-mo trial	**Placebo**	Investigators reported that of all 27 patients randomized to treatment, 4 reported weight gain (treatment N/S); 2 reported having hemiparaesthesia and apprehension, as well as other (unspecified) AEs, after being treated with placebo.
	Number of patients evaluable for AEs:	(See note)	(See note)	Of 27 patients, several withdrew from the trial. One withdrew after treatment with pizotifen for feeling "drugged, dazed, hungry, and depressed"; 2 withdrew for weight gain (treatment N/S); 1 withdrew because of depression (treatment N/S); and 1 withdrew because of "worsening HA" (treatment N/S).
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Carroll, Reidy, Savundra, et al., 1990		**Propranolol (long-acting),** 160 mg/day for 12 wks	**Propranolol (long-acting),** 80 mg/day for 12 wks	Four patients reported "tiredness" during the placebo washout period, one of whom withdrew for this reason. Three additional patients withdrew after failure to respond to the trial medication, and five withdrew for unspecified reasons.
	Number of patients evaluable for AEs:	51* (See note)	51* (See note)	
	Number of patients reporting AEs:	27 (53%)	18 (35%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*Propranolol (long-acting) 160 mg vs. propranolol (long-acting) 80 mg:* 0.17 (-0.017 to 0.35)
	Tiredness	9 (18%)	11 (22%)	
	Withdrawals due to AEs:	3 (dizziness, visual disturbance, insomnia & depression)	1 (nausea & drowsiness)	
Cerbo, Casacchia, Formisano, et al., 1986		**Flunarizine,** 15 mg/day for 2 mos	**Pizotifen,** 1.5 mg/day for 2 mos	
	Number of patients evaluable for AEs:	21*	21*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	17	24	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	9 (43%)	10 (48%)	
	Weight gain	4 (19%)	11 (52%)	
	Asthenia	2 (10%)	2 (10%)	
	Constipation	1 (5%)	0	
	Xerostomia	1 (5%)	0	
	Decrease of libido	0	1 (5%)	
	Withdrawals due to AEs:	0	4 (weight gain [1], reasons for other three withdrawals N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Couch, Bearss, and Verhulst, 1987		**Fenoprofen**, 600 mg, 3x/day for 12 wks	**Fenoprofen**, 200 mg, 3x/day for 12 wks	**Placebo**	No information provided on AEs.
	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	N/S	
Couch and Hassanein, 1979 *and* Couch and Hassanein, 1976		**Amitriptyline**, 50-100 mg/day for 4-8 wks		**Placebo**	Limited information reported (none in interim report [1976]). Patients were questioned about specific AEs. "Dry mouth," "bad taste," and "drowsiness" were significantly more common with amitriptyline. There were no significant differences in the occurrence of other AEs.
	Number of patients evaluable for AEs:	55		61	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	5 (rash [2], hypertension [1], nausea [1], numbness in hands and feet [1])		2 (both chest pain)	
Dahlöf, 1987		**Propranolol**, 40 mg, 3x/day for 1 mo		**Placebo**	Limited information was provided on AEs. Patients had been asked to record any central nervous system-related AEs on a visual analog scale. Investigators reported that such AEs were "significantly more frequent during the month of propranolol treatment in comparison to placebo."
	Number of patients evaluable for AEs:	28* (See note)		28* (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Das, Ahuja, and Narainaswamy, 1979		**Clonidine,** 25 µg, 2x/day for 6 wks	**Placebo**	Investigators did not report information on withdrawals (for any reason), so data at left concern only those patients who completed the crossover.
	Number of patients evaluable for AEs:	20*	20*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	0	N/S	Investigators reported that "[n]o side effects of clonidine were observed" but did not report whether or not patients taking placebo experienced AEs.
	Withdrawals due to AEs:	0 (See note)	N/S (See note)	
De Benedittis and Massei, 1986		**Oxitriptan,** 400 mg/day orally for 2 mos	**Placebo**	Data on AEs at left are from the 31/40 patients from whom efficacy data were obtained.
	Number of patients evaluable for AEs:	31*	31*	
	Number of patients reporting AEs:	5 (16%)	6 (19%)	*Oxitriptan vs. placebo*: -0.032 (-0.22 to 0.16)
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Gastric distress:	2 (6%)	3 (10%)	
	Drowsiness:	1 (3%)	0	
	Pyrosis:	1 (3%)	0	
	Weight gain:	1 (3%)	0	
	Dizziness:	0	1 (3%)	
	Palpitations:	0	1 (3%)	
	Unspecified:	0	2 (6%)	
	Withdrawals due to AEs:	0	1 (N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Dennerstein, Morse, Burrows, et al., 1988		**Estradiol gel**, 1.5 mg/day, 7 days/mo for 2 mos	**Placebo**	*Estradiol vs. placebo:* 0.18 (0.0013 to 0.34)
	Number of patients evaluable for AEs:	22*	22*	
	Number of patients reporting AEs:	4 (18%)	0	
	Total number of AEs reported:	4	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Amenorrhea	2 (9%)	0	
	Skin rash	1 (5%)	0	
	Ache in leg	1 (5%)	0	
	Withdrawals due to AEs:	2 (skin rash, ache in leg)	0	
Diamond and Freitag, 1993		**Flunarizine**, 10 mg/day for 5 mos	**Placebo**	No further information provided on AEs.
and	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
Freitag, Diamond, and Diamond, 1991	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	5 (causative AEs N/S)	3 (causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Diamond and Medina, 1976		**Propranolol**, 80 mg (or up to 160 mg/day) for 4 wks (or up to 8 wks)	**Placebo**	The data at left concern all patients randomized to treatment in this crossover trial. Investigators reported that "most side effects were transient and clinically unimportant." AEs occurring on both treatments were nausea, light-headedness, fatigue, difficulty catching breath, mild depression, and heartburn. AEs occurring only after treatment with propranolol were diarrhea, abdominal cramps, irritability, insomnia, and sleepiness. Investigators did not report AEs occurring only after treatment with placebo. One patient treated with the active drug had precordial pain, with a normal electrocardiogram, and blood in sputum and stools. The relationship of these symptoms to propranolol was not proven. *Propranolol vs. placebo:* 0.072 (-0.036 to 0.18)
	Number of patients evaluable for AEs:	83*	83*	
	Number of patients reporting AEs:	15 (18%)	9 (11%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	6 (N/S)	1 (N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Diamond, Solomon, Freitag, et al., 1987		**Fenoprofen**, 600 mg, 3x/day for 12 wks	**Fenoprofen**, 200 mg, 3x/day for 12 wks	**Placebo**	
	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Gastrointestinal symptoms	N/S (13.5%)	N/S (10%)	N/S (4%)	
	Fatigue and/or somnolence	N/S (4%)	N/S (16%)	N/S (3.3%)	
	Withdrawals due to AEs:	4 (GI symptoms, 3; fatigue, 1)	3 (GI symptoms, 3)	4 (GI symptoms, 1; fatigue, 1; photosensitivity, 1; blurred vision, 1)	
Ekbom, 1975		**Alprenolol**, 200 mg, 2x/day for 6 wks		**Placebo**	The data at left appear to concern all patients randomized to treatment, but this is not clear. Investigators reported that two additional patients withdrew from treatment with the active drug "because of illness," but did not clarify whether the illness was considered an AE.
	Number of patients evaluable for AEs:	33* (See note)		33* (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Retrosternal burning sensations on swallowing	3 (9%)		0	
	Perspiration	2 (6%)		0	
	Dryness of mouth	1 (3%)		0	
	Dizziness	1 (3%)		0	
	Tiredness and dizziness	1 (3%)		0	
	Withdrawals due to AEs:	1 (depression and palpitation)		N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ekbom and Lundberg, 1972		**Pindolol**, 2.5 -5 mg, 3x/day for 1 mo		**Placebo**	No further information provided. Data on withdrawals due to AEs were not reported separately for the two doses of pindolol.
	Number of patients evaluable for AEs:	20		10	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	4 (orthostatic hypotension [2], increased HA [1], dizziness and cystopyelitis [1])		0	
Ekbom and Zetterman, 1977		**Oxprenolol**, 80 mg, 3x/day for 2 mos		**Placebo**	Investigators stated only that "no serious side-effects were noted" (p. 183).
	Number of patients evaluable for AEs:	34*		34*	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		0	
Elkind, Webster, Herbertson, et al., 1989a		**Guanfacine,** 1.0 mg/day for 12 wks	**Guan-facine,** 0.5 mg/day for 12 wks	**Placebo**	Three patients withdrew due to unspecified AEs. Investigators did not identify treatment groups from which patients withdrew, but reported that no AEs were "serious."
	Number of patients evaluable for AEs:	12	13	12	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	N/S (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 1**		**Tropisetron** 50 mg/day for 3 mos	**Tropisetron,** 25 mg/day for 3 mos	**Placebo**	Investigators reported that they assessed all patients randomized to treatment for AEs. Data at left concern the 7/146 patients (5%) who withdrew due to AEs, who were excluded from efficacy analyses. Additional AEs reported were constipation in 54, 55, and 9 cases occurring in the tropisetron 50 mg, tropisetron 25 mg, and placebo groups, respectively. "Other" unspecified AEs were reported in 33, 19, and 24 cases in patients treated with tropisetron 50 mg, tropisetron 25 mg, and placebo, respectively. In 13 patients (tropisetron 50 mg, 7; tropisetron 25 mg, 5; placebo, 1), constipation led to the reduction of the dose by 0.5 -1 capsule every other day.
	Number of patients evaluable for AEs:	50 (See note)	47 (See note)	49 (See note)	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	87	74	33	
	Number of patients *withdrawing* due to:	*n* (%)	*n* (%)	*n* (%)	
	Constipation	2 (4%)	2 (4%)	0	
	Skin reaction	2 (4%)	0	0	
	Tremor (hands/foot)	0	0	1 (2%)	
	Withdrawals due to AEs:	4 (listed above)	2 (listed above)	1 (listed above)	
Ferrari, Wilkinson, Hirt, et al., 1991 **Study 2**		**Tropisetron,** 15 mg/day for 3 mos		**Placebo**	Investigators reported that they assessed all patients randomized to treatment for AEs. Data at left concern the 3/58 patients (5%) who withdrew due to AEs, who were excluded from efficacy analyses. Additional AEs reported were constipation in 42 cases occurring in the group treated with tropisetron 15 mg. No cases of constipation were reported in the placebo group. "Other" unspecified AEs were reported in 37 and 35 cases in patients treated with tropisetron 15 mg and placebo, respectively.
	Number of patients evaluable for AEs:	38 (See note)		20 (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	79		35	
	Number of patients *withdrawing* due to:	*n* (%)		*n* (%)	
	Constipation	1 (3%)		0	
	Hypoglycemia	1 (3%)		0	
	Nausea/vomiting	1 (3%)		0	
	Withdrawals due to AEs:	3 (listed above)			

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Fiorini, Sances, Martignoni, et al., 1991		**Dihydroergokryptine (DEK),** 10 mg, 2x/day for 2 mos	**Placebo**	Abstract reporting limited information. No data reported on AEs.
	Number of patients evaluable for AEs:	20*	20*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	
Formisano, Falaschi, Cerbo, et al., 1991		**Nimodipine,** 120 mg/day for 4 mos	**Propranolol,** 120 mg/day for 4 mos	
	Number of patients evaluable for AEs:	12	10	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	12	6	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastric discomfort	4 (33%)	0	
	Paraesthesia	2 (17%)	1 (10%)	
	Weight gain	2 (17%)	0	
	Flushing	2 (17%)	0	
	Menstrual irregularities	1 (8%)	1 (10%)	
	Dizziness	0	2 (20%)	
	Insomnia	1 (8%)	0	
	Arterial hypotension	0	1 (10%)	
	Asthma	0	1 (10%)	
	Withdrawals due to AEs:	1 (flushing)	2 (arterial hypotension [1], asthma [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Forssman, Henriksson, Johannsson, et al., 1976		**Propranolol**, 80 mg, 3x/day for 10 wks (gradually increased)	**Placebo**	
	Number of patients evaluable for AEs:	38*	38*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	22	9	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Increase in weight > 2 kg	5 (13%)	0	
	Insomnia	5 (13%)	1 (3%)	
	Tiredness	4 (11%)	3 (8%)	
	Uncharacteristic dizziness	3 (8%)	2 (5%)	
	Feeling of numbness, paraesthesiae	2 (5%)	1 (3%)	
	Nausea	2 (5%)	1 (3%)	
	Increased appetite	1 (3%)	0	
	Palpitations	1 (3%)	1 (3%)	
	Withdrawals due to AEs:	2 (tiredness, dizziness)	2 (tiredness, dizziness)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Forssman, Henriksson, and Kihlstrand, 1972		**Pizotifen**, 2-3 mg/day for 10 wks	**Methysergide**, 4-6 mg/day for 10 wks	One patient suspended treatment during *both* treatment periods due to AEs (drowsiness and irritation).
	Number of patients evaluable for AEs:	22*	22*	
	Number of patients reporting AEs:	20 (91%)	20 (91%)	*Pizotifen vs. methysergide:*
	Total number of AEs reported:	19	25	0 (-0.18 to 0.18)
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	9 (41%)	8 (36%)	
	Increased appetite and weight gain	6 (27%)	3 (14%)	
	Nausea	0	5 (23%)	
	Dizziness	2 (9%)	1 (5%)	
	Diarrhea	1 (5%)	2 (9%)	
	Depression	0	3 (14%)	
	Feelings of irritation	1 (5%)	1 (5%)	
	Feeelings of tightness	0	2 (9%)	
	Withdrawals due to AEs:	**1** (See note)	1 (See note)	
Forssman, Lindblad, and Zbornikova, 1983		**Atenolol**, 100 mg/day for 3 mos	**Placebo**	The data at left appear to concern all 24 patients randomized to treatment in this crossover trial, but this is not clear.
	Number of patients evaluable for AEs:	24* (See note)	24* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Slight dizziness of orthostatic type	6 (25%)	1 (4%)	
	Diffuse tiredness	2 (8%)	0	
	Withdrawals due to AEs:	1 (mood alterations)	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Frediani, Grazzi, Zanotti, et al., 1991		**Dihydroergokryptine (DEK),** 10 mg, 2x/day for 4 mos	**DHE (timed-release),** 5 mg, 2x/day for 4 mos	*DEK vs. DHE:* 0.067 (-0.14 to 0.27)
	Number of patients evaluable for AEs:	29*	29*	
	Number of patients reporting AEs:	7 (24%)	5 (17%)	
	Total number of AEs reported:	8	6	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastric pain	3 (10%)	1 (3%)	
	Constipation	2 (7%)	2 (7%)	
	Nausea	2 (7%)	1 (3%)	
	Dizziness	1 (3%)	0	
	Malaise	0	1 (3%)	
	Skin rash	0	1 (3%)	
	Withdrawals due to AEs:	3 (gastric pain and/or nausea)	1 (skin rash)	
Freitag and Diamond, 1984		**Nadolol,** up to 240 mg/day (3 groups combined) for 3 mos	**Placebo**	Investigators reported that one patient developed a significant bradycardia (< 45 beats per minute). Medication was discontinued and the patient was subsequently dropped from the study.
	Number of patients evaluable for AEs:	24	8	
	Number of patients reporting AEs:	4 (17%)	N/S	
	Total number of AEs reported:	5 (21%)	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Fatigue	3 (13%)	N/S	
	Bradycardia	1 (4%)	N/S	
	Withdrawals due to AEs:	1 (See note)	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Frenken and Nuijten, 1984		**Flunarizine**, 10 mg/day for 12 wks	**Placebo**	*Flunarizine vs. placebo:* 0.14 (-0.18 to 0.44)
	Number of patients evaluable for AEs:	17	18	
	Number of patients reporting AEs:	10 (59%)	8 (44%)	
	Total number of AEs reported:	12	8	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Daytime sedation	7 (41%)	3 (17%)	
	Weight gain	3 (18%)	0	
	Stomach complaints	0	4 (22%)	
	Other	2 (12%)	1 (6%)	
	Withdrawals due to AEs:	0	0	
Gawel, 1987		**Nimodipine**, 120 mg/day for 3 mos	**Pizotifen**, 3 mg/day for 3 mos	Abstract reporting limited results. The most common AEs associated with nimodipine were nausea and flushing, and with pizotifen, weight gain and sedation. Six patients overall withdrew prematurely, but it is not clear how many (if any) of these were due to AEs.
	Number of patients evaluable for AEs:	60*	60*	
	Number of patients reporting AEs:	21 (35%)	15 (25%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	*Nimodipine vs. pizotifen:* 0.099 (-0.064 to 0.26)
Gawel, Kreeft, Nelson, et al., 1992		**Flunarizine**, 10 mg/day for 4 mos	**Propranolol**, 160 mg/day for 4 mos	Investigators did not provide a numerical breakdown of specific AEs, but reported that propranolol was associated with a greater incidence of dizziness, hypo-aesthesia, insomnia, agitation, nausea, diarrhea, and dyspepsia. Fatigue and weight gain were more common in the flunarizine group. The incidence of depression was comparable in the two groups (3.3%).
	Number of patients evaluable for AEs:	44	45	
	Number of patients reporting AEs:	33 (75%)	36 (80%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	3 (depression, weight gain, fatigue)	5 (bloating, weight gain; bloating; rash; increased HA; increased HA, depression)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Gelmers, 1983		**Nimodipine**, 40 mg, 3x/day for 3 mos		**Placebo**	*Nimodipine vs. placebo:* -0.098 (-0.31 to 0.12)
	Number of patients evaluable for AEs:	30		30	
	Number of patients reporting AEs:	6 (20%)		9 (30%)	
	Total number of AEs reported:	6		19	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Vertigo and/or dizziness	0		6 (20%)	
	Abdominal discomfort	5 (17%)		0	
	Weight loss	1 (3%)		0	
	Back pain	0		1 (3%)	
	Blurred vision	0		1 (3%)	
	Derealization	0		1 (3%)	
	Bifrontal HA	0		1 (3%)	
	Total body pruritus	0		1 (3%)	
	Withdrawals due to AEs:	0		0	
Gerber, Diener, Scholz, et al., 1991		**Nifedipine**, 40 mg/day for 2 mos	**Metoprolol**, 200 mg/day for 2 mos	**Propranolol**, 160 mg/day for 2 mos	AEs reported for high-dosage phase of trial only. Percentages at left are estimated from graph.
	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Fatigue	(38%)	(60%)	(33%)	
	Vertigo	(32%)	(20%)	(22%)	
	Sleep disorders	(9%)	(10%)	(11%)	
	Body weight increase	(15%)	(5%)	(11%)	
	Circulatory disturbances	(8%)	(5%)	(28%)	
	Swollen legs	(31%)	0	(5%)	
	Withdrawals due to AEs:	N/S	0	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Gerber, Schellenberg, Thom, et al., 1995		**Cyclandelate**, 1200 mg/day for 8 wks, 1600 mg/day for 8 wks	**Propranolol**, 120 mg/day for 8 wks, 160 mg/day for 8 wks	The only AEs described were those deemed by the investigators to be drug-related.
	Number of patients evaluable for AEs:	42	42	
	Number of patients reporting AEs:	4 (10%)	6 (14%)	*Cyclandelate vs. propranolol:*
	Total number of AEs reported:	6	8	-0.047 (-0.18 to 0.093)
	Number of patients reporting:	*n (%)*	*n (%)*	
	Allergic reaction/exanthema	1 (2%)	3 (7%)	
	GI or cardiovascular problems	1 (2%)	3 (7%)	
	Dizziness	2 (5%)	1 (2%)	
	Worsening of HA	1 (2%)	0	
	Tiredness/loss of motivation	0	1 (2%)	
	Excessive thirst	1 (2%)	0	
	Withdrawals due to AEs:	N/S	N/S	
Gomersall and Stuart, 1973		**Amitriptyline**, 30-60 mg/day for 27 wks	**Placebo**	Data reported at left are for the 20 patients (of 26) who completed the trial. One patient withdrew prematurely due to increased HAs while taking placebo.
	Number of patients evaluable for AEs:	20*	20*	
	Number of patients reporting AEs:	16 (80%)	13 (65%)	
	Total number of AEs reported:	26	15	*Amitriptyline vs. placebo:*
				0.15 (-0.13 to 0.40)
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	10 (50%)	4 (20%)	
	Dry mouth	7 (35%)	2 (10%)	
	Nausea	2 (10%)	2 (10%)	
	Increased HAs	1 (5%)	3 (15%)	
	Weight gain	1 (5%)	2 (10%)	
	Depression	1 (5%)	1 (5%)	
	Hypertension	1 (5%)	1 (5%)	
	Constipation	1 (5%)	0	
	Disturbing dreams	1 (5%)	0	
	Dizziness	1 (5%)	0	
	Withdrawals due to AEs:	0	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Grotemeyer, Scharafinski, Schlake, et al., 1990		**Aspirin**, 500 mg, 3x/day for 3 mos	**Metoprolol**, 200 mg, 1x/day for 3 mos	Investigators reported data only on those patients who withdrew from the trial due to AEs.
	Number of patients evaluable for AEs:	28*	28*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	5 (gastrointestinal AEs)	2 (drowsiness)	
Grotemeyer, Schlake, and Husstedt, 1989		**Etilefrene pivalate**, 20 mg/day for 3 mos	**Flunarizine**, 5 mg/day for 3 mos	Abstract reporting limited results.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	1 (gastritis)	
Grotemeyer, Schlake, Husstedt, et al., 1987		**Flunarizine**, 10 mg/day for 3 mos	**Metoprolol**, 200 mg/day for 3 mos	Abstract reporting limited results. Some (unspecified number of) patients in both groups reported weight gain, which was more pronounced with flunarizine than with metoprolol (2.6% vs. 0.8% on average).
	Number of patients evaluable for AEs:	28*	28*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	2 (hypotonic reaction)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Havanka-Kanniainen, Hokkanen, and Myllylä, 1985b		**Nimodipine**, 120 mg/day for 8 wks	**Placebo**	Limited information was provided on AEs. Investigators reported that "no marked side effects were reported." Patients recorded possible AEs in their HA diaries.
	Number of patients evaluable for AEs:	33*	33*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Vertigo	3 (9%)	N/S	
	Flushing	2 (6%)	N/S	
	Itching	1 (3%)	N/S	
	Withdrawals due to AEs:	0	0	
Havanka-Kanniainen, Hokkanen, and Myllylä, 1987		**Nimodipine**, 120 mg/day for 3 mos	**Pizotifen**, 1.5 mg/day for 3 mos	
	Number of patients evaluable for AEs:	50*	50*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	0	16 (32%)	
	Fatigue	0	5 (10%)	
	Vertigo	0	4 (8%)	
	Nausea	0	4 (8%)	
	Withdrawals due to AEs:	0	0	
Havanka-Kanniainen, Hokkanen, and Myllylä, 1988		**Propranolol (long-acting)**, 160 mg, 1x/day for 3 mos	**Propranolol (long-acting)**, 80 mg, 1x/day for 3 mos	Limited information reported on AEs. 1 patient withdrew due to AEs (nausea, vomiting, tiredness, and insomnia) associated with propranolol (dose N/S). Other side effects reported included cold hands and feet, fatigue, and vivid dreams.
	Number of patients evaluable for AEs:	48*	48*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Hering and Kuritzky, 1992		**Sodium valproate,** 400 mg, 2x/day for 8 wks	**Placebo**	Figures at left are for those patients who completed the trial (29/32). Three patients withdrew prematurely due to unspecified AEs, one while taking sodium valproate and two while taking placebo. Data on AEs were collected during monthly clinic visits.
	Number of patients evaluable for AEs:	29*	29*	
	Number of patients reporting AEs:	6 (21%)	2 (7%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	*Sodium valproate vs. placebo:* 0.13 (-0.044 to 0.30)
	Dyspepsia	2 (7%)	0	
	Nausea	2 (7%)	0	
	Mild weariness	2 (7%)	0	
	Constipation	0	1 (3%)	
	Dizziness	0	1 (3%)	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Herrmann, Horowski, Dannehl, et al., 1977		**Lisuride**, 25 mcg, 3x/day for 3 mos	**Methysergide**, 2 mg, 3x/day for 3 mos	Detailed information was provided only about those AEs that led patients to withdraw from the trial. Investigators reported that the difference in the number of patients withdrawing due to AEs was significant ($p<0.05$).
	Number of patients evaluable for AEs:	130	123	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients *withdrawing* due to:	*n (%)*	*n (%)*	Data on AEs were collected at monthly clinic visits, where patients were specifically asked about AEs commonly associated with ergot therapy. Investigators acknowledged that this may have had the effect of increasing the overall frequency of reported AEs.
	Nausea	7 (5%)	21 (17%)	
	Vomiting	2 (2%)	18 (15%)	
	Dizziness	3 (2%)	16 (13%)	
	Gastrointestinal complaints	6 (5%)	10 (8%)	
	Drowsiness	4 (3%)	5 (4%)	
	Myalgia and neuralgia	0	6 (5%)	
	Paraesthesia	0	5 (4%)	
	Tachycardia	0	4 (3%)	
	Angina-like symptoms	0	3 (2%)	
	Eye pain	0	3 (2%)	
	Tiredness	0	3 (2%)	
	Withdrawals due to AEs:	22 (See note)	48 (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Herrmann, Krištof, and Sastre y Hernandez, 1978		**Lisuride**, dose gradually increased during first wk of trial up to 0.075 mg/day for 6 mos	**Placebo**	The data at left appear to concern all 240 patients randomized to treatment, not just the 214 from whom efficacy data were obtained; however, this is not clear.
	Number of patients evaluable for AEs:	103 (See note)	111 (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	The AEs at left are those for which significant differences were found between the treatments. Investigators stated that significant differences had also been noted between the two treatments for these AEs prior to treatment.
	Number of patients reporting:	*n* (%)	*n* (%)	
	Cold feelings in extremities	44 (43%)	13 (12%)	
	Skin manifestations	14 (14%)	6 (5%)	
	Tachycardia	12 (12%)	6 (5%)	
	Vertigo	25 (24%)	7 (6%)	
	Withdrawals due to AEs:	2 (N/S)	0	Investigators reported having "examined" other AEs both prior to and during the trial, but it is not clear whether or not those AEs were reported by patients. The other AEs were: euphoria, nausea, sleep disturbances, dryness of mouth, dysphoric mood, diarrhea, stenocardial complaints, numbness, hallucinations, hot flushes, muscular weakness and pains, and vomiting.

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Hübbe, 1973		**Pizotifen**, 1 mg, 3x/day for 8 wks	**Prochlorperazine**, 5 mg, 3x/day for 8 wks	Data at left are for those patients who completed the trial and were included in the efficacy analysis. Three patients withdrew before completing the trial, one due to lack of efficacy and two for unknown reasons.
	Number of patients evaluable for AEs:	40*	40*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	76	33	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	29 (73%)	16 (40%)	
	Drowsiness	19 (48%)	9 (23%)	
	Increased appetite	8 (20%)	1 (3%)	
	Irritability	6 (15%)	2 (5%)	
	Dizziness	5 (13%)	3 (8%)	
	Dyspepsia	3 (8%)	0	
	Hot flushes	1 (3%)	2 (5%)	
	Edema	2 (5%)	0	
	Paresthesia	2 (5%)	0	
	Palpitations	1 (3%)	0	
	Withdrawals due to AEs:	(See note)	(See note)	
Hudgson, Foster, and Newell, 1967		**Flumedroxone**, 5 mg, 3x/day for 4 mos	**Methysergide**, 1 mg, 3x/day for 4 mos	*Flumedroxone vs. methysergide:* 0.20 (0.053 to 0.33)
	Number of patients evaluable for AEs:	40*	40*	
	Number of patients reporting AEs:	9 (23%)	1 (3%)	
	Total number of AEs reported:	15	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Polymenorrhea	5 (13%)	0	
	Worsening of HA	3 (8%)	0	
	Syncope	1 (3%)	0	
	Nausea, vomiting, and vertigo	0	1 (3%)	
	Withdrawals due to AEs:	4 (worsening of HA [3], syncope [1])	1 (nausea, vomiting, and vertigo)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Hughes and Foster, 1971		**Pizotifen (BC105)**, inc'd from 0.5 mg, 1x/day to 0.5 mg, 3x/day for 10 days; then 1 mg, 3x/day for 6 wks	**Placebo**	
	Number of patients evaluable for AEs:	26*	26*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Facial flushing	1 (4%)	N/S	
	Increased appetite (voracious)	2 (8%)	0	
	Increased tiredness	5 (19%)	N/S	
	Increased vomiting	1 (4%)	N/S	
	Increased weight gain	10 (38%)	0	
	Withdrawals due to AEs:	0	0	
Jacobs, 1972		**Opipramol**, 50 mg, 3x/day for 12 wks	**Placebo**	No patients known to have withdrawn due to AEs; no further information provided.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Jensen, Brinck, and Olesen, 1994		**Sodium valproate (slow-release)**, 1000-1500 mg/day for 12 wks	**Placebo**	Data on AEs were collected during monthly clinic visits. *Sodium valproate vs. placebo:* 0.16 (-0.020 to 0.33)
	Number of patients evaluable for AEs:	43*	43*	
	Number of patients reporting AEs:	14 (33%)	7 (16%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Nausea	5 (12%)	2 (5%)	
	Drowsiness	5 (12%)	2 (5%)	
	Weight gain	3 (7%)	1 (2%)	
	Vertigo	3 (7%)	0	
	Abdominal pain	2 (5%)	1 (2%)	
	Increased appetite	1 (2%)	1 (2%)	
	Diarrhea	1 (2%)	0	
	Restless legs	1 (2%)	0	
	Dry mouth	1 (2%)	0	
	Tremor	1 (2%)	0	
	Pain in neck/shoulders	1 (2%)	0	
	Dyspnea	1 (2%)	0	
	Tinnitus	0	1 (2%)	
	Withdrawals due to AEs:	4 (nausea [3], vertigo [2], weight gain [1], dry mouth [1], tremor [1])	2 (abdominal pain [1], weight gain [1], increased appetite [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Johannsson, Nilsson, Widelius, et al., 1987		**Atenolol**, 100 mg, 1x/day for 3 mos		**Placebo**	No further information provided on AEs.
	Number of patients evaluable for AEs:	63*		63*	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		3 (intolerable HA [1], nausea and fatigue [1], sleep disturbances [1])	
Johnson, Hornabrook, and Lambie, 1986		**Mefenamic acid**, 250 mg, 3x/day for 3 mos	**Propranolol**, 40 mg, 3x/day for 3 mos	**Placebo**	Investigators described only those AEs they believed could be attributed to the study medication.
	Number of patients evaluable for AEs:	22*	23*	24*	*Mefenamic acid vs. placebo:* 0.049 (-0.11 to 0.20)
	Number of patients reporting AEs:	2 (9%)	2 (9%)	1 (4%)	
	Total number of AEs reported:	2	2	1	*Propranolol vs. placebo:* 0.044 (-0.11 to 0.19)
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	GI symptoms/diarrhea	2 (9%)	1 (4%)	0	*Mefenamic acid vs. propranolol:* 0.0046 (-0.17 to 0.18)
	Depression	0	1 (4%)	0	
	Dizziness	0	0	1 (4%)	
	Withdrawals due to AEs:	1 (diarrhea)	1 (N/S)	1 (dizziness)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Johnson, Kadam, Hylands, et al., 1985		**Continuation of feverfew,** 50 mg/day for 6 mos	**Withdrawal of feverfew (placebo)**	The data at left appear to concern all 17 patients randomized to treatment rather than the 15 who completed treatment, but this is not clear. Investigators noted that all patients taking placebo reported at least one AE, whereas four patients taking feverfew reported none.
	Number of patients evaluable for AEs:	8 (See note)	9 (See note)	
	Number of patients reporting AEs:	4 (50%)	9 (100%)	
	Total number of AEs reported:	9	19	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Nervousness, tension, less calm, jumpy	0	5 (56%)	Two patients taking placebo withdrew because they experienced recurring headaches after having been in remission prior to the trial. (Note: In this report, "worsening headaches" are not considered AEs.)
	Tension or frequent non-migrainous HAs	0	3 (33%)	
	Insomnia, disturbed sleep, nocturnal restlessness	0	2 (22%)	
	Stiffness or pain in joints	2 (25%)	3 (33%)	
	Tiredness	0	2 (22%)	The two patients taking feverfew who reported stiffness or pain in joints had always had these symptoms.
	Nausea	0	1 (11%)	
	Lighter, irregular periods	0	1 (11%)	
	Slightly heavier periods	1 (13%)	1 (11%)	
	Palpitations	1 (13%)	0	*Continuation vs. withdrawal:* -0.46 (-0.75 to -0.086)
	Colicky abdominal pain	1 (13%)	0	
	Urinary frequency	0	1 (11%)	
	Withdrawals due to AEs:	0 (See note)	1 (disturbed sleep & stiffness in joints) (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions				Notes; Difference in proportion of patients reporting adverse events (95% CI)
Kallanranta, Hakkarainen, Hokkanen, et al., 1977		(Study 1) **Clonidine,** 75 µg/day for 4 wks	(Study 1) **Placebo**	(Study 2) **Clonidine,** 150 µg/day for 8 wks	(Study 2) **Practolol,** 150 mg/day for 8 wks	No information was provided for withdrawals (for any reason). Investigators stated that "increased clonidine use was associated with increased side effects, especially nausea and sedation." *Clonidine vs. placebo (Study 1):* 0 (-0.14 to 0.14) *Clonidine vs. practolol (Study 2):* -0.16 (-0.34 to 0.03)
	Number of patients evaluable for AEs:	50*	50*	50*	50*	
	Number of patients reporting AEs:	8 (16%)	8 (16%)	15 (30%)	23 (46%)	
	Total number of AEs reported:	8	8	18	27	
	Number of patients reporting:	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
	Dry mouth	1 (2%)	3 (6%)	0	0	
	Nausea	2 (4%)	1 (2%)	7 (14%)	9 (18%)	
	Sedation	1 (2%)	2 (4%)	6 (12%)	13 (26%)	
	Vertigo	0	1 (2%)	4 (8%)	4 (8%)	
	Weight gain	1 (2%)	0	1 (2%)	0	
	Other (mood changes, skin irritations)	3 (6%)	1 (2%)	0	1 (2%)	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	N/S (See note)	N/S (See note)	
Kallos and Kallos-Deffner, 1971		**Cafergot comp.®**, 1 cap, 2x/day for 2 menstrual periods		**Placebo**		
	Number of patients evaluable for AEs:	20*		20*		
	Number of patients reporting AEs:	N/S		N/S		
	Total number of AEs reported:	N/S		N/S		
	Number of reports of (NB: a single patient may have reported a given symptom twice):	*n (%)*		*n (%)*		
	Nausea/vomiting	11		24		
	Muscle pain	9		5		
	Visual disturbances	0		0		
	Withdrawals due to AEs:	N/S		N/S		

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Kangasniemi, 1979		**Pizotifen (Sandomigrin®)**, inc'd from 0.5 mg, 1x/day to 0.5 mg, 3x/day for 3 mos (or 14 wks, not clear)	**Iprazochrome (Migrenon®)**, inc'd from 5 mg, 1x/day to 5 mg, 3x/day for 3 mos (or 14 wks, not clear)	Data at left concern only the 34/50 patients who completed the trial and from whom efficacy data were obtained. An additional 3 patients, excluded from efficacy analyses, withdrew from the trial due to unspecified AEs (2 from pizotifen, 1 from iprazochrome).
	Number of patients evaluable for AEs:	34*	34*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	31	5	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Weight gain	25 (74%)	4 (12%)	
	Tiredness	5 (15%)	0	
	Palpitations	1 (3%)	0	
	Vertigo, dizziness	0	1 (3%)	
	Withdrawals due to AEs:	(See note)	(See note)	
Kangasniemi, Andersen, Andersson, et al., 1987		**Metoprolol** 200 mg/day for 8 wks	**Placebo**	The data at left are for the 73 of 77 patients included in the efficacy analyses.
	Number of patients evaluable for AEs:	73* (See note)	73* (See note)	
	Number of patients reporting AEs:	26 (36%)	13 (18%)	
	Total number of AEs reported:	52	25	
	Number *of AEs* reported:	*n (%)*	*n (%)*	
	Gastrointestinal	16 (31%)	3 (6%)	
	Others	16 (31%)	15 (29%)	
	Fatigue/tiredness	13 (25%)	4 (8%)	
	Sleep disturbances	4 (8%)	0	
	Cardiovascular	3 (6%)	3 (6%)	
	Withdrawals due to AEs:	1 (bradycardia)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Kangasniemi, Falck, Långvik, et al., 1978		**Oxitriptan,** 500 mg, 4x/day for 3 mos	**Placebo (levoleucine),** 320 mg, 4x/day for 3 mos	Investigators reported that no AEs were reported from pts taking oxitriptan. No information was provided on AEs resulting from the placebo treatment.
	Number of patients evaluable for AEs:	8*	8*	
	Number of patients reporting AEs:	0	0	
	Total number of AEs reported:	0	0	
	Withdrawals due to AEs:	0	0	
Kangasniemi and Hedman, 1984		**Metoprolol (controlled-release),** 200 mg/day, 1x/day for 8 wks	**Propranolol,** 80 mg, 2x/day for 8wks	
	Number of patients evaluable for AEs:	36*	36*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	54	65	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Fatigue	14 (39%)	11 (31%)	
	CNS symptoms	11 (31%)	14 (39%)	
	GI symptoms	8 (22%)	9 (25%)	
	Sleep disturbances	3 (8%)	10 (28%)	
	CV or respiratory symptoms	2 (6%)	5 (14%)	
	Others	16 (44%)	16 (44%)	
	Withdrawals due to AEs:	0	2 (causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Kangasniemi, Nyrke, Lang, et al., 1983		**Femoxetine**, 200 mg, 2x/day for 3 mos; dose reduced by half during first week	**Propranolol**, 80 mg, 2x/day for 3 mos; dose reduced by half during first week	Data at left are (apparently) for the 24 patients who completed the trial. Three other patients withdrew due to AEs associated with propranolol (tiredness, dizziness, increase in weight). There were no withdrawals due to AEs associated with femoxetine.
	Number of patients evaluable for AEs:	24*	24*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	14	38	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Dizziness	3 (13%)	10 (42%)	
	Tiredness	1 (4%)	9 (38%)	
	Sleep disturbances	1 (4%)	5 (21%)	
	Feeling unwell	2 (8%)	3 (13%)	
	Exanthema	1 (4%)	3 (13%)	
	Palpitations	1 (4%)	3 (13%)	
	Increase in weight	0	3 (13%)	
	Gastric distress	1 (4%)	1 (4%)	
	Sweating	1 (4%)	1 (4%)	
	Decrease in weight	2 (8%)	0	
	Dry mouth	1 (4%)	0	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Kåss and Nestvold, 1980		**Clonidine (Catapresan®),** 50 µg, 2x/day for 16 wks	**Propranolol (Inderal®),** 80 mg, 2x/day for 16 wks	Data at left appear to concern those 21 patients (of 23) who completed the crossover, but this is unclear.
	Number of patients evaluable for AEs:	21* (See note)	21* (See note)	
	Number of patients reporting AEs:	11 (52%)	13 (62%)	Prior to trial, patients given a test dose of 40 mg propranolol followed by testing of blood pressure and pulse rate after 30 min and 3 hrs to "exclude unwanted immediate side effects."
	Total number of AEs reported:	11	15	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Anxiety	0	1 (5%)	
	Dizziness	1 (5%)	5 (24%) (See note)	
	Fatigue	8 (38%)	4 (19%)	Investigators reported that 2 patients taking propranolol received reduced daily dosage due to dizziness.
	Gastrointestinal	1 (5%)	0	
	Insomnia	0	5 (24%)	
	Hair loss	1 (5%)	0	
	Withdrawals due to AEs:	0	0	*Clonidine vs. propranolol:* -0.09 (-0.37 to 0.20)
Kjærsgård Rasmussen, Holt-Larsen, Borg, et al., 1994		**Tolfenamic acid,** 100 mg, 3x/day for 12 wks	**Propranolol,** 40 mg, 3x/day for 12 wks	*Tolfenamic acid vs. propranolol:* 0.0015 (-0.17 to 0.17)
	Number of patients evaluable for AEs:	62*	67*	
	Number of patients reporting AEs:	26 (42%)	28 (42%)	
	Total number of AEs reported:	28	20	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastrointestinal symptoms	11 (18%)	11 (16%)	
	Dysuria	6 (10%)	1 (1%)	
	Dizziness, fatigue, tremor, drop in BP	8 (13%)	7 (10%)	
	Weight gain	2 (3%)	1 (1%)	
	Rash	1 (2%)	0	
	Withdrawals due to AEs:	5 (GI symptoms [4], rash [1])	9 (GI symptoms [4]; dizziness, etc. [5])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Klapper, 1994		**Divalproex sodium**, average dose 1100 mg/day, for 2 mos	**Propranolol**, average dose 140 mg/day, for 2 mos	Investigator reported data on AEs only for those patients who *withdrew* due to AEs.
	Number of patients evaluable for AEs:	24*	24*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients *withdrawing* due to:	*n* (%)	*n* (%)	
	Fatigue	2 (8%)	2 (8%)	
	Gastrointenstinal symptoms	3 (13%)	0	
	Increasing HAs	1 (4%)	1 (4%)	
	Low white blood count	2 (8%)	0	
	Rash	1 (4%)	0	
	Withdrawals due to AEs:	9 (See note)	3 (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions				Notes; Difference in proportion of patients reporting adverse events (95% CI)
Klapper, 1996		**Divalproex sodium, 1500 mg/day** for 12 wks	**Divalproex sodium, 1000 mg/day** for 12 wks	**Divalproex sodium, 500 mg/day** for 12 wks	**Placebo**	"Gastrointestinal events" were the primary cause of withdrawal from the divalproex sodium groups (3 in the 500-mg group, 2 in the 1000-mg group, and six in the 1500-mg group). No other details were provided.
	Number of patients evaluable for AEs:	44	43	45	44	
	Number of patients reporting AEs:	38 (86%)	32 (74%)	34 (76%)	35 (80%)	
	Total number of AEs reported:	N/S	N/S	N/S	N/S	*Divalproex sodium 1500 mg vs. placebo:* 0.067 (-0.090 to 0.22)
	Number of patients reporting most common AEs (> 10% of pts treated with active med):	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*Divalproex sodium 1000 mg vs. placebo:* -0.051 (-0.22 to 0.12)
	Nausea	34 (77%)	9 (21%)	27 (60%)	7 (16%)	
	Infection	20 (45%)	16 (37%)	18 (40%)	18 (41%)	*Divalproex sodium 500 mg vs. placebo:* -0.039 (-0.21 to 0.13)
	Dyspepsia	16 (36%)	19 (44%)	7 (16%)	9 (20%)	
	Asthenia	23 (52%)	9 (21%)	9 (20%)	9 (20%)	
	Dizziness	20 (45%)	7 (16%)	7 (16%)	5 (11%)	
	Somnolence	18 (41%)	7 (16%)	7 (16%)	5 (11%)	
	Back pain	14 (32%)	5 (12%)	7 (16%)	9 (20%)	
	Diarrhea	18 (41%)	5 (12%)	7 (16%)	5 (11%)	
	Pain	11 (25%)	7 (16%)	9 (20%)	7 (16%)	
	Tremor	16 (36%)	7 (16%)	0	0	
	Vomiting	11 (25%)	5 (12%)	4 (9%)	2 (5%)	
	Withdrawals due to AEs:	12 (See note)	6 (See note)	7 (See note)	2 (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Krakowski and Engisch, 1973		**Pizotifen,** 2 mg, 3x/day for 12 wks	**Placebo**	Data at left are for all 29 patients randomized to treatment and include the 7 patients who withdrew early and for whom efficacy data were not analyzed.
	Number of patients evaluable for AEs:	15 (See note)	14 (See note)	
	Number of patients reporting AEs:	7 (47%)	9 (64%)	
	Total number of AEs reported:	39	33	*Pizotifen vs. placebo:* 0.20 (-0.048 to 0.43)
	Number of patients reporting:	*n* (%)	*n* (%)	
	Swelling of feet	12 (80%)	1 (7%)	
	Drowsiness	8 (53%)	4 (29%)	
	Dizziness	4 (27%)	1 (7%)	
	Dry mouth	4 (27%)	1 (7%)	
	Nervousness	3 (20%)	9 (64%)	
	Depressed	2 (13%)	5 (36%)	
	Nausea	2 (13%)	5 (36%)	
	Bloated feeling	1 (7%)	2 (14%)	
	Febrile feeling	1 (7%)	0	
	Backache	0	1 (7%)	
	Muscle cramps	1 (7%)	0	
	Pruritis	1 (7%)	0	
	Stimulated	0	1 (7%)	
	Tremor	0	1 (7%)	
	Twitching	0	1 (7%)	
	Weight gain	0	1 (7%)	
	Withdrawals due to AEs:	0	N/S	
Kuritzky and Herling, 1987		**Propranolol (long-acting),** 160 mg, 1x/day for 1 mo	**Placebo**	Abstract reporting limited information. Investigators stated that the most common AEs associated with propranolol were tiredness, insomnia, and dizziness.
	Number of patients evaluable for AEs:	38*	38*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	2 (dizziness, somnolence)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Lamsudin and Sadjimin, 1993		**Nifedipine**, 20 mg/day for 3 mos	**Flunarizine**, 10 mg/day for 3 mos	Investigators reported figures for tachycardia and sedation only, broken down by treatment month. Figures at left are for the last month of treatment (3).
	Number of patients evaluable for AEs:	38	40	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Tachycardia	12 (32%)	6 (15%)	
	Sedation	6 (16%)	8 (20%)	
	Withdrawals due to AEs:	0	0	
Lance and Anthony, 1968		**Pizotifen** inc'd from 0.025 mg, 3x/day to 1 mg, 3x/day for 1 mo	**Placebo**	Data at left for pizotifen appear to include not only the 25 patients in this trial, but an additional 15 patients treated with pizotifen from another study described in the article.
	Number of patients evaluable for AEs:	40 (See note)	25 (See note)	
	Number of patients reporting AEs:	19 (48%)	N/S	
	Total number of AEs reported:	29	7	Two patients who were included in efficacy analyses withdrew due to AEs, one because of aching in the legs and one because of a continual feeling of unsteadiness and heaviness in the head "like a drunken hangover." Investigators did not specify from which treatment groups the patients withdrew.
	Number of patients reporting:	*n* (%)	*n* (%)	
	Drowsiness, languour	12 (30%)	0	
	Increased appetite, craving for sweets, gain in weight	7 (18%)	0	
	Aching of legs	2 (5%)	0	
	Swelling of ankles	2 (5%)	0	
	Swelling of abdomen	2 (5%)	0	
	Depression, irritability	2 (5%)	3 (12%)	
	Nausea	2 (5%)	1 (4%)	
	Blurred vision	1 (3%)	0	
	Dizziness	0	2 (8%)	
	Skin rash	0	1 (4%)	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Lance, Fine, and Curran, 1963		**Methysergide**, 2 mg, 3x/day for 1 mo	**Placebo**	This report described results of treatment of patients with several different types of HA, and from controlled and uncontrolled portions of the trial. The data on AEs were not reported separately for *migraine* patients participating in the *controlled* portion of the trial; thus, the data at left are for all patients included in all phases of the trial. It *was* reported that 6 of 56 migraine patients taking methysergide during the controlled portion of the trial withdrew due to AEs.
	Number of patients evaluable for AEs:	183	50	
	Number of patients reporting AEs:	66 (36%)	6 (12%)	
	Total number of AEs reported:	128	6	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Nausea	29 (16%)	1 (2%)	
	Giddiness	12 (7%)	1 (2%)	
	Drowsiness	9 (5%)	0	
	Lassitude	9 (5%)	0	
	Anxiety, insomnia, vivid dreams	4 (2%)	3 (6%)	
	Abdominal pain	5 (3%)	0	
	Aching in legs	5 (3%)	0	*Methysergide vs. placebo:*
	Blocked nose	5 (3%)	0	0.23 (0.12 to 0.35)
	More frequent periods	5 (3%)	0	
	Sensation of swelling of throat, tongue	5 (3%)	0	
	Diarrhea	4 (2%)	1 (2%)	
	Depression	4 (2%)	0	
	Uncoordination, ataxia of gait	4 (2%)	0	
	Blurred vision	3 (2%)	0	
	Paresthesia	3 (2%)	0	
	Faintness	3 (2%)	0	
	Skin rash	3 (2%)	0	
	Epistaxis	3 (2%)	0	
	Vomiting	2 (1%)	0	
	Tightness in chest	2 (1%)	0	
	Palpitations	2 (1%)	0	
	Hot flushes	2 (1%)	0	
	Constipation	1 (< 1%)	0	
	Flatulence	1 (< 1%)	0	
	Dyspnea	1 (< 1%)	0	
	Sensation of swelling of face	1 (< 1%)	0	
	Sensation of swelling of legs	1 (< 1%)	0	
	Withdrawals due to AEs:	16	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Langohr, Gerber, Koletzki, et al., 1985		**Clomipramine**, dose gradually increased to 100 mg/day for total of 4 wks	**Metoprolol**, gradually increased to 100 mg/day for total of 4 wks	**Placebo**	Little information provided on AEs. Individual AEs listed at left were the most common AEs in the two active treatment groups.
	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	79	30	16	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Insomnia	15	2	N/S	
	Sweating	9	1	N/S	
	Tiredness	7	9	N/S	
	Constipation	6	1	N/S	
	Nausea	5	2	N/S	
	Dizziness	4	1	N/S	
	Loss of appetite	3	1	N/S	
	Restlessness	2	2	N/S	
	Withdrawals due to AEs:	18	N/S	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Lawrence, Hossain, and Littlestone, 1977		**Pizotifen,** inc'd from 0.5 mg, 1x/day to 0.5 mg, 3x/day for 10 days; then 1.0 mg, 3x/day for 10 wks	**Placebo**	Data at left concern only those 28/36 patients from whom efficacy data were obtained.
	Number of patients evaluable for AEs:	14 (See note)	14 (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Weight gain	4 (29%)	2 (14%)	
	Nausea and vomiting	1 (7%)	1 (7%)	
	Withdrawals due to AEs:	0	1 (dizziness)	
Leandri, Rigardo, Schizzi, et al., 1990		**Nicardipine**, 40 mg/day for 2 mos	**Placebo**	Investigators reported that no patients complained of symptoms related to low blood pressure. No significant changes in weight were observed.
	Number of patients evaluable for AEs:	36*	36*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	16	16	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastralgia	5 (14%)	8 (22%)	
	Dizziness	6 (17%)	5 (14%)	
	HA precipitated (once)	4 (11%)	1 (3%)	
	Dyspepsia	1 (3%)	2 (6%)	
	Withdrawals due to AEs:	1 (dyspepsia)	2 (dyspepsia)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Lindegaard, Övrelid, and Sjaastad, 1980		**Naproxen (Naprosyn®)**, 250 mg, 2x/day for 6 wks	**Placebo**	The article did not describe dropouts. On AEs, the authors stated only that "there was no difference between naproxen and placebo with regard to side-effects."
	Number of patients evaluable for AEs:	28*	28*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	
Louis, 1981		**Flunarizine**, 10 mg/day for 3 mos	**Placebo**	Possible AEs recorded at monthly clinic visits.
	Number of patients evaluable for AEs:	29	29	*Flunarizine vs. placebo:*
	Number of patients reporting AEs:	2 (7%)	2 (7%)	0 (-0.14 to 0.14)
	Total number of AEs reported:	2	2	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Daytime sedation	2 (7%)	0	
	Dry mouth	0	2 (7%)	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Louis, Schoenen, and Hedman, 1985a		**Clonidine,** 50 µg, 2x/day for 8 wks	**Metoprolol,** 50 mg, 2x/day for 8 wks	Data at left appear to concern all patients, including those who withdrew prematurely from study. Three patients withdrew after treatment with clonidine (subjective toxic effect, lack of effect; nervousness, lack of effect; dizziness, lack of effect). One additional patient withdrew during the washout period due to thrombosis in superior retinal half of left eye. No patients withdrew because of AEs associated with metoprolol. Following the baseline period but prior to treatment, 8 patients in addition to those at left reported 12 AEs: cardiovascular (1); CNS-related (3); fatigue (3); gastrointestinal (4); others (1). *Clonidine vs. metoprolol:* -0.03 (-0.25 to 0.19)
	Number of patients evaluable for AEs:	31* (See note)	31* (See note)	
	Number of patients reporting AEs:	21 (68%)	22 (71%)	
	Total number of AEs reported:	42	41	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Cardiovascular	2 (6%)	0	
	CNS-related	14 (45%)	16 (52%)	
	Fatigue	7 (23%)	10 (32%)	
	Gastrointestinal	9 (29%)	7 (23%)	
	Others	10 (32%)	8 (26%)	
	Withdrawals due to AEs:	(See note)	0 (See note)	
Louis and Spierings, 1982		**Flunarizine**, 10 mg/day for 4 mos	**Pizotifen**, 2-3 mg/day for 4 mos	
	Number of patients evaluable for AEs:	38	34	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	20	15	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	8 (21%)	7 (21%)	
	Daytime sedation	6 (16%)	4 (12%)	
	Gastric discomfort	6 (16%)	4 (12%)	
	Withdrawals due to AEs:	1 (weight gain)	1 (weight gain)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Lücking, Oestreich, Schmidt, et al., 1988 (Study 1)		**Flunarizine**, 10 mg/day for 4 mos	**Propranolol**, 120 mg/day for 4 mos	*Flunarizine vs. propranolol:* -0.049 (-0.13 to 0.034)
	Number of patients evaluable for AEs:	211	223	
	Number of patients reporting AEs:	52 (25%)	66 (30%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	GI disorders	15 (7%)	22 (10%)	
	Sedation/fatigue	17 (8%)	18 (8%)	
	Vertigo	11 (5%)	16 (7%)	
	Weight gain	6 (3%)	8 (4%)	
	Hyposthenia	5 (2%)	5 (2%)	
	Withdrawals due to AEs:	6 (nausea, sedation, gastric pain, vertigo [numbers with each N/S])	11 (nausea, changes in heart rate, hallucinations, sedation, vertigo, GI disorders, weight gain, eczema)	
Lücking, Oestreich, Schmidt, et al., 1988 (Study 2)		**Flunarizine**, 10 mg/day for 4 mos	**Propranolol**, 120 mg/day for 4 mos	*Flunarizine vs. propranolol:* -0.10 (-0.30 to 0.10)
	Number of patients evaluable for AEs:	43	44	
	Number of patients reporting AEs:	16 (37%)	21 (48%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Sedation/fatigue	10 (23%)	4 (9%)	
	GI disorders	0	9 (21%)	
	Weight gain	5 (12%)	3 (7%)	
	Vertigo	1 (2%)	2 (5%)	
	Hyposthenia	1 (2%)	2 (5%)	
	Withdrawals due to AEs:	2 (causative AEs N/S)	4 (causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ludin, 1989		**Flunarizine**, 10 mg/day for 4 mos	**Propranolol**, 120 mg/day for 4 mos	*Flunarizine vs. propranolol:* 0.013 (-0.23 to 0.26)
	Number of patients evaluable for AEs:	27	32	
	Number of patients reporting AEs:	13 (48%)	15 (47%)	
	Total number of AEs reported:	18	23	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Tiredness/sleepiness	7 (26%)	3 (9%)	
	GI symptoms	2 (7%)	6 (19%)	
	Dizziness	3 (11%)	2 (6%)	
	Weight gain	2 (7%)	3 (9%)	
	Increased appetite	0	4 (13%)	
	Insomnia	1 (4%)	2 (6%)	
	Hair loss	0	2 (6%)	
	Dyspnoea	1 (4%)	0	
	Urticaria/pruritus	1 (4%)	0	
	Oedema	1 (4%)	0	
	Nausea	0	1 (3%)	
	Withdrawals due to AEs:	2 (tiredness/sleepiness, insomnia)	3 (hair loss, GI symptoms, tiredness/sleepiness)	
Lundberg, 1969		**Flumedroxone**, 5 mg, 2x/day for 1 mo	**Placebo**	Limited information provided on AEs. 8/30 women completing the trial (apparently some in each treatment group) reported "menstrual disturbances." Other AEs were characterized as "infrequent" and "mild."
	Number of patients evaluable for AEs:	25	25	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Malvea, Gwon, and Graham, 1973		**Propranolol,** dose N/S, for 6 wks	**Placebo**	
	Number of patients evaluable for AEs:	31*	31*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	17	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Nausea	5 (16%)	N/S	
	Fatigue	5 (16%)	N/S	
	Numbness	1 (3%)	N/S	
	Heartburn	1 (3%)	N/S	
	Heaviness in leg and arm	1 (3%)	N/S	
	Light-headedness	1 (3%)	N/S	
	Vomiting	1 (3%)	N/S	
	Tingling in leg and arm	1 (3%)	N/S	
	Depression	1 (3%)	N/S	
	Withdrawals due to AEs:	0	0	
Markley, Cheronis, and Piepho, 1984		**Verapamil,** 240 mg/day for 8 wks	**Placebo**	
	Number of patients evaluable for AEs:	14*	14*	
	Number of patients reporting AEs:	6 (43%)	N/S	
	Total number of AEs reported:	6	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Constipation	6 (43%)	0	
	Withdrawals due to AEs:	1 (severe constipation)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Martucci, Manna, Mattesi, et al., 1983		**DHE (timed-release)**, 5 mg, 2x/day for 45 days	**Placebo**	Limited information provided on AEs.
	Number of patients evaluable for AEs:	90*	90*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	6 (pyrosis and epigastralgia [4], insomnia [1], allergic skin reaction [1])	0	
Masel, Chesson, Peters, et al., 1980		**Aspirin + dipyridamole**, 325 + 25 mg, 3x/day, for 3 mos	**Placebo**	The data at left appear to refer only to the 25/40 patients who completed the trial. None of the 15 patients who withdrew prematurely did so due to AEs.
	Number of patients evaluable for AEs:	25*	25*	
	Number of patients reporting AEs:	0	0	
	Total number of AEs reported:	0	0	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Mastrosimone, Iaccarino, and de Caterina, 1992		**Cyclandelate**, 1600 mg/day for 3 mos	**Pizotifen**, 1.5 mg/day for 3 mos	*Cyclandelate vs. pizotifen:* -0.49 (-0.69 to -0.26)
	Number of patients evaluable for AEs:	35	26	
	Number of patients reporting AEs:	8 (23%)	19 (73%)	
	Total number of AEs reported:	8	19	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	1 (3%)	6 (23%)	
	Asthenia	2 (6%)	3 (12%)	
	GI disturbances	2 (6%)	2 (8%)	
	Somnolence	1 (3%)	2 (8%)	
	Visual disturbances	0	3 (12%)	
	Vertigo	1 (3%)	1 (4%)	
	Other	1 (3%)	2 (8%)	
	Withdrawals due to AEs:	0	0	
Mathew, 1978		**Oxitriptan**, 300 mg/day for 8 wks	**Placebo**	Limited information was provided on AEs. Investigators only reported that "slight drowsiness and mild diarrhea" were the most common AEs from oxitriptan. They did not report the number of AEs from placebo.
	Number of patients evaluable for AEs:	12* (See note)	12* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Mathew, 1981		See notes column, at right. Trial reported results separately for migraine-only and mixed HA patients. Eight interventions were tested over 6 mos: **Ergotamine + analgesics**, used abortively (control) **Propranolol**, 60-160 mg/day **Amitriptyline**, 25-75 mg/day **Biofeedback (+ relaxation)** **Propranolol + amitriptyline** **Propranolol + biofeedback** **Amitriptyline + biofeedback** **Propranolol + amitriptyline + biofeedback**		Very limited data were reported on AEs. Among migraine-only patients, the incidence of AEs was "more or less comparable" in the various treatment groups; 18/340 patients (5%) withdrew due to AEs. Among patients with mixed HAs, 29/375 (8%) withdrew due to AEs; AEs were highest in the control (ergotamine) group. In both HA groups, no unusual AEs were reported when propranolol and amitriptyline were used simultaneously.
Mathew, Saper, Silberstein, et al., 1995		**Divalproex sodium**, average dose 1087 mg/day, for 12 wks	**Placebo**	Investigators reported data only on those AEs for which there was a significant difference between the two groups.
	Number of patients evaluable for AEs:	70	37	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Nausea	32 (46%)	5 (14%)	
	Asthenia	22 (31%)	3 (8%)	
	Somnolence	21 (30%)	2 (5%)	
	Vomiting	13 (19%)	0	
	Tremor	9 (13%)	0	
	Alopecia	9 (13%)	0	
	Withdrawals due to AEs:	9 (nausea [2], rash [1], vomiting [1], decreased mental acuity [1], fatigue [1], elevated liver function test results [1], chest/GI pain [1], weight gain [1])	2 (rash [1], depression [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
McArthur, Marek, Pestronk, et al., 1989		**Nifedipine**, 60-90 mg/day for 3 mos	**Placebo**	
	Number of patients evaluable for AEs:	24*	24*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	46	10	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Dizziness	11 (46%)	0	
	Edema	11 (46%)	0	
	Gastric symptoms	4 (17%)	6 (25%)	
	Flushing	7 (29%)	2 (8%)	
	Exacerbation of HA severity	4 (17%)	0	
	Mental symptoms	3 (13%)	0	
	Acute onset of HA w/ dose titration	2 (8%)	0	
	Weight gain	2 (8%)	0	
	Fatigue	2 (8%)	0	
	Diarrhea	0	1 (4%)	
	Leg cramps	0	1 (4%)	
	Withdrawals due to AEs:	5 (causative AEs N/S)	1 (causative AEs N/S)	
Mendeno-poulos, Manafi, Logothetis, et al., 1985		**Flunarizine**, 10 mg/day for 3-4 mos	**Placebo**	No indication of how data on AEs were gathered.
	Number of patients evaluable for AEs:	9	11	*Flunarizine vs. placebo:* 0.0084 (-0.16 to 0.18)
	Number of patients reporting AEs:	0	0	
	Total number of AEs reported:	0	0	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Meyer and Hardenberg, 1983		**Nimodipine**, 60 mg/day for 8 wks and 120 mg/day for 8 wks		This was a dose-comparison trial, but AEs were not reported separately for the two doses.
	Number of patients evaluable for AEs:	27*		
	Number of patients reporting AEs:	11 (40%)		
	Total number of AEs reported:	28		
	Number of patients reporting:	*n (%)*		
	Muscular complaints	12 (44%)		
	GI complaints	5 (19%)		
	Behavioral changes	5 (19%)		
	Other CNS symptoms	3 (11%)		
	Vascular complaints	2 (7%)		
	Dermatological changes	1 (1%)		
	Withdrawals due to AEs:	N/S		
Micieli, Trucco, Agostinis, et al., 1985		**Nimodipine**, 120 mg/day for 3 mos	**Pizotifen**, 1.5 mg/day for 3 mos	Abstract reporting limited information. Authors stated that no significant AEs were reported with nimodipine.
	Number of patients evaluable for AEs:	20*	20*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	0	9 (45%)	
	Weight gain (1-3 kg)	0	6 (30%)	
	Withdrawals due to AEs:	N/S	N/S	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Migraine-Nimodipine European Study Group (MINES), 1989a		**Nimodipine**, 120 mg/day for 12 wks	**Placebo**	*Nimodipine vs. placebo:* 0.10 (-0.070 to 0.27)
	Number of patients evaluable for AEs:	43	46	
	Number of patients reporting AEs:	12 (28%)	8 (17%)	
	Total number of AEs reported:	12	8	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Increased HA	4 (9%)	2 (4%)	
	Dizziness	1 (2%)	3 (6%)	
	Vasodilatation	2 (5%)	1 (2%)	
	Asthenia	2 (5%)	0	
	Myalgia	2 (5%)	0	
	Depression	0	2 (4%)	
	Tachycardia	1 (2%)	0	
	Withdrawals due to AEs:	3 (increased HA [2], tachycardia [1])	4 (causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Migraine-Nimodipine European Study Group (MINES), 1989b		**Nimodipine**, 120 mg/day for 12 wks	**Placebo**	*Nimodipine vs. placebo:* 0.12 (0.010 to 0.23)
	Number of patients evaluable for AEs:	94	98	
	Number of patients reporting AEs:	24 (26%)	13 (13%)	
	Total number of AEs reported:	24	13	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Increased HA	8 (9%)	2 (2%)	
	GI problems	4 (4%)	4 (4%)	
	Vasodilatation	5 (5%)	1 (1%)	
	Nausea	2 (2%)	1 (1%)	
	Palpitation	2 (2%)	1 (1%)	
	Dizziness	1 (1%)	2 (2%)	
	Tachycardia	2 (2%)	0	
	Rash	0	2 (2%)	
	Withdrawals due to AEs:	5 (4 due to increased HA; 1 due to unspecified AEs)	3 (causative AEs N/S)	
Mikkelsen and Falk, 1982		**Tolfenamic acid**, 100 mg, 3x/day for 10 wks	**Placebo**	Gastrointestinal symptoms are said to have included mild dyspepsia, gaseous abdominal distension, constipation, diarrhea, and bloating. "Other" AEs included difficulty breathing, insomnia, failure of impressing ability, and a pressing feeling in the head.
	Number of patients evaluable for AEs:	38*	38*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	21	19	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastrointestinal symptoms (see note)	13 (34%)	12 (32%)	
	Increase in weight and oedema	4 (11%)	5 (13%)	
	Dysuria	1 (2%)	1 (2%)	
	Other AEs (see note)	3 (6%)	1 (2%)	
	Withdrawals due to AEs:	2 (increase in weight, diarrhea)	1 (tingling in hands and feet)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Mikkelsen, Kjærsgaard-Pedersen, and Christiansen, 1986		**Propranolol**, 40 mg, 3x/day for 12 wks	**Tolfenamic acid**, 100 mg, 3x/day for 12 wks	**Placebo**	Data at left are for those patients who completed the trial (31/39). Three patients withdrew due to AEs before completing the trial: two due to AEs associated with propranolol (fatigue and difficulty working; fatigue, tremor, and general indisposition), and one due to AEs associated with tolfenamic acid ("indistinct psychical symptoms").
	Number of patients evaluable for AEs:	31*	31*	31*	
	Number of patients reporting AEs:	3 (10%)	2 (6%)	3 (10%)	
	Total number of AEs reported:	3	2	3	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Diarrhea	0	1 (3%)	1 (3%)	*Propranolol vs. placebo:* 0 (-0.15 to 0.15)
	Fatigue	1 (3%)	0	0	
	Polyuria	1 (3%)	0	0	
	Low back pain	1 (3%)	0	0	*Tolfenamic acid vs. placebo:* -0.031 (-0.17 to 0.11)
	Slight sedation	0	1 (3%)	0	
	Slight neurological symptoms	0	0	1 (3%)	
	Hot flushes	0	0	1 (3%)	*Propranolol vs. tolfenamic acid:* 0.031 (-0.11 to 0.17)
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	
Mondrup and Møller, 1977		**Clonidine,** 50-75 µg, 2x/day for 12 wks		**Placebo,** 2-3 tabs, 2x/day for 12 wks	Data at left appear to concern only the 21 patients (of 32) who completed the crossover, but it is unclear. No patients withdrew due to AEs. However, 5 patients (2 on clonidine and 3 on placebo) were withdrawn from the study because of "unacceptable worsening of the headaches." One patient (on placebo) became HA free and withdrew.
	Number of patients evaluable for AEs:	21* (See note)		21* (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	18 (86%)		8 (38%)	
	Number of patients reporting:	*n* (%)		*n* (%)	
	Dryness of mouth	3 (14%)		1 (5%)	
	Dyspepsia	3 (14%)		1 (5%)	
	Slight dizziness	4 (19%)		1 (5%)	
	Slight tiredness	8 (38%)		5 (24%)	
	Withdrawals due to AEs:	0 (See note)		0 (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Monro, Swade, and Coppen, 1985		**Mianserin**, 30 mg/day for 1 wk, 60 mg/day for 15 wks	**Placebo**	No information provided on AEs.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	
Murphy, Heptinstall, and Mitchell, 1988 #4580		**Feverfew**, ≈82 mg/day (mean dose) for 4 mos	**Placebo**	Data at left appear to concern all 72 patients randomized to treatment, but this is not clear.
	Number of patients evaluable for AEs:	72* (See note)	72* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	28	36	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Mouth ulceration	10 (14%)	16 (22%)	
	Indigestion	4 (6%)	2 (3%)	
	Heartburn	3 (4%)	3 (4%)	
	Dizziness/lightheadedness	2 (3%)	2 (3%)	
	Skin rash	1 (1%)	3 (4%)	
	Diarrhea	1 (1%)	2 (3%)	
	Abdominal bloating	1 (1%)	1 (1%)	
	Sore mouth	1 (1%)	1 (1%)	
	Nausea	1 (1%)	1 (1%)	
	Flatulence	1 (1%)	1 (1%)	
	Weight gain	2 (3%)	0	
	Constipation	1 (1%)	0	
	Night sweats	0	1 (1%)	
	Paraesthesiae in legs	0	1 (1%)	
	Bleeding per rectum	0	1 (1%)	
	Somnolence	0	1 (1%)	
	Withdrawals due to AEs:	2 (heartburn [1], dizziness/lightheadedness [1])	3 (paraesthesiae in legs [1], skin rash [1], bleeding per rectum [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Nanda, Johnson, Gray, et al., 1978		**Acebutolol**, 400 mg, 2x/day for 12 wks	**Placebo**	Limited information provided on AEs. Investigators stated that "no serious side-effects were reported" during the trial (p. 21).
	Number of patients evaluable for AEs:	43*	43*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	
Nappi, Sandrini, Savoini, et al., 1987		**Cyclandelate**, 1600 mg/day for 3 mos	**Flunarizine**, 5 mg/day for 3 mos	Limited information provided on AEs. Incidence of specific AEs reported at left is for the third month of treatment only.
	Number of patients evaluable for AEs:	20	20	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	N/S	9 (45%)	
	Drowsiness	N/S	5 (25%)	
	Gastric complaints	3 (15%)	N/S	
	Asthenia	N/S	2 (10%)	
	Withdrawals due to AEs:	1 (gastric complaints)	2 (drowsiness)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Nattero, Biale, Savi, et al., 1991		**Pizotifen,** 1.5 mg, 3x/day for 16 wks	**Lisuride,** 0.075 mg, 3x/day for 16 wks	Data at left are for the "most common" AEs reported and appear to concern only those 47/110 patients who completed both cycles of the crossover trial, but this is not clear. No information was provided on other AEs or on the number of patients who withdrew due to AEs.
	Number of patients evaluable for AEs:	N/S (See note)	N/S (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Weight gain	38%	N/S	
	Gastrointestinal disorders	32%	50%	
	Somnolence	12%	12%	
	Withdrawals due to AEs:	N/S	N/S	
Neuman, Demarez, Harmey, et al., 1986		**DHE (timed-release),** 5 mg, 2x/day for 1 mo	**Placebo**	Investigators stated only that "no notable side-effects were registered in either of the two groups" (p. 13).
	Number of patients evaluable for AEs:	20	20	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	
Noone, 1980		**Clomipramine,** 10 mg, 3x/day for 8 wks	**Placebo**	These data are for those patients who completed the trial (10/21 randomized to treatment). Two patients withdrew before completing due to unspecified AEs; both were taking clomipramine at the time.
	Number of patients evaluable for AEs:	10*	10*	
	Number of patients reporting AEs:	6 (60%)	1 (10%)	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	0	*Clomipramine vs. placebo:* 0.47 (0.086 to 0.76)

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Olerud, Gustavsson, and Furberg, 1986		**Nadolol**, 40-160 mg, 1x/day for 6 mos	**Propranolol**, 40-80 mg, 2x/day for 6 mos	Limited information provided. Investigators stated that "most" reported AEs were typical of beta-blockers.
	Number of patients evaluable for AEs:	13	15	
	Number of patients reporting AEs:	6 (46%)	5 (33%)	*Nadolol vs. propranolol:*
	Total number of AEs reported:	N/S	N/S	0.12 (-0.22 to 0.45)
	Withdrawals due to AEs:	1 (cold fingers, tiredness)	0	
Olsson, Behring, Forssman, et al., 1984		**Metoprolol**, 50 mg, 2x/day for 8 wks	**Propranolol**, 40 mg, 2x/day for 8 wks	
	Number of patients evaluable for AEs:	56*	56*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	158	141	
	Number of patients reporting:	*n (%)*	*n (%)*	
	CNS symptoms	36 (64%)	24 (43%)	
	GI symptoms	24 (43%)	16 (29%)	
	Sleep disturbances	17 (30%)	22 (39%)	
	Fatigue	14 (25%)	17 (30%)	
	Cardiovascular symptoms	12 (21%)	12 (21%)	
	Other	55 (98%)	50 (89%)	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
O'Neill and Mann, 1978		**Aspirin,** 650 mg, 2x/day for 3 mos	**Placebo**	*Aspirin vs. placebo:* 0.24 (-0.033 to 0.47)
	Number of patients evaluable for AEs:	12*	12*	
	Number of patients reporting AEs:	3 (25%)	0	
	Total number of AEs reported:	3	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Gastritis	3 (25%)	0	
	Withdrawals due to AEs:	1 (gastritis)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Orholm, Honoré, and Zeeberg, 1986		**Femoxetine**, 200 mg/day initially, increasing over first nine days to 600 mg/day for total of 16 wks	**Placebo**	These data appear to include only those patients who completed the trial or were known to have withdrawn due to AEs (59/65 patients randomized to treatment), though this is not entirely clear.
	Number of patients evaluable for AEs:	29	30	
	Number of patients reporting AEs:	8 (28%)	3 (10%)	
	Total number of AEs reported:	14	3	*Femoxetine vs. placebo:* 0.17 (-0.027 to 0.36)
	Number of patients reporting:	*n (%)*	*n (%)*	
	Tremor	3 (10%)	0	
	Nausea	3 (10%)	0	
	Palpitation	1 (3%)	1 (3%)	
	Vomiting	1 (3%)	0	
	Stomach pain	1 (3%)	0	
	Orthostatic dizziness	1 (3%)	0	
	Tiredness	1 (3%)	0	
	Lack of appetite	1 (3%)	0	
	Constipation	1 (3%)	0	
	Perspiration	1 (3%)	0	
	Edema	0	1 (3%)	
	Urticarial exanthema	0	1 (3%)	
	Withdrawals due to AEs:	4 (nausea, orthostatic dizziness; tiredness, stomach pain; tremor, nausea, palpitation, lack of appetite; tremor)	2 (edema, palpitation)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Osterman, 1977		**Pizotifen**, inc'd from 0.5 mg, 1x/day to 1 mg, 3x/day for 8 wks	**Iprazo-chrome**, inc'd from 2.5 mg, 1x/day to 5 mg, 3x/day for 8 wks	**Placebo**	The data at left appear to concern only those 27 patients who completed all three treatments of the crossover trial, plus one patient who only completed treatment with iprazochrome and placebo. These were the patients (of the 30 originally randomized to treatment) for whom efficacy data were analyzed. One patient, not included in efficacy analyses, withdrew due to "abdominal problems due to both placebo and pizotifen."
	Number of patients evaluable for AEs:	27* (See note)	27* (See note)	27* (See note)	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	68	12	11	
	Number of patients reporting:	*n* (%)	*n* (%)	*n* (%)	Investigators stated that AEs were frequent during treatment with pizotifen, with drowsiness and weight gain being the most common. Investigators also reported that there was no difference between iprazochrome and placebo with respect to AEs.
	Weight gain > 1.5 kg	21 (78%)	1 (4%)	2 (7%)	
	Weight gain > 4 kg	8 (30%)	0	0	
	Drowsiness	15 (56%)	6 (22%)	4 (15%)	
	Of above "drowsiness," those which were "severe"	9 (33%)	1 (4%)	1 (4%)	
	Increased appetite and hunger	12 (44%)	2 (7%)	3 (11%)	
	Depression	3 (11%)	2 (7%)	1 (4%)	
	Withdrawals due to AEs:	1 (N/S)	0	0	
Palferman, Gibberd, and Simmonds, 1983		**Propranolol**, 40 mg, 3x/day for 2 mos		**Placebo**	Investigators stated that, among patients completing the trial, minor AEs, most commonly fatigue, were reported exclusively in association with propranolol.
	Number of patients evaluable for AEs:	16*		16*	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		1 (dizziness)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Pedersen and Møller, 1966		**Methysergide (prolonged-action)**, 6 mg/day for 6 wks	**Placebo**	Data at left are for those patients who completed the trial (60/102). Seven patients withdrew prematurely due to AEs associated with methysergide (intermittent claudication [3]; cardiac symptoms [2]; severe dizziness, nausea, and vomiting [2], in one case accompanied by generalized edema and an increase in body weight). No patients withdrew due to AEs associated with placebo. *Methysergide vs. placebo:* 0.15 (-0.0075 to 0.30)
	Number of patients evaluable for AEs:	60*	60*	
	Number of patients reporting AEs:	20 (33%)	11 (18%)	
	Total number of AEs reported:	31	16	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Leg symptoms	12 (20%)	5 (8%)	
	Fatigue	6 (10%)	4 (7%)	
	Cardiac symptoms	4 (7%)	4 (7%)	
	Dizziness	3 (5%)	1 (2%)	
	Nausea	3 (5%)	1 (2%)	
	Edema	3 (5%)	1 (2%)	
	Withdrawals due to AEs:	(See note)	(See note)	
Pini, Ferrari, Guidetti, et al., 1985		**Flunarizine**, 20 mg/day for 14 days, then 10 mg/day for up to 106 days	**Placebo**	Limited information provided on AEs. No patients experienced AEs requiring them to withdraw or impairing their usual activities. Significant weight gain was reported by 29% of patients on flunarizine. Motor disturbances such as extra-pyramidal reactions were not observed.
	Number of patients evaluable for AEs:	14 or 15	14 or 15	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Pita, Higueras, Bolaños, et al., 1977		**Propranolol**, 40 mg, 4x/day for 2 mos	**Placebo**	*Propranolol vs. placebo:* 0.31 (-0.024 to 0.59)
	Number of patients evaluable for AEs:	9*	9*	
	Number of patients reporting AEs:	3 (33%)	0	
	Total number of AEs reported:	3	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Orthostatic hypotension	1 (11%)	0	
	Light pyrosis	2 (22%)	0	
	Withdrawals due to AEs:	1 (orthostatic hypotension)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Pradalier, Serratrice, Collard, et al., 1989b		**Propranolol (long-acting),** 160 mg, 1x/day for 3 mos	**Placebo**	
	Number of patients evaluable for AEs:	31	24	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting (in response to questionnaire):	*n (%)*	*n (%)*	
	Tiredness	8 (26%)	7 (29%)	
	Insomnia	5 (16%)	5 (21%)	
	Constipation	3 (10%)	7 (29%)	
	Dyspnea	6 (19%)	1 (4%)	
	Depression	2 (6%)	5 (21%)	
	Dizziness	3 (10%)	2 (8%)	
	Dyspepsia	2 (6%)	3 (13%)	
	Diarrhea	3 (10%)	1 (4%)	
	Cold extremities	0	4 (17%)	
	Headache	1 (3%)	2 (8%)	
	Nausea	1 (3%)	0	
	Eye troubles	0	1 (4%)	
	Rash	0	1 (4%)	
	Wheezing	0	1 (4%)	
	Impotence	0	1 (4%)	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Presthus, 1971		**Pizotifen**, 0.5 mg, 3x/day for 5 wks	**Methysergide**, 1 mg, 3x/day for 5 wks	
	Number of patients evaluable for AEs:	21*	21*	
	Number of patients reporting AEs:	N/S	1 (5%)	
	Total number of AEs reported:	20	1	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	14 (67%)	0	
	Fatigue	3 (14%)	0	
	Drowsiness	1 (5%)	0	
	Dysphoria	1 (5%)	0	
	Restless legs	1 (5%)	0	
	Exanthema	0	1 (5%)	
	Withdrawals due to AEs:	0	1 (exanthema accompained by fatigue, nausea, vomiting, and diarrhea)	
Rascol, Montastruc, and Rascol, 1986		**Flunarizine**, 10 mg/day for 2 mos	**Pizotifen**, 2.19 mg/day for 2 mos (lower during 1st wk)	*Flunarizine vs. pizotifen:* -0.0047 (-0.29 to 0.29)
	Number of patients evaluable for AEs:	21	14	
	Number of patients reporting AEs:	6 (29%)	4 (29%)	
	Total number of AEs reported:	10	5	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Weight gain	6 (29%)	4 (29%)	
	Oversleeping	1 (5%)	0	
	Dreaming	1 (5%)	0	
	Hot flushes	1 (5%)	0	
	Drowsiness	1 (5%)	0	
	Asthenia	0	1 (7%)	
	Withdrawals due to AEs:	1 (weight gain and drowsiness)	1 (weight gain and asthenia)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Rompel and Bauermeister, 1970		**Carbamazepine**, 600 mg/day for 6 wks	**Placebo**	*Carbamazepine vs. placebo:* 0.39 (0.20 to 0.56)
	Number of patients evaluable for AEs:	48*	48*	
	Number of patients reporting AEs:	30 (63%)	11 (23%)	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n* (%)	*n* (%)	
	Vertigo or giddiness	23 (48%)	2 (4%)	
	Drowsiness	5 (10%)	0	
	Nausea	4 (8%)	3 (6%)	
	Dry mouth	2 (4%)	0	
	Heavy eyes	2 (4%)	0	
	Constipation	2 (4%)	0	
	Vomiting	1 (2%)	0	
	Weight gain	1 (2%)	1 (2%)	
	Sweating	1 (2%)	0	
	Rash	1 (2%)	0	
	Dysuria	1 (2%)	0	
	Blocked nose	0	1 (2%)	
	Lack of drive	0	1 (2%)	
	Flushing	0	1 (2%)	
	Blunted feeling	0	1 (2%)	
	Heavy head	0	1 (2%)	
	Withdrawals due to AEs:	1 (causative AEs N/S)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ryan, 1968		**Pizotifen**, 2 mg, 2x/day for 4 wks	**Methyser-gide**, 2 mg, 2x/day for 4 wks	**Placebo**	This article says nothing about dropouts and therefore appears to be reporting only on those patients who completed the trial.
	Number of patients evaluable for AEs:	62*	62*	62*	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	34	24	10	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Drowsiness	14 (23%)	4 (6%)	3 (5%)	
	Weight gain	8 (13%)	1 (2%)	0	
	Nausea	2 (3%)	4 (6%)	2 (3%)	
	Dry mucous membranes	4 (6%)	1 (2%)	2 (3%)	
	Nervousness	1 (2%)	3 (5%)	1 (2%)	
	Vertigo	1 (2%)	2 (3%)	1 (2%)	
	Abdominal cramps	2 (3%)	1 (2%)	0	
	Bloated sensation	1 (2%)	2 (3%)	0	
	Leg cramps	0	2 (3%)	0	
	Insomnia	0	2 (3%)	0	
	Increased appetite	1 (2%)	0	0	
	Vomiting	0	1 (2%)	0	
	Floating sensation	0	0	1 (2%)	
	Edema in extremities	0	1 (2%)	0	
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ryan, 1971		**Pizotifen (BC105),** inc'd from 0.5 mg, 1x/day to 1.0 mg, 3x/day for 2 wks; then dosage adjusted according to a protocol for 10 wks	**Placebo**	Data at left on AEs appear to concern all patients randomized to treatment, but this is unclear. Investigators reported that one patient withdrew from pizotifen treatment due to increased blood pressure. Three others withdrew for unspecified reasons (pizotifen 1, placebo 2).
	Number of patients evaluable for AEs:	27 (See note)	24 (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	54	14	
	Number of patients reporting	*n* (%)	*n* (%)	
	Increased appetite	17 (63%))	0	
	Drowsy	16 (60%)	6 (25%)	
	Weight gain	7 (26%)	0	
	Nausea	6 (22%)	5 (21%)	
	Ankle edema	2 (7%)	0	
	Nervous	2 (7%)	1 (4%)	
	Vertigo	2 (7%)	0	
	Dry mouth	1 (4%)	0	
	Vomiting	1 (4%)	2 (8%)	
	Withdrawals due to AEs:	1 (increased blood pressure)	N/S (See note)	
Ryan, 1978		**Ovral®** (norgestrel 0.5 mg + ethinyl estradiol 0.05 mg), 1x/day for 2 mos	**No treatment**	Limited information provided on AEs. AEs reported with Ovral® included nausea and/or vomiting, abdominal cramping, depression, drowsiness, dry mouth, and pigmented skin (no n's reported).
	Number of patients evaluable for AEs:	40*	40*	
	Number of patients reporting AEs:	28 (70%)	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ryan, 1984		**Nadolol**, 160 mg/day for 3 mos	**Nadolol**, 80 mg/day for 3 mos	**Propranolol**, 160 mg/day for 3 mos	No further information provided on AEs.
	Number of patients evaluable for AEs:	16	16	16	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	0	1 (gastric symptoms)	0	
Ryan, Diamond, and Ryan, 1975		**Clonidine**, 0.025 - 0.075 mg, 2x/day for 8 wks		**Placebo**	Investigators did not provide the number of patients affected, the number of AEs reported, or the treatment groups associated with AEs. Authors only reported that the same number of AEs were experienced with each treatment and that no AEs incapacitated patients. The most common AEs were nausea, nervousness, and tiredness. Other rare AEs were dry mouth, drowsiness, vertigo, sleepiness, insomnia, and an increased number of HAs.
	Number of patients evaluable for AEs:	133*		133*	
	Number of patients reporting AEs:	N/S (See note)		N/S (See note)	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions				Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ryan and Ryan, 1981		**Aspirin + dipyridamole**, 325 + 75 mg, 4x/day for 8 wks	**Aspirin**, 325 mg, 4x/day for 8 wks	**Dipyridamole** 75 mg, 4x/day for 8 wks	**Placebo**	No information on dropouts was provided. Data at left may be for those patients who completed the trial only; this is unclear.
	Number of patients evaluable for AEs:	40	40	40	40	
	Number of patients reporting AEs:	N/S	N/S	N/S	N/S	
	Total number of AEs reported:	20	2	16	5	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Increased HA	5 (13%)	0	6 (15%)	2 (5%)	
	Nausea	6 (15%)	1 (3%)	4 (10%)	0	
	Vomiting	2 (5%)	0	1 (3%)	0	
	Vertigo	1 (3%)	0	2 (5%)	0	
	Cramps	2 (5%)	0	0	0	
	Head pressure	2 (5%)	0	0	0	
	Skin bruises	1 (3%)	0	0	0	
	Frequent urination	1 (3%)	0	0	0	
	Hot flashes	0	1 (3%)	0	0	
	Diarrhea	0	0	1 (3%)	0	
	Chest pain	0	0	1 (3%)	0	
	Tinnitus	0	0	1 (3%)	0	
	Sensitivity to odors	0	0	0	1 (3%)	
	Chills	0	0	0	1 (3%)	
	Rapid heart beat	0	0	0	1 (3%)	
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions				Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ryan, Ryan, and Sudilovsky, 1983		**Nadolol**, 240 mg/day for 3 mos	**Nadolol**, 160 mg/day for 3 mos	**Nadolol**, 80 mg/day for 3 mos	**Placebo**	Data at left on AEs concern all 80 patients randomized to treatment. One patient dropped out. Investigators did not report the treatment group from which the patient withdrew or the reason for withdrawal.
	Number of patients evaluable for AEs:	20	20	20	20	
	Number of patients reporting AEs:	10 (50%)	5 (25%)	5 (25%)	5 (25%)	
	Total number of AEs reported:	N/S	N/S	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
	Drowsiness	1	1	3	1	
	Vertigo	1	2	1	0	
	Insomnia	2	0	0	0	
	Sweaty	1	0	0	0	
	Blurred vision	1	0	0	0	
	Tinitus	0	0	0	1	
	Kidney stone	0	0	0	0	
	Bloating	0	1	1	1	
	General weakness	1	0	0	0	
	Nausea	1	0	0	0	
	Chest pain	1	0	0	0	
	Weak extremities	0	0	0	1	
	Decreased sex	0	1	0	0	
	Numbness in extremities	1	0	0	0	
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sances, Martignoni, Fioroni, et al., 1990		**Naproxen sodium**, 550 mg, 2x/day for 3 (n = 17) or 6 (n = 18) mos	**Placebo**, for 3 mos	The article appears to report data on AEs only for those patients who completed the trial (35/40), and does not separately report data from the controlled (mos 1-3) and uncontrolled (mos 4-6) portions of the trial. Two patients withdrew due to AEs (severe gastralgia and nausea) before completing the controlled trial; it is not stated which treatment they were using at the time they withdrew. On the trial design, see Evidence Table 1.
	Number of patients evaluable for AEs:	35 (See note)	17 (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Mild-mod nausea and epigastric distress	9 (26%)	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	
Sances, Martignoni, Rosettino, et al., 1989		**Lisuride**, 0.05 mg, 3x/day for 3 mos	**Placebo**	Limited data on AEs were provided. Investigators reported that 4/40 patients (10%) dropped out due to nausea, vomiting, and hypotension, but did not specify from which treatment groups they withdrew or whether or not dropouts were included in efficacy analyses.
	Number of patients evaluable for AEs:	20	20	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Saper, Silberstein, Lake, et al., 1994		**Fluoxetine**, doses ranging from 20-40 mg/day, for 12 wks		**Placebo**	Combined AE data were reported for migraine (n = 57) and CDH (n = 54) patients. List of specific AEs does not represent all AEs reported by patients.
	Number of patients evaluable for AEs:	61 (See note)		50 (See note)	
	Number of patients reporting AEs:	51 (84%)		33 (66%)	
	Number of patients reporting *severe* AEs:	5 (8%)		2 (4%)	*Fluoxetine vs. placebo:* 0.18 (0.012 to 0.33)
	Total number of AEs reported:	N/S		N/S	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Fatigue	15 (25%)		13 (26%)	
	Sleeping problems	17 (28%)		4 (8%)	
	Tremors	12 (20%)		3 (6%)	
	Stomach pain	8 (13%)		0	
	Weight loss (5-15 lbs)	5 (8%)		1 (2%)	
	Withdrawals due to AEs:	0		0	
Sargent, Solbach, Damasio, et al., 1985		**Naproxen sodium**, 550 mg, 2x/day for 15 wks	**Propranolol**, 40 mg, 2x/day for 2 wks, 3x/day for 12 wks, 2x/day for 1 wk	**Placebo**	AE data were reported for the 149 patients who started the first active treatment period, but investigators did not report how these patients were distributed among the three treatment groups.
	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	38	30	28	The authors reported that patients in the naproxen sodium group reported more GI complaints than patients in the other two groups, and that the incidence and severity of non-GI AEs were comparable in the naproxen sodium and propranolol groups.
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	3 (rash)	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Shafar, Tallett, and Knowlson, 1972		**Clonidine,** 50 µg, 2x/day for 16 wks	**Placebo**	AEs reported at left are for the 50 patients (of 65) included in efficacy analyses only. Of those dropping out of study, 2 withdrew after being treated with clonidine (1 for "general malaise," 1 because HAs worsened). Three others withdrew for reasons unrelated to AES, and 10 withdrew for reasons unknown to investigators.
	Number of patients evaluable for AEs:	50* (See note)	50* (See note)	
	Number of patients reporting AEs:	20 (40%)	12 (24%)	
	Total number of AEs reported:	36	17	
	Number of patients reporting (complete list:)	n (%)	n (%)	
	Anxiety:	6 (12%)	2	
	Depression:	0	1 (2%)	*Clonidine vs. placebo:* 0.16 (-0.02 to 0.33)
	Dry mouth:	8 (16%)	2 (4%)	
	Fatigue:	1 (2%)	0	
	Gastrointestinal:	12 (24%)	9 (18%)	
	Palpitation, flushes:	5 (10%)	2 (4%)	
	Rash:	1 (2%)	0	
	Others (trivial):	3 (6%)	1 (2%)	
	Withdrawals due to AEs:	(See note)	(See note)	
Shekelle and Ostfeld, 1964		**Methysergide**, 2 mg, 3x/day for 5 wks	**Placebo**	Data at left are for those patients who completed the trial (13/16). None of the three patients who withdrew prematurely did so due to AEs.
	Number of patients evaluable for AEs:	13*	13*	
	Number of patients reporting AEs:	2 (15%)	1 (8%)	
	Total number of AEs reported:	2	1	*Methysergide vs. placebo:* 0.073 (-0.18 to 0.32)
	Number of patients reporting:	*n (%)*	*n (%)*	
	Mild ache in calves	1 (8%)	1 (8%)	
	Hair loss	1 (8%)	0	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Shimell, Fritz, and Levien, 1990		**Flunarizine**, 10 mg/day (dose achieved gradually over 4 days) for 4 mos	**Propranolol**, 180 mg/day (dose achieved gradually over 20 days) for 4 mos	
	Number of patients evaluable for AEs:	28	29	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	17	31	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Sleepiness/tiredness	6 (21%)	8 (28%)	
	Weight gain	9 (32%)	4 (14%)	
	Nightmares	2 (7%)	3 (10%)	
	Drowsiness	0	3 (10%)	
	Irritability	0	3 (10%)	
	Disturbed sleep	0	3 (10%)	
	Lethargy	0	2 (7%)	
	Skin rash	0	1 (3%)	
	Bitter taste	0	1 (3%)	
	Tingling sensation	0	1 (3%)	
	Hot flushes	0	1 (3%)	
	Excessive diuresis	0	1 (3%)	
	Withdrawals due to AEs:	2 (weight gain)	3 (nightmares [2], rash [1])	
Shukla, Garg, Nag, et al., 1995		**Nifedipine**, 15 mg/day for 4 wks	**Placebo**	Data reported appear to be for those patients who completed the trial (28/36), though this is unclear. Investigators stated that they did not observe any cases of worsening of HA or hypotension associated with nifedipine. Patients were asked about AEs at end of each treatment period.
	Number of patients evaluable for AEs:	28*	28*	
	Number of patients reporting AEs:	1 (4%)	0	
	Total number of AEs reported:	1	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Nervousness	1 (4%)	0	
	Withdrawals due to AEs:	0	0	*Nifedipine vs. placebo:* 0.035 (-0.058 to 0.13)

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sicuteri, 1973		**Oxitriptan (L-5-hydroxytryptophan or 5-HTP)**, 100 mg, 2x/day for 40 days	**Methysergide**, 1 mg, 2x/day for 40 days	Very limited information was provided about AEs. Authors reported that oxitriptan was very well tolerated: an increase in appetite and/or body weight was reported in a few cases, but no patients withdrew due to AEs.
	Number of patients evaluable for AEs:	20	20	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	N/S	
Sjaastad and Stensrud, 1969		**Pizotifen,** 1 mg, 4x/day for 8 wks	**Placebo**	Limited data on AEs were provided for this crossover trial, and investigators did not report whether information on AEs were from all 24 patients randomized to treatment or from the 20 from whom efficacy data were obtained. Fourteen patients treated with pizotifen gained weight and all had "tremendous appetites." An unspecified number of patients were drowsy and easily fatigued (treatment N/S). Two patients (treatment N/S) also experienced vertigo.
	Number of patients evaluable for AEs:	(See note)	(See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	(thrombophlebitis [1])	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sjaastad and Stensrud, 1971		**Clonidine (Catapresan®),** 25 µg, 3x/day for 3 wks	**Placebo**	Data at left appear to concern only those patients who completed the crossover. Investigators reported that a few patients experienced the throbbing, pounding sensation of a HA attack, but without any accompanying pain.
	Number of patients evaluable for AEs:	26* (See note)	26* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	12 (46%)	0	
	Number of patients reporting:	*n* (%)	*n* (%)	Investigators stated that 4 patients withdrew for unknown reasons.
	Drowsiness	8 (31%)	0	
	Dryness of mouth	3 (12%)	0	
	Thirst	1 (4%)	0	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sjaastad and Stensrud, 1972		**Pindolol**, 2.5 or 5 mg, 3x/day for 4 wks	**Placebo**	
	Number of patients evaluable for AEs:	28*	28*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	22	2	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Dizziness or faintness	6 (21%)	0	
	Nausea	3 (11%)	0	
	Lethargy	3 (11%)	0	
	Chest discomfort	1 (4%)	1 (4%)	
	Increased appetite, weight gain	1 (4%)	1 (4%)	
	Flushing	1 (4%)	0	
	Palpitations	1 (4%)	0	
	Restlessness	1 (4%)	0	
	Dryness of mouth	1 (4%)	0	
	Dyspnea	1 (4%)	0	
	Reduced ability to concentrate	1 (4%)	0	
	"Feeling of unreality"	1 (4%)	0	
	Feeling of inability to judge distance	1 (4%)	0	
	Withdrawals due to AEs:	3 (causative AEs N/S)	0	
Smits, van der Meer, Pfeil, et al., 1993		**Estradiol** (Estraderm TTS®) patch), 50 µg/day for 8 days during 1-2 menstrual cycles	**Placebo**	Limited information reported on AEs. Itching in the area of the patch was reported in 9% of menstrual cycles during which Estraderm TTS® was used and in no cycles during which the placebo patch was used. Breast tenderness and bleeding pattern changes were no more common with Estraderm TTS® than with placebo.
	Number of patients evaluable for AEs:	20*	20*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Stensrud and Sjaastad, 1976a		**Clonidine (Catapresan®),** 75-150 µg/day for 7 wks		**Placebo**	Investigators provided no information on AEs. Two patients withdrew from the study, one for a reason unrelated to AEs. No explanation was given for the other's withdrawal.
	Number of patients evaluable for AEs:	27* (See note)		27* (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	N/S (See note)		N/S (See note)	
Solomon, 1986		**Verapamil,** 240 mg/day for 2 mos	**Propranolol (long-acting),** 120 mg/day for 2 mos	**Placebo**	Abstract reporting limited results. Data at left are for those patients who completed the trial (15/?). Investigators reported that, apart from the specific AEs listed at left, AEs were "similar" in the three groups. Three patients withdrew before completing the trial due to AEs associated with verapamil (1 rash, 2 headache). Two withdrew due to AEs associated with propranolol (1 wheezing, 1 fatigue).
	Number of patients evaluable for AEs:	15*	15*	15*	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Constipation	5	N/S	N/S	
	Lightheadedness/fatigue	N/S	3	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Solomon and Kunkel, 1993		**Flurbiprofen,** 100 mg, 2x/day for 8 wks	**Placebo**	Investigators reported only AEs they considered to be "drug-related."
	Number of patients evaluable for AEs:	31*	31*	*Flurbiprofen vs. placebo:* 0.16 (0.019 to 0.29)
	Number of patients reporting *drug-related* AEs:	5 (16%)	0	
	Total number of *drug-related* AEs reported:	8	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Blood in stool	2 (6%)	0	
	Burning (no further specification)	1 (3%)	0	
	Drop in hemoglobin	1 (3%)	0	
	Drop in hematocrit	1 (3%)	0	
	Abdominal cramps with diarrhea	1 (3%)	0	
	Epigastric pain with emesis	1 (3%)	0	
	Cold sores in mouth	1 (3%)	0	
	Withdrawals due to AEs:	2 (abdominal pain and burning)	0	
Solomon, Steel, and Spaccavento, 1983		**Verapamil**, 320 mg/day for 3 mos	**Placebo**	Limited information provided on AEs. Investigators reported that there were no major side effects with verapamil. One patient had symptomatic hypotension during last month of trial.
		N/S	N/S	
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	0	2	
	Withdrawals due to AEs:		(causative AEs N/S)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Somerville and Herrmann, 1978		**Lisuride,** dose gradually increased to 0.025 mg, 3x/day, on Day 5 and used thereafter for 3 mos	**Placebo**	Data at left are for 17/150 patients (11%) who *withdrew* due to AEs and were included in efficacy analyses. Investigators reported that other less severe AEs were "encountered frequently" by patients in both treatment groups. These AEs, all of which occurred more frequently in the lisuride-treated group, were muscle aches and pains, dizziness, cold feelings in the extremities, and palpitations.
	Number of patients evaluable for AEs:	66 (See note)	66 (See note)	
	Number of patients *withdrawing* due to AEs:	12 (18%)	5 (8%)	
	Total number of AEs reported:	18	8	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Fatigue, weakness	3 (5%)	0	
	Nausea	2 (3%)	2 (3%)	*Lisuride vs. placebo:* 0.10 (-0.0097 to 0.22)
	Chest pains	2 (3%)	1 (2%)	
	Back pains	1 (2%)	0	
	Blurred vision	1 (2%)	0	
	Depersonalization	1 (2%)	0	
	Depression	1 (2%)	1 (2%)	
	Drowsiness	1 (2%)	1 (2%)	
	Eye irritation	1 (2%)	0	
	Hallucinations	1 (2%)	0	
	Impotence	1 (2%)	0	
	Muscle aches and pains	1 (2%)	0	
	Numbness of tongue	0	1 (2%)	
	Subcutaneous hemorrhage	1 (2%)	2 (3%)	
	Vertigo	1 (2%)	0	
	Withdrawals due to AEs:	12 (for reasons listed above)	5 (for reasons listed above)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sørensen, Hansen, and Olesen, 1986		**Flunarizine**, 10 mg/day for 4 mos	**Placebo**	Data on AEs collected at monthly clinic visits. *Flunarizine vs. placebo:* 0.067 (-0.071 to 0.20)
	Number of patients evaluable for AEs:	29*	29*	
	Number of patients reporting AEs:	3 (10%)	1 (3%)	
	Total number of AEs reported:	3	1	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Daytime sedation	3 (10%)	1 (3%)	
	Withdrawals due to AEs:	1 (daytime sedation)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sørensen, Larsen, Rasmussen, et al., 1991		**Flunarizine**, 10 mg/day for 5 mos	**Metoprolol (slow-release)**, 200 mg/day for 5 mos	
	Number of patients evaluable for AEs:	72	75	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	72	69	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness/sedation	26 (36%)	21 (28%)	
	Weight gain	23 (32%)	9 (12%)	
	GI symptoms	5 (7%)	10 (13%)	
	Sleep disturbances/vivid dreams	4 (6%)	10 (13%)	
	Muscle fatigue/cold paresthesia	3 (4%)	10 (13%)	
	Depression	6 (8%)	2 (3%)	
	Dizziness/vertigo	1 (1%)	4 (5%)	
	Cardiovascular symptoms/hypotension	2 (3%)	1 (1%)	
	Extrapyramidal symptoms	2 (3%)	1 (1%)	
	Respiratory symptoms	0	1 (1%)	
	Withdrawals due to AEs:	10 (depression [4], weight gain [4], drowsiness/sedation [1], unknown [1])	1 (depression)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Steardo, Bonuso, Di Stasio, et al., 1982		**Propranolol**, 40 mg, 3x/day for 6 mos	**Metoprolol**, 100 mg, 3x/day for 6 mos	**Methysergide**, 6-10 mg/day for 6 mos	Limited information provided on AEs.
	Number of patients evaluable for AEs:	33	30	36	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	4 (dizziness [2], bradycardia [1], precordialgia [1])	8 (bradycardia [5], hypotension [3])	6 (paresthesia [3], gastralgia [2], precordialgia [1])	
Steardo, Marano, Barone, et al., 1986		**Flunarizine**, 10 mg/day for 5 mos	**Methysergide**, 6 mg/day for 5 mos		Limited information on AEs was reported. Investigators stated that fewer than 7% of patients reported daytime sedation/drowsiness with flunarizine. No weight gain was associated with flunarizine.
	Number of patients evaluable for AEs:	53	51		
	Number of patients reporting AEs:	N/S	N/S		
	Total number of AEs reported:	N/S	N/S		
	Withdrawals due to AEs:	0	7 (gastric disturbances [5], peripheral circulatory insufficiency [2])		

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Steiner, Joseph, Hedman, et al., 1988		**Metoprolol,** 50 mg, 2x/day for 2 mos	**Placebo**	Investigators reported that drowsiness and dizziness were experienced with both treatments, but did not state how many patients reported these AEs. *Metoprolol vs. placebo:* 0.049 (-0.14 to 0.23)
	Number of patients evaluable for AEs:	28	31	
	Number of patients reporting AEs:	5 (18%)	4 (13%)	
	Total number of AEs reported:			
	Number of patients reporting:	*n (%)*	*n (%)*	
	Drowsiness	(See note)	(See note)	
	Dizziness	(See note)	(See note)	
	Nightmares	1 (4%)	0	
	Weight increase	1 (4%)	0	
	Dyspnea	1 (4%)	0	
	Heartburn	1 (4%)	0	
	Milk pruritis	0	1 (3%)	
	Withdrawals due to AEs:	1 (heartburn)	0	
Stellar, Ahrens, Meibohm, et al., 1984		**Timolol,** 20-30 mg/day, taken in two doses, for 2 mos	**Placebo**	
	Number of patients evaluable for AEs:	107*	107*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting (most common AEs):	*n (%)*	*n (%)*	
	Insomnia	7 (7%)	2 (2%)	
	Light-headedness	3 (3%)	2 (2%)	
	Fatigue	3 (3%)	1 (1%)	
	Withdrawals due to AEs:	2 (chest pain [1], severe epigastric distress [1])	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Stensrud and Sjaastad, 1974		**Ketoprofen**, 50 mg, 3x/day for 6 wks	**Placebo**	Investigators reported only those AEs considered to be drug-related, and appear to have reported them only for those patients who completed the trial (24/26). Two patients withdrew before completing the trial for unspecified reasons. *Ketoprofen vs. placebo:* 0.080 (-0.048 to 0.21)
	Number of patients evaluable for AEs:	24*	24*	
	Number of patients reporting *drug-related* AEs:	2 (8%)	0	
	Total number of *drug-related* AEs reported:	2	0	
	Number of patients reporting:	*n (%)*	*n (%)*	
	Nausea	2 (8%)	0	
	Withdrawals due to AEs:	(See note)	(See note)	
Stensrud and Sjaastad, 1976b		**Propranolol**, 40 mg, 4x/day for 4 wks	**Placebo**	Limited information was provided on AEs. Investigators reported only that "in practically all cases, a varying degree of bradycardia and a slight reduction in blood pressure were found during the Inderal® [propranolol] period."
	Number of patients evaluable for AEs:	20* (See note)	20* (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	1 (dyspnoea & palpitations)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Stensrud and Sjaastad, 1979		**Clonazepam (Rivotril®),** 1-2 mg/day for 4 wks to 1 yr		**Placebo**	Investigators did not provide separate AE data for the 1-mg/day and 2-mg/day doses of clonazepam, or for the 4-wk controlled trial treatment period and the extended open trial. The incidence of AEs associated with placebo was also not reported.
	Number of patients evaluable for AEs:	38*		38*	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Drowsiness	23 (61%)		N/S	
	Dizziness	10 (26%)		N/S	
	Irritability	2 (5%)		N/S	
	Withdrawals due to AEs:	3 (lethargy and sleepiness [3 -- all after completing controlled portion of trial])		0	
Stensrud and Sjaastad, 1980a		**Atenolol,** 50 mg, 2x/day for 6 wks	**Propranolol,** 80 mg, 2x/day for 6 wks	**Placebo**	*Atenolol vs. placebo:* 0.028 (-0.047 to 0.10)
	Number of patients evaluable for AEs:	35*	35*	35*	
	Number of patients reporting AEs:	1 (3%)	N/S	0	
	Total number of AEs reported:	1	12	0	
	Number of patients reporting:	*n (%)*	*n (%)*	*n (%)*	
	Reduced physical capacity	1 (3%)	6 (17%)	0	
	Nausea	0	3 (9%)	0	
	Cold hands/feet	0	1 (3%)	0	
	Dizziness	0	1 (3%)	0	
	Sleeping difficulties	0	1 (3%)	0	
	Withdrawals due to AEs:	0	1 (dizziness)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sternieri, Bussone, Manzoni, et al., 1991		**Lornoxicam**, 4 mg, 3x/day for 2 mos		**Placebo**	*Lornoxicam vs. placebo:* 0.17 (0.021 to 0.32)
	Number of patients evaluable for AEs:	48		52	
	Number of patients reporting AEs:	13 (27%)		5 (10%)	
	Total number of AEs reported:	N/S		N/S	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Abdominal discomfort	9 (19%)		0	
	Withdrawals due to AEs:	4 (causative AEs N/S)		2 (causative AEs N/S)	
Sudilovsky, Elkind, Ryan, et al., 1987		**Nadolol**, 160 mg, 1x/day for 2 mos	**Nadolol**, 80 mg, 1x/day for 2 mos	**Propranolol**, 80 mg, 2x/day for 2 mos	No further information provided on AEs.
	Number of patients evaluable for AEs:	47	49	44	
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	2 (fatigue and depression [1], urticaria [1])	2 (HA and dizziness [1], nausea [1])	4 (fatigue and memory disturbance [1], vertigo and urticaria [1], dyspnea and chest tightness [1], paresthesia [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Sudilovsky, Stern, and Meyer, 1986b		**Nadolol**, 240, 160, or 80 mg/day for 2 mos	**Placebo**	Abstract -- no data reported on AEs.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	
Szekely, Merryman, Croft, et al., 1989		**Naproxen sodium**, 550 mg, 2x/day, during perimenstrual period for 2 mos	**Placebo**	Data at left are for those patients who completed the trial (22/30). Investigators reported that 2 patients withdrew before completing the trial due to AEs, one with stomatitis, one with ecchymoses. There is no indication which treatment these two patients were taking at the time of their withdrawal.
	Number of patients evaluable for AEs:	22*	22*	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting (most common) AEs:	*n (%)*	*n (%)*	
	Gastrointestinal symptoms	10 (45%)	8 (36%)	
	Central nervous symptom complaints	5 (23%)	7 (32%)	
	Withdrawals due to AEs:	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Tfelt-Hansen, Standnes, Kangasniemi, et al., 1984		**Propranolol,** 80 mg, 2x/day for 3 mos	**Timolol,** 10 mg, 2x/day for 3 mos	**Placebo**	*Propranolol vs. placebo:* 0.14 (-0.0010 to 0.28) *Timolol vs. placebo:* 0.18 (0.033 to 0.32) *Propranolol vs. timolol:* -0.036 (-0.18 to 0.11)
	Number of patients evaluable for AEs:	83*	83*	83*	
	Number of patients reporting AEs:	35 (42%)	38 (46%)	23 (28%)	
	Total number of AEs reported:	N/S	N/S	N/S	
	Number of patients reporting (most common AEs):	*n (%)*	*n (%)*	*n (%)*	
	Fatigue/tiredness	11 (13%)	18 (22%)	15 (18%)	
	Dizziness	4 (5%)	5 (6%)	2 (2%)	
	Nausea	5 (6%)	2 (2%)	2 (2%)	
	Sleep disturbances	3 (4%)	4 (5%)	2 (2%)	
	Depression	3 (4%)	2 (2%)	0	
	Abnormal dreaming	0	2 (2%)	0	
	Withdrawals due to AEs:	N/S	N/S	N/S	
Thomas, Behari, and Ahuja, 1991		**Flunarizine,** 10 mg/day for 12 wks		**Placebo**	Limited information provided on AEs. Data at left concern only those 15 patients (of 29) who completed the crossover. One patient withdrew prematurely due to AEs associated with flunarizine (galactorrhea).
	Number of patients evaluable for AEs:	15*		15*	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Daytime sedation	10 (67%)		N/S	
	Weight gain (2-5 kg)	8 (53%)		N/S	
	Withdrawals due to AEs:	(See note)		(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Titus, Dávalos, Alom, et al., 1986		**Oxitriptan (5-hydroxytryptophan or 5-HTP)**, 600 mg/day for 6 mos	**Methysergide**, 3 mg/day for 6 mos	The article reports unclear and (at least apparently) inconsistent information about the number of patients who had to "discontinue treatment" (5, all methysergide) or who had treatment "withdrawn" (4 methysergide, 5 oxitriptan) due to AEs.
	Number of patients evaluable for AEs:	45	40	
	Number of patients reporting AEs:	13 (29%)	10 (25%)	
	Total number of AEs reported:	18	10	
	Number of patients reporting:	*n (%)*	*n (%)*	*Methysergide vs. oxitriptan:*
	Abdominal pain	6 (13%)	0	0.038 (-0.15 to 0.22)
	Gain in weight	4 (9%)	1 (3%)	
	Nausea	3 (7%)	2 (5%)	
	Diarrhea	3 (7%)	0	
	Numbness or pain in legs	0	3 (8%)	
	Insomnia and anxiety	1 (2%)	1 (3%)	
	Impotence	0	2 (5%)	
	Drowsiness	0	1 (3%)	
	Amenorrhea	1 (2%)	0	
	Withdrawals due to AEs:	? (See note)	? (See note)	
Vilming, Standnes, and Hedman, 1985		**Pizotifen**, inc'd from 0.5 mg, 1x/day to 0.5 mg, 3x/day for 8 wks	**Metoprolol**, 50 mg, 2x/day for 8 wks	Data at left concern only the patients who completed the crossover trial and from whom efficacy data were obtained. The total number of patients and AEs are the sum of the numbers reported for the first and second months of treatment.
	Number of patients evaluable for AEs:	30* (See note)	30* (See note)	
	Number of patients reporting AEs:	Unclear	Unclear	
	Total number of AEs reported:	76	66	
	Withdrawals due to AEs:	3 (edema/lack of effect [1], sedation [1], weight gain/depression/restless legs [1])	1 (nightmares)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Weber and Reinmuth, 1972		**Propranolol,** 20 mg, 4x/day for 3 mos	**Placebo**	Limited data were provided on AEs. Investigators only reported that one patient complained of abdominal cramps and diarrhea, but did not specify which treatment the patient was receiving.
	Number of patients evaluable for AEs:	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	0	0	
Welch, Ellis, and Keenan, 1985		**Naproxen sodium,** 550 mg, 2x/day for 8 wks	**Placebo**	Of the 46 patients who entered the first treatment period, 6 dropped out before ever taking naproxen sodium, and 3 dropped out before ever taking placebo.
	Number of patients evaluable for AEs:	40*	43*	
	Number of patients reporting AEs:	9 (23%)	9 (21%)	
	Total number of AEs reported:	14	14	*Naproxen sodium vs. placebo*: 0.016 (-0.16 to 0.19)
	Number of patients reporting AEs:	*n (%)*	*n (%)*	
	Gastrointestinal problems	6 (15%)	3 (7%)	
	Dizziness/faintness	2 (5%)	0	
	Pains	1 (3%)	2 (5%)	
	Urinary problems	1 (3%)	1 (2%)	
	Other	1 (3%)	3 (7%)	
	Withdrawals due to AEs:	4 (exacerbation of tachycardia [1], fear of developing GI problems [1], gastric burning [2])	1 ("vague somatic complaints" [1])	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Wessely, Baumgartner, Klingler, et al., 1987		**Gabapentin,** 900 mg/day for 3 mos		**Placebo**	Very limited information was reported on AEs. Withdrawals were due to nausea, tiredness, and dizziness (no breakdown by treatment group).
	Number of patients evaluable for AEs:	16		20	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	2 (See note)		1 (See note)	
Widerøe and Vigander, 1974		**Propranolol,** 40 mg, 4x/day for 3 mos		**Placebo**	No information was reported on AEs from this controlled trial.
	Number of patients evaluable for AEs:	30* (See note)		30* (See note)	
	Number of patients reporting AEs:	N/S		N/S	
	Total number of AEs reported:	N/S		N/S	
	Withdrawals due to AEs:	0		0	
Wilkinson, 1970		**Clonidine,** 50 µg, 2x/day for 6 wks	**Clonidine,** 25 µg, 2x/day for 6 wks	**Placebo (lactose)**	Four patients withdrew from the study, 2 for unspecified reasons, 2 because they "were worse."
	Number of patients evaluable for AEs:	23*	23*	23*	Little information on AEs was reported. The investigator only stated that there were "no serious side effects" and that "a few patients ha[d] become depressed."
	Number of patients reporting AEs:	N/S	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	N/S (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Wilkinson, Agnoli, Gerber, et al., 1989		**Lisuride (Cuyalit®)**, 0.05 mg, 3x/day for 3 mos	**Lisuride (Cuyalit®)**, 0.025 mg, 3x/day for 3 mos	Limited data were provided on AEs. Investigators reported only that AEs were infrequent and that there were no statistically significant differences between the two treatments for AEs.
	Number of patients evaluable for AEs:	49	43	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	6 (N/S)	9 (N/S)	
Wörz, Reinhardt-Benmalek, Foeh, et al., 1992		**Bisoprolol**, 5 mg, 1x/day for 3 mos	**Metoprolol**, 100 mg/day for 3 mos	14 patients withdrew due to unspecified AEs, but no breakdown was provided by intervention.
	Number of patients evaluable for AEs:	125*	125*	
	Number of patients reporting AEs:	23 (18%)	19 (15%)	*Bisoprolol vs. metoprolol:* 0.032 (-0.061 to 0.12)
	Total number of AEs reported:	N/S	N/S	
	Number of patients reporting (most common AEs only):	*n (%)*	*n (%)*	
	Dizziness	8 (6%)	4 (3%)	
	Tiredness/fatigue	3 (2%)	7 (6%)	
	Sleep disturbances	2 (2%)	6 (5%)	
	Cardiovascular/hypotensive reactions	6 (5%)	1 (<1%)	
	GI disturbances	5 (4%)	2 (2%)	
	Withdrawals due to AEs:	N/S (See note)	N/S (See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Zeeberg, Orholm, Dalsgaard Nielsen, et al., 1981		**Femoxetine**, 200 mg/day for first wk, 300 mg/day therafter, for total of 12 wks	**Placebo**	These data appear to include only those patients who completed the trial or were known to have withdrawn due to AEs (48/59 patients randomized to treatment), though this is not entirely clear.
	Number of patients evaluable for AEs:	23	25	
	Number of patients reporting AEs:	6 (26%)	1 (4%)	
	Total number of AEs reported:			
				Femoxetine vs. placebo:
	Number of patients reporting:	*n (%)*	*n (%)*	0.22 (0.012 to 0.40)
	Nausea	3 (13%)	0	
	Changes in mood	2 (9%)	0	
	Prolonged menstrual bleeding	1 (4%)	0	
	Tiredness, indisposition	1 (4%)	0	
	Palpitation	1 (4%)	0	
	Dry mouth	1 (4%)	0	
	Paraesthesia (tongue)	1 (4%)	0	
	Excessive sweating	0	1 (4%)	
	Withdrawals due to AEs:	3 (nausea and prolonged menstrual bleeding; nausea and changes in mood; tiredness and indisposition)	0	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions			Notes; Difference in proportion of patients reporting adverse events (95% CI)
Ziegler and Ellis, 1985		**Naproxen sodium,** 550 mg, 2x/day for 8 wks		**Placebo**	*Naproxen sodium vs. placebo:* -0.049 (-0.20 to 0.11)
	Number of patients evaluable for AEs:	40*		40*	
	Number of patients reporting AEs:	5 (13%)		7 (18%)	
	Total number of AEs reported:	7		8	
	Number of patients reporting:	*n (%)*		*n (%)*	
	Gastrointestinal symptoms	4 (10%)		4 (10%)	
	Drowsiness	1 (3%)		1 (3%)	
	Aches and pains	0		1 (3%)	
	Other (incl. uncoordination, slurred speech, blurred vision, hypertension, and itching)	0		2	
	Withdrawals due to AEs:	1 (stomach pain and burning)		0	
Ziegler, Hurwitz, Hassanein, et al., 1987		**Amitriptyline,** 50-150 mg/day for 4-8 wks	**Propranolol,** 80-240 mg/day for 4-8 wks	**Placebo**	Investigators stated that 3 patients withdrew prematurely due to unspecified "toxic reactions." They did not say which of the interventions were associated with these reactions. No further information was provided on AEs.
and	Number of patients evaluable for AEs:	N/S	N/S	N/S	
	Number of patients reporting AEs:	N/S	N/S	N/S	
Ziegler, Hurwitz, Preskorn, et al., 1993	Total number of AEs reported:	N/S	N/S	N/S	
	Withdrawals due to AEs:	(See note)	(See note)	(See note)	

[1] See last page of this table for key to abbreviations.

[2] An asterisk denotes a crossover trial.

Report	Adverse events	Interventions		Notes; Difference in proportion of patients reporting adverse events (95% CI)
Zuddas, Mulas, Del Zompo, et al., 1985		**Lisuride**, dose gradually increased until it was 0.025 mg, 3x/day on Day 7 and thereafter for 3 mos	**Placebo**	No data provided on AEs.
	Number of patients evaluable for AEs:	15 (See note)	15 (See note)	
	Number of patients reporting AEs:	N/S	N/S	
	Total number of AEs reported:	N/S	N/S	
	Withdrawals due to AEs:	N/S	N/S	

1 Key to abbreviations: µg = microgram; 5-HTP = oxitriptan; AEs = adverse; BP = blood pressure; CDH = chronic daily headache; CI = confidence interval; CNS = central nervous system; DEK = dihydroergokryptine; DHE = dihydroergotamine; GI = gastrointestinal; HA = headache; inc'd = increased; kg = kilogram; L-5-hydroxytryptophan = oxitriptan; max. = maximum; mg = milligram; mo = month; n = sample size; N/S = not specified; OTC = over-the-counter; tab = tablet; vs. = versus; TTS = transdermal therapeutic system; wk = week

Appendix A:
Miscellaneous Trials Not Reviewed in This Report

The following is a list of trials of miscellaneous agents which appear to meet our basic inclusion criteria but which we did not review in this report. The agents included on the list have been studied in only a small number of controlled trials and are not widely available and/or have been shown to be ineffective.

Publication	**Active agent(s) studied**
Anthony, Lord, and Lance (1978)	Cimetidine Cimetidine + chlorpheniramine maleate
Baxter, Marsden, Parkes, et al. (1972)	Amantadine
Burns (1965)	Prostigmine bromide Chorionic gonadotropin
Carasso and Yehuda (1984)	Migraleve® (acetaminophen + codeine phosphate + buclizine + dioctyl sodium sulphosuccinate)
Facchinetti, Sances, Borella, et al. (1991)	Magnesium
Gennari, Chierichetti, Gonnelli, et al. (1986)	Salmon calcitonin
Jorgensen, Weightman, and Foster (1974)	Buclizine Migraleve® (acetaminophen + codeine phosphate + buclizine + dioctyl sodium sulphosuccinate)
Martelletti, Bussone, Centonze, et al. (1991)	Cromolyn sodium
Matts (1974)	Metoclopramide
Micieli, Cavallini, Martignoni, et al. (1988)	Salmon calcitonin
Minervini and Pinto (1987)	Captopril
Monro, Carini, and Brostoff (1984)	Sodium cromoglycate
Nanda, Arthur, Johnson, et al. (1980)	Cimetidine Cimetidine + chlorpheniramine maleate
Opavsky (1991)	Magnesium lactate Magnesium sulphate Magnesium sulphate + cinnarizine
Scopa, Jorgensen, and Foster (1974)	Migraleve® (acetaminophen + codeine phosphate + buclizine + dioctyl sodium sulphosuccinate)

Appendix B:
MEDLINE Search Strategy

Efficacy of headache treatments

1 randomized controlled trials/
2 random allocation/
3 double-blind method/
4 single-blind method/
5 randomized controlled trial.pt.
6 1 or 2 or 3 or 4 or 5
7 animal/
8 human/
9 7 and 8
10 7 not 9
11 6 not 10

12 clinical trial.pt.
13 exp clinical trials/
14 (clin$ adj trial$).tw.
15 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
16 placebos/
17 placebo$.tw.
18 random$.tw
19 research design/
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 20 not 10

22 comparative-study/
23 exp evaluation studies/
24 follow-up studies/
25 prospective-studies/
26 (control$ or prospectiv$ or volunteer$).tw.
27 22 or 23 or 24 or 25 or 26
28 27 not 10
29 21 not 11
30 28 not (21 or 11)

31 exp headache/
32 11 and 31
33 29 and 31
34 30 and 31

Appendix C: Data Collection Form

Data Abstraction Form ver 5.19.95 Reviewer _____
First Author (last name): _____ Pro-Cite no.: _____ Todays date: ___/___/___

EXCLUDE Why?

Are most or all of the patients in this study in the **pediatric** age group (0-17)? No Yes **-> STOP**

State the **inclusion criteria** (headache diagnoses first)

Headache diagnosis: Migraine Tension-type Cluster mixed
other_____

Diagnostic criteria: IHS Ad hoc other none/NS

State the exclusion criteria (headache diagnoses first)

Patient enrollment site *(circle all that apply)*

Primary Care Clinic General Neurology Clinic Headache Clinic Not Stated

Emergency Clinic Pain Clinic Psychology clinic Other _____

Design: Unclear
Single-period parallel-group
Crossover
Matched pair (or paired)

For Cross-over design only-> Was there a significant carry-over effect? Yes No Not Stated
If "yes" then abstract "period one" data **only** as if the trial used a parallel group design.

Instrument to measure bias in pain research reports (Jadad, 1996)		Response	Score
1	Was the study described as **randomized** (this includes the use of words such as randomly, random and randomization)?	Yes No	1 0
1a	If the method of generating the randomization sequence was described, was it **adequate** *(table of random numbers, computer-generated, coin tossing, etc.)* or **inadequate** *(alternating, date of birth, hospital number, etc.)*?	Not described/NA Adequate Inadequate	0 1 -1
2	Was the study described as **double-blind**?	Yes No	1 0
2a	If the method of blinding was described, was it **adequate** *(identical placebo, active placebo, etc.)* or **inadequate** *(comparison of tablet vs. injection with no double dummy)*?	Not described/NA Adequate Inadequate	0 1 -1
3	Was there a description of **withdrawals** and **drop-outs**?	Yes No	1 0

Appendix C: Data Collection Form

Data Abstraction Form ver 5.19.95 Reviewer _____

First Author (last name): _____ Pro-Cite no.: _____ Todays date: ___/___/___

Describe the elements of the study design common to all groups (eg, 4 wk lead in, 12 wk treatment period)	
Brief description of intervention	Details (including dose, duration, timing, etc.)
Intervention 1 (placebo or control or wait-list)	
Intervention 2	
Intervention 3	
Intervention 4	

Patient characteristics (overall: if figures are given by treatment groups, then calculate weighted average)

Age _____ ± _____ or _____ (_____ to _____)
mean ± std dev median and (lower to upper) range

Female (%) _____

Chronicity of H/A d/o ($\bar{x}$, years) _____

HA frequency (#HA/mo) _____

Patient characteristics describe: pre-treatment (trial entry) post-treatment (completion)

Adverse Event Frequency *(%)*	Overall	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Total entered study, n					
Total completed study, n					
Dropouts 2° S/E, (%)					
Dropouts, total, (%)					

Appendix C: Data Collection Form

Data Abstraction Form ver 5.19.95 Reviewer _____

First Author (last name): _____ Pro-Cite no.: _____ Todays date: ___/___/___

Outcome measure Primary or secondary	Def"n (e.g. from 2 or 3 to 0 or 1)	How measured? (e.g. 4 pt scale)	When assessed? (2 hrs, 2 mo)	When were sx recorded? (daily, etc)

BEFORE/Period 1/single-period parallel-group design	Gp 1	Gp 2	Gp 3	Gp 4
Sample size				
Mean				
SD / VAR / SEM *(circle one)*				
AFTER/Period 2				
Sample size				
Mean				
SD / VAR / SEM *(circle one)*				
BEFORE/AFTER comparisons				
Mean				
SD/ VAR / SEM of difference *(circle one)*				
Test statistic for diff				
Degrees of freedom for test statistic				
p-value of test statistic				
Name of test statistic (e.g.; t, F, etc.)				
BETWEEN GROUP COMPARISONS				
Mean				
SD/ VAR / SEM of difference *(circle one)*				
Test statistic for diff				
Degrees of freedom for test statistic				
p-value of test statistic				
Name of test statistic (e.g.; t, F, etc.)				
	F statistic	d.f.	p-value	
OVERALL COMPARISON/ANOVA				

Appendix C: Data Collection Form

Data Abstraction Form ver 5.19.95 Reviewer _____

First Author (last name): _____ Pro-Cite no.: _____ Todays date: ___/___/___

Outcome measure Primary or secondary	Def"n (e.g. from 2 or 3 to 0 or 1)	How measured? (e.g. 4 pt scale)	When assessed? (2 hrs, 2 mo)	When were sx recorded? (daily, etc)

	Outcomes (fill in dichotomous outcomes, categories, or ranges for groups as column headers)					Totals
	worst				best	
Treatments	N (%)	N (%)	N (%)	N (%)	N (%)	N (100%)
A						
B						
C						
D						

Outcome measure Primary or secondary	Def"n (e.g. from 2 or 3 to 0 or 1)	How measured? (e.g. 4 pt scale)	When assessed? (2 hrs, 2 mo)	When were sx recorded? (daily, etc)

	worst				best	Totals
Treatments	N (%)	N (%)	N (%)	N (%)	N (%)	N (100%)
A						
B						
C						
D						