Chapter 58

Nonsteroidal Anti-Inflammatory and Miscellaneous Drugs in Migraine Prophylaxis

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INTRODUCTION

In addition to the recognized drugs of first choice for migraine prophylaxis such as β-adrenoceptor blockers, antiserotonin drugs, calcium antagonists, and antiepileptic drugs, many other drugs and remedies have been tested in migraine prophylaxis. Most of these other drugs have not been tested in controlled randomized clinical trials. However, their use is sometimes recommended even in modern handbooks. This chapter aims to present the data on miscellaneous drugs that have been tested for migraine prophylaxis and for which controlled randomized trials are available. For drugs with established efficacy in migraine prophylaxis, details of their therapeutic use are mentioned briefly. The description will focus on the clinical evidence for efficacy of these drugs rather than on their pharmacologic properties.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

The rationale for using NSAIDs in the prophylaxis of migraine is based on the observation that some patients taking NSAIDs for other reasons (e.g., secondary prophylaxis of stroke) experience fewer migraine attacks and on the possible general involvement of prostaglandins in the inflammatory pathophysiologic components of the migraine process. The NSAIDs that have been most extensively tested in migraine prophylaxis are acetylsalicylic acid (ASA) (aspirin), naproxen and naproxen sodium, and tolfenamic acid.

Pharmacologic Background

The pharmacologic actions of the NSAIDs relevant to migraine prophylaxis are described in Chapter 49. Briefly, NSAIDs possess antiinflammatory, analgesic, and antipyretic properties. They exert their effect by inhibiting the ubiquitous cyclooxygenase-1 and cyclooxygenase-2 enzymes, thereby preventing the synthesis of prostaglandins and thromboxanes from ASA. The inhibition by ASA, but not other NSAIDs, is irreversible because ASA acetylates cyclooxygenase. The NSAIDs usually are classified as peripheral analgesics, although they have central effects as well.

Absorption after oral ASA, as with other NSAIDs, is high, in excess of 80% (1). ASA is metabolized rapidly by plasma and tissue esterases to salicylic acid before it reaches the systemic circulation. The peak plasma concentration of ASA is achieved 15 minutes after oral administration, whereas the peak concentration of salicylate is reached after 30 to 60 minutes. The plasma half-life of ASA is 15 to 30 minutes. Salicylic acid exhibits dose-dependent kinetics; thus, its half-life after 250 mg of ASA is about 3 hours and after 1 g about 6 hours. The range of bioavailability is between greater than 90% for naproxen/naproxen sodium and 60% for tolfenamic acid. The plasma half-lives of these NSAIDs are in the range of 2 to 4 hours, with the exception of naproxen, which has a half-life of 12 to 15 hours.

Possible Mode of Action in Migraine Prophylaxis

The mode of action of NSAIDs in migraine therapy and whether this mode of action involves prostaglandins in the migraine process are discussed in Chapter 49. One of

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

the major obstacles to inhibition of cyclooxygenase being responsible for the prophylactic efficacy of these agents is the lack of effect of the potent NSAID indomethacin in a double-blind, placebo-controlled trial in migraine patients (2).

It has been suggested that the prophylactic usefulness of NSAIDs in migraine could be through the inhibition of platelet aggregation, thereby correcting an underlying hyperaggregability (3,4). However, high oral doses of ASA (650 to 1300 mg daily) in combination with 75 to 300 mg dipyridamole daily were marginally superior to placebo in migraine prophylaxis in one trial (5) and superior to placebo in another (3), but these effects were not correlated with whether the patients had hyperaggregable platelets. In one placebo-controlled crossover trial in which a low dose of ASA (160 mg) was evaluated for migraine prophylaxis (see below), the active medication was of no benefit despite inhibition of platelet function (6). In the Physicians' Health Study (7) of ASA (325 mg on alternate days), however, a 20% reduction in the incidence of migraine was suggested compared with placebo (see below). No correlation was observed between the degree of platelet inhibition and the efficacy as a migraine prophylactic drug for naproxen (8). Therefore, it is most unlikely that an action of platelets is responsible for the beneficial prophylactic effect of NSAIDs. Thus, the mode of action of NSAIDs in migraine prophylaxis is—as it is for any other migraine prophylactic drug—still not fully understood.

Results of Controlled Clinical Trials

A summary of 20 controlled double-blind randomized trials on the efficacy of oral NSAIDs in migraine prophylaxis is given in Table 58-1. All but two trials (3,10) included migraine patients both with and without aura; the two exceptions did not include any aura patients.

Higher doses of aspirin (1300 mg and 900 mg daily, respectively) showed superior efficacy compared with placebo (11) and were apparently comparable in efficacy to propranolol (9) in two small trials (12 patients in each), although the latter trial was too small to demonstrate comparability. In another trial, however, ASA (1500 mg daily) was less effective than metoprolol (10). This was confirmed by a recent large trial showing a superiority of 200 mg of metoprolol over 300 mg of ASA for all efficacy parameters (12). The outcome results for ASA were regarded by the investigators as in the range of typical placebo response. Trials of low doses of ASA have also failed to provide convincing evidence of efficacy. ASA (160 mg daily) did not achieve better results than placebo (6), and no correlation was found between the number of attacks and inhibition of adenosine diphosphate (ADP)–induced platelet aggregation. In children aged 7 to 17 years, the effect of ASA (100 to 200 mg daily) was comparable to that of flunarizine (13); however, because no placebo was used in this trial, conclusions concerning the efficacy of ASA cannot be made.

There are three large cohort studies with a comparison between ASA and placebo not primarily designed to examine the influence on migraine prophylaxis but showing interesting relevant results. The Physicians' Health Study (7) indicated some effect of low-dose ASA (325 mg every other day for the prevention of cardiovascular disease) with the finding that 6% of subjects reported migraine compared with 7.4% of subjects taking placebo during a 60-month period (i.e., a 20% reduction in migraine frequency). Similar results were obtained in the earlier British Doctors Trial showing a reduction of migraine attacks by about 30% in the group taking 500 mg of ASA (14). However, in the Women's Health Study, 100 mg of ASA daily did not result in a significant reduction of migraine frequency as compared to placebo, but showed a trend to a decrease in severity, duration, and migraine-related incapacitation (15). The study result was regarded as only a small treatment effect of ASA in the prophylaxis of migraine among middle-aged women. The question of whether low-dose ASA has a minor effect in migraine prophylaxis thus remains open.

In the first trial of naproxen (500 mg daily), this drug proved only questionably better than placebo (16). Naproxen sodium (1100 mg daily), however, was demonstrated to have better efficacy than placebo in three trials (4,8,17), and in one of these trials (17) it was comparable to pizotifen. In another trial (18), naproxen sodium (1100 mg daily) was comparable to propranolol, but the superiority of both drugs over placebo was restricted to patients' evaluations. Comparability in each of these trials was not substantiated by narrow confidence intervals.

Tolfenamic acid had significantly better results than placebo (19,20), and comparability to propranolol was indicated in one of the trials (20) by rather narrow confidence intervals. In another trial (21), tolfenamic acid was comparable to propranolol, but no placebo control was included.

Only single trials are available for the remaining NSAIDs listed in Table 58-1. Ketoprofen showed marginally superior results compared with placebo in a group of severely afflicted migraine patients (22). In one small trial (17 patients), mefenamic acid had superior efficacy compared with placebo (23), but the claimed comparability to propranolol cannot be substantiated from a trial that included so few patients. Fenoprofen (1800 mg daily but not 600 mg daily) was superior to placebo (24), indobufen also had greater effects than placebo in one trial (25), and even flurbiprofen led to a significant decrease of headache intensity but not frequency in a double-blind placebo-controlled trial (26). Very recently, the new selective cyclooxygenase-2 inhibitor rofecoxib was studied for migraine prophylaxis. In a double-blind, placebo-controlled trial with 175 randomized (147 evaluated) patients, rofecoxib 25 mg/day

TABLE 58-1 Double-Blind Randomized Clinical Trials Comparing NSAIDs with Placebo and Other Drugs in the Prophylaxis of Migraine

Trial	*Drug and Dosage (mg)*	*Study Design*	*No. of Patients (no. Evaluated)*	*Run-in Period*	*Duration of Treatment*	*Efficacy Parameter*	*Investigators' Conclusions*
(11)	ASA 650 bid Placebo bid	CO	12	Nil	3 mo × 2	Frequency	ASA > placebo
(9)	ASA 4.5/kg tid Propranolol 0.6/kg tid	CO	18 (12)	30 days open	3 mo × 2 (2 wk washout)	Frequency, headache index[a]	ASA vs propranolol, ns; both > run-in
(6)	ASA 160 od Placebo od	CO	38 (27)	Nil	3 mo × 2	Frequency, severity	ASA vs placebo, ns
(13)	ASA 100–200 od Flunarizine 5–10 od	Pa	30 (29)[b]	4 wk open	3 mo	Frequency	ASA vs flunarizine, ns; both > run-in
(10)	Metoprolol 200 od ASA 1,500 od	CO	28 (21)	8 wk	12 wk × 2	Frequency, 50% frequency decrease	Metoprolol > ASA; both > run-in
(16)	Naproxen 250 bid Placebo bid	CO	28	2 mo (no drug)	6 wk × 2 (1 wk washout)	Frequency, duration, headache index[c], preference	Naproxen > placebo for preference, other parameters dubious
(4)	Naproxen-sodium 550 bid Placebo bid	CO	34 (28)	2 wk placebo	8 wk × 2 (2 wk washout)	rating of efficacy, headache index[c], duration, medication	naproxen, sodium > placebo for all parameters
(8)	Naproxen-sodium 550 bid Placebo bid	CO	51 (33)	2 wk placebo	8 wk × 2 (2 wk washout)	Rating of efficacy, headache index, days with severe headache	Naproxen, sodium > placebo for all parameters
(18)	Naproxen-sodium 550 bid Propranolol 40 tid Placebo	Pa	170 (129)	2 wk placebo	14 wk	Headache days, severity, overall evaluation	Naproxen, sodium vs propranolol vs placebo ns for headache days and severity; naproxen, sodium = propranolol > placebo for patients' evaluation
(17)	Naproxen-sodium 550 bid Pizotifen 0.5 tid Placebo tid	Pa	176 (151)	8 wk placebo	12 wk	Headache unit index	Naproxen, sodium = pizotifen > placebo
(19)	Tolfenamic acid 100 tid Placebo tid	CO	38 (31)	Nil	10 wk × 2 (2 wk washout)	Frequency, severity, duration, preference	Tolfenamic acid > placebo for all parameters
(20)	Tolfenamic acid 100 tid Propranolol 40 tid Placebo tid	CO	39 (31)	Nil	12 wk × 3	Frequency, duration, severity, medication	Tolfenamic acid = propranolol > placebo for frequency and medication; tolfenamic acid > propranolol = placebo for severity
(21)	Tolfenamic acid 100 tid Propranolol 40 tid	CO	76 (56)	4 wk (no drug)	12 wk × 2 (4 wk washout)	Migraine days, duration, severity	Both > run-in; tolfenamic acid = propranolol for all parameters

(*continued*)

TABLE 58-1 Double-Blind Randomized Clinical Trials Comparing NSAIDs with Placebo and Other Drugs in the Prophylaxis of Migraine (*Continued*)

Trial	*Drug and Dosage (mg)*	*Study Design*	*No. of Patients (no. Evaluated)*	*Run-in Period*	*Duration of Treatment*	*Efficacy Parameter*	*Investigators' Conclusions*
(22)	Ketoprofen 50 tid Placebo tid	CO	26 (24)	Nil	6 wk × 2 (1 wk washout)	Headache index[c], headache days	Ketoprofen > placebo for both parameters
(23)	Mefenamic acid 500 tid Propranolol 80 tid Placebo tid	CO	29 (17)	1 mo open	3 mo × 3	Frequency, duration, severity	Frequency, mefenamic acid = propranolol > placebo; severity and duration, ns
(24)	Fenoprofen 200 tid Fenoprofen 600 tid Placebo tid	Pa	118 (110)	4 wk placebo	12 wk	Frequency, headache index, medication	Fenoprofen 600 > placebo for all parameters; fenoprofen 200 vs placebo, ns
(25)	Indobufen 200 bid Pl bid	Pa	42 (35)	4 wk (no drug)	3 mo	Frequency, duration, headache index[c], evaluation of treatment	Indobufen > placebo for all parameters
(12)	ASA 300 od Metoprolol 200 od	Pa	270 (115)	4 wk placebo	4 mo	Frequency, responders	Metoprolol > ASA for all parameters
(27)	Rofecoxib 12.5 bid Placebo bid	Pa	175 (147)	2 mo	3 mo	Responders, frequency	Rofecoxib > placebo for responders; ns for frequency
(26)	Flurbiprofen100 bid Placebo bid	CO	23	Nil	8 wk × 2 (2 wk washout)	Intensity, frequency	Flurbiprofen > placebo for intensity but not for frequency

ASA = aspirin; ns = not significant; od = once daily; bid = twice daily; tid = three times daily; co = crossover; pa = parallel-groups comparison; wk = week(s); mo = month(s); > = more effective than.
[a] = frequency × severity × duration
[b] = children, 7 to 17 years old
[c] = frequency × severity.

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GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

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GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

was superior to placebo with respect to the responder rate but not to the absolute decrease of migraine frequency; there were no significant differences in the rate of adverse events between rofecoxib and placebo (27).

Gastrointestinal problems were the most common side effects during NSAID treatment, including dyspepsia and diarrhea, but their frequencies of occurrence were generally not greater than those encountered in subjects who took placebo, probably because of the relatively small size of the trials. In only one trial (naproxen sodium) was it necessary for a patient to withdraw because of peptic ulceration (17). The possibility that rofecoxib (recently withdrawn in several countries) and other selective cyclooxygenase-2 inhibitors may increase the risk of adverse cardiovascular events might preclude their use in migraine prophylaxis.

Menstrual Migraine

Since about 50% of women migraineurs suffer migraine exclusively or also during menstruation (28), it has been suggested that NSAIDs might be particularly effective for menstrual-related migraine. Naproxen sodium (550 mg twice daily) has been shown to reduce pain including headache in the premenstrual syndrome (29). Its specific effects on menstrual migraine (550 mg twice daily) have also been evaluated (18,30,31). In one trial (18), a subset of 30 of 129 patients taking naproxen sodium or placebo continuously was analyzed for headache activity occurring before and after the onset of menstruation; patients treated with naproxen sodium reported fewer and less severe headaches during the week before menstruation than patients treated with placebo, but only severity was significantly reduced. In the other two placebo-controlled trials, naproxen sodium, given during 1 week before and 1 week after the start of menstruation, resulted in fewer perimenstrual headaches; in one study, severity was not reduced (31), but in the other both severity and analgesic requirements were decreased (30). Recently, 25 or 50 mg of rofecoxib, the selective cyclooxygenase-2 inhibitor, was studied in a small randomized open trial in 14 women with perimenstrual migraine (32). Both doses resulted in a significant decrease of days with migraine as compared to baseline, but the absence of a placebo control does not allow any final conclusion on the efficacy of this drug.

Therapeutic Use

When first-line migraine prophylactics (i.e., β-adrenoceptor blockers and antiepileptic drugs) are ineffective, contraindicated, or inappropriate, NSAIDs may be tried. Only naproxen sodium (500 to 1000 mg) and tolfenamic acid (300 mg) have been demonstrated convincingly to be superior to placebo. For ASA (at least 300 mg) there is, however, only some inconsistent evidence of efficacy in migraine prophylaxis. For migraine occurring at the time of menstruation, which often does not respond to prophylactic treatment, naproxen sodium, 550 mg twice daily (or equivalent dose of naproxen), can be tried for 1 week before and 1 week after menstruation. The main adverse effects include dyspepsia, erosive gastritis, peptic ulceration, diarrhea, hematologic complications, and hypersensitivity reactions. Contraindications include hypersensitivity to ASA or any NSAID, active peptic ulceration, liver or kidney disease, coagulation disorders or treatment with other anticoagulants, and (for most of the NSAIDs) age below 12 years.

ERGOT ALKALOIDS

Dihydroergotamine (DHE) is extensively used in the acute treatment of migraine (see Chapter 50, which also describes its pharmacology); however, it has also been subjected to seven controlled double-blind clinical trials of its efficacy in migraine prophylaxis, using a long-acting oral formulation. In three trials (33–35) with treatment periods from 30 to 45 days, DHE (10 mg daily) was superior to placebo in reducing the frequency of attacks. In one study (33), however, most patients probably did not suffer from migraine, and one study (34) was reported only briefly, making it difficult to judge, although this trial suggested that DHE was most effective in migraine occurring in the night. In one very large study (384 randomized patients), DHE 10 mg/day was not superior to placebo with respect to the responder rate in the total sample but reduced significantly the duration of attacks and the intake of symptomatic medication; in the subgroup of migraine patients with poor quality of life, however, the responder rate was significantly higher in the DHE group than in the placebo group (36). Three other trials showed that drugs like flunarizine (10 mg once daily) (37), indoramin (25 mg twice daily) (38), and dihydroergocryptine (20 mg twice daily) (39) are better than run-in and no different from DHE (5 mg twice daily); all these comparative studies, however, suffer from a lack of placebo control, and the results may be merely a time effect.

In a further double-blind crossover trial, the combination of long-acting DHE (10 mg) plus ASA (80 mg) daily reduced attack frequency compared with placebo (40), but the use of two drugs concurrently in this trial makes it impossible to draw definitive conclusions as to the efficacy of either. In another double-blind trial in children, DHE (3 to 6 mg daily, administered as drops two or three times per day) did not produce better results than placebo during 3 months of treatment (41). Overall, the trials reviewed herein indicate a possible efficacy of DHE in migraine prophylaxis, but definite scientific proof remains weak.

Dihydroergocryptine is a hydrogenated ergot alkaloid that possesses dopamine D_1 and D_2 receptor agonist

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

activity. In a double-blind crossover trial (42), oral dihydroergocryptine (20 mg daily) was compared with placebo as a prophylactic agent in migraine without aura patients. Dihydroergocryptine was probably superior to placebo, but appropriate statistical evaluation was not presented. As noted above, it was comparable to DHE in a subsequent controlled trial and showed a considerable time effect (39). In migraine without aura patients, dihydroergocryptine (20 mg daily) was comparable to flunarizine (5 mg daily) in two studies (43,44) and to propranolol (80 mg daily) in another study (45), but no placebo controls were included. Thus, no conclusion regarding the efficacy of this compound can be drawn.

In migraine prophylaxis, DHE in a dose of 10 mg daily should be used only in very selected cases. The main adverse effects include nausea, vomiting, diarrhea, and abdominal pain. Contraindications include known hypersensitivity to ergot alkaloids, pregnancy, breastfeeding, coronary artery and other vascular disease, and concomitant use of triptans (46). It should be used with caution in patients with hepatic or renal disease.

DRUGS WITH AFFINITY FOR α-ADRENOCEPTORS

The antihypertensive agent clonidine is a centrally acting selective α_2-adrenoceptor agonist. It has some vasoconstrictor activity, mediated through a partial agonist action at α_2-adrenoceptors in some vascular smooth muscle. It was introduced as a potential migraine prophylactic agent, however, on the basis of studies in cats where low doses of clonidine had a direct inhibitory effect on vasoconstrictor and vasodilator responses to noradrenaline, adrenaline, isoprenaline, and angiotensin (47). Subsequent studies on the monkey cranial vasculature using mediators implicated in migraine could not reproduce these findings, however, and therefore have refuted the pharmacologic basis shown in animal models for an action of clonidine in migraine (48).

Three early double-blind, placebo-controlled trials apparently demonstrated the efficacy of clonidine in migraine prophylaxis (49,50), but the methodology used in these trials has been questioned (51). Ten other such trials failed to show superiority of clonidine compared with placebo (51–53), whereas in one trial clonidine showed superior effects compared with placebo (49). In crossover comparative trials with β-adrenoceptor antagonists, clonidine had better efficacy than practolol (49), it had equal efficacy to propranolol (54), pindolol (55), carbamazepine (55), and pizotifen (56), and it was inferior to metoprolol (57). In most cases, clonidine is clearly ineffective, and there is no conclusive evidence of at the least a mild superiority over placebo.

Indoramin is a selective competitive α_1-adrenoceptor antagonist that was introduced as an antihypertensive agent; in addition, competitive antagonism of histamine H_1 and 5-HT receptors is also evident (58). In an initial double-blind, controlled study, indoramin had better efficacy than placebo in migraine prophylaxis (59). In an unpublished trial (cited in [51]), indoramin did not have better efficacy than placebo. In another study (38), indoramin was comparable to DHE in the prophylaxis of migraine, but the lack of placebo precludes a definite conclusion.

ANTIDEPRESSANT DRUGS

Monoamine Uptake Inhibitors

The only antidepressant drug with established efficacy in the prophylaxis of migraine is the tricyclic agent amitriptyline. In the controlled clinical trials summarized in this section, a consistent finding is that its antimigraine effect is unrelated to its antidepressant action. Amitriptyline inhibits both noradrenaline and 5-HT uptake to a similar extent, but inhibition of uptake does not appear to correlate with efficacy in migraine. Another tricyclic antidepressant, imipramine, which is a relatively selective noradrenaline uptake inhibitor, is said to have little effect in migraine prophylaxis (60), although no controlled trials have been reported. Clomipramine, a tricyclic antidepressant with a selective inhibitory effect on 5-HT uptake, is also inactive in controlled migraine prophylaxis trials (61,62).

Of the nontricyclic antidepressants that selectively inhibit 5-HT uptake, femoxetine had no significant effect in placebo-controlled migraine prophylaxis trials (63,64), and it was inferior to propranolol with regard to headache index (65,66) and attack frequency (66). Zimelidine was reported to be better than placebo (67), but this was a single-blind trial with an unusual design (placebo after zimelidine), and a difference was found for only one parameter.

The efficacy of the selective 5-HT reuptake inhibitor fluoxetine in migraine prophylaxis is uncertain. In a small double-blind, placebo-controlled trial with parallel group design (but 14 of 32 were dropouts), fluoxetine (10 to 40 mg daily) was superior to placebo (68). In a larger trial of similar design (completed by 58 patients), however, fluoxetine (20 to 40 mg daily) did not show better efficacy than placebo on any measure (69). A study with S-fluoxetine, the longer-acting enantiomer of racemic fluoxetine, showed that 40 mg daily for 3 months was superior to placebo, with attack frequency reduced 52% by S-fluoxetine and 27% by placebo, although attack severity was unaltered (70). The longer half-life of S-fluoxetine (7 days, compared with 8 hours for R-fluoxetine) may have resulted in higher blood levels than those achieved in the previous trials. A recent double-blind, placebo-controlled trial of fluoxetine for migraine prophylaxis found a significant reduction of a total pain index as compared to baseline for the fluoxetine (20 mg/day) group ($n = 32$) but not for the placebo group ($n = 20$); in a direct comparison, however,

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

there was no significant difference between fluoxetine and placebo (71). The possible efficacy of fluoxetine in migraine prophylaxis was supported by an open trial on the habituation of visually evoked potentials in migraine patients (72). The patients showed a significant reduction of migraine frequency but not intensity or duration following 20 mg of fluoxetine daily for a month, and simultaneously a normalization of the migraine-typical loss of habituation in VEP amplitudes. Fluvoxamine has been evaluated for migraine prophylaxis in a controlled comparative trial with amitriptyline (73); both drugs significantly reduced attack frequency and headache index values to a similar extent, but the relatively low dose of amitriptyline used (25 mg daily) and the lack of placebo make it difficult to gauge efficacy. Sertraline had no significant effect on a headache frequency and severity index in a small placebo-controlled migraine prophylaxis trial, in which 11 of 27 patients were dropouts (74).

Overall, amine uptake inhibition does not seem to be responsible for the prophylactic effect of some antidepressants in migraine. The possibility that 5-HT_2 receptor blockade might explain the efficacy of amitriptyline in migraine has been raised (50,75), but 5-HT_2 receptor blockade is probably not responsible for the effect of antiserotonin drugs in migraine. Many antidepressants (including amitriptyline, imipramine, and fluoxetine) induce a gradual downregulation in central 5-HT_2 receptors and β-adrenoceptors, although the data are not always consistent (76). The possible role of such more subtle and localized regulatory effects on receptor densities and monoaminergic transmission remains to be investigated.

A summary of five controlled double-blind randomized clinical trials on the efficacy of oral amitriptyline in migraine prophylaxis is given in Table 58-2. The doses of amitriptyline used varied considerably, from 10 to 150 mg daily. Amitriptyline had better efficacy than placebo in all four placebo-controlled trials (77–80). It was equieffective to propranolol (79) and fluvoxamine (73) in two trials. No clear correlation was found between antidepressant activity and migraine prophylactic effect of amitriptyline in the trials in which depression was assessed objectively (77,79). In two of the placebo-controlled trials (77,79), the results were given only as a composite headache score, and no estimates of the variability in the mean data were provided, which makes it difficult to judge the clinical nature of the results, but in the other placebo-controlled trials, amitriptyline reduced attack frequency by 42% (78) and by up to 51% (80) compared with placebo. In the latter trial, amitriptyline appeared to be superior to propranolol because it improved all efficacy parameters whereas propranolol improved only a severity and headache score.

In migraine prophylaxis, the effective dosage of amitriptyline varies considerably among subjects, probably reflecting the wide variation in its bioavailability. The recommended starting dose is 10 mg taken at night; depending on efficacy and adverse effects, this dose may be increased by 10 mg every 2 weeks to a daily dose normally between 20 and 50 mg. Adverse effects often limit the doses to 50 mg (78). For long-term treatment, however, at least 75 mg at night should be tried.

Adverse effects of amitriptyline include drowsiness (the most common adverse effect), dry mouth, weight gain, skin reactions, orthostatic hypotension, nausea, and constipation. Contraindications include narrow-angle glaucoma, urinary retention, pregnancy, breastfeeding, and concomitant use of monoamine oxidase inhibitors. It should be used with caution in patients with kidney, liver, cardiovascular, and thyroid disease.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors were introduced in migraine prophylaxis based on the hypothesis that migraine is a low 5-HT syndrome with resulting vasodilation and that the drug would increase plasma 5-HT levels; the only evidence of efficacy, however, comes from two open trials of phenelzine (81,82) and a retrospective analysis of the effects of moclobemide alone or in combination with other migraine prophylactic drugs (83). Modulation of central nervous system monoaminergic neurotransmission is more likely to be responsible for any effects of phenelzine or moclobemide in migraine. Like other antidepressants, monoamine oxidase inhibitors produce a gradual downregulation in central 5-HT_2 receptors and β-adrenoceptors (76). Because of the serious side effects of monoamine oxidase inhibitors and the caution required regarding serious interactions with foods and drugs (less likely with moclobemide, which is reversible and monoamine oxidase A–selective but still an important risk), their use should be reserved for patients who have frequent attacks and who have failed to respond to other forms of prophylactic or acute treatments.

Other Antidepressants

The atypical antidepressant mianserin appears to have insufficient prophylactic effect in migraine (84), despite its high affinity for 5-$HT_{2A/2C}$ receptors. A placebo-controlled crossover trial of trazodone in pediatric migraine prophylaxis (85) demonstrated significant superiority over placebo, despite a substantial initial improvement with placebo. The most prominent pharmacologic action of trazodone is 5-$HT_{2A/2C}$ receptor antagonism; it also has some α-adrenoceptor antagonist and weak 5-HT uptake inhibitory activity. Paradoxically, its major metabolite, m-chlorophenylpiperazine, can induce a migrainelike headache (86), although no such adverse events were reported in this pediatric migraine trial (85). Venlafaxine, a selective 5-HT and noradrenaline reuptake inhibitor, has only been studied in an open retrospective trial on 114 patients; there was a significant reduction of migraine attacks with doses of 37.5 to 300 mg (87).

TABLE 58-2 Double-Blind Randomized Clinical Trials Comparing Amitriptyline with Placebo and Other Drugs in the Prophylaxis of Migraine

Trial	*Drug and Dosage (mg)*	*Study Design*	*No. of Patients (no. Evaluated)*	*Run-in Period*	*Duration of Treatment*	*Efficacy Parameter*	*Investigators' Conclusions*
(78)	Amitriptyline 10–60[a] Placebo	CO	26 (20)	Nil	6 mo × 2	Frequency, duration	Amitriptyline > placebo for frequency
(77)	Amitriptyline 50–100 Placebo	Pa	162 (100)[b]	4 wk placebo	8 wk	Migraine score, depression scores[c]	Amitriptyline > placebo for migraine score; unrelated to depression
(79)	Amitriptyline 50–150 Propranolol 80–240 Placebo	CO	54 (30)	4 wk placebo	10 wk × 3 (2 wk washout)	Headache score, depression scores[c]	Amitriptyline = propranolol > placebo for headache score; unrelated to depression
(80)	Amitriptyline 40–150 Propranolol 25–240 Placebo	CO	30	4 wk placebo	10 wk × 3 (2 wk washout)	Frequency, duration, severity, headache score	Amitriptyline > placebo for all parameters; propranolol > placebo for severity, headache score
(73)	Amitriptyline 25 Fluvoxamine 50	Pa	70 (49)	4 wk placebo	12 wk	Frequency, headache index	Amitriptyline = fluvoxamine > run-in for both parameters

co = crossover; pa = parallel-groups comparison; wk = week(s); mo = month(s); > = more effective than.
[a] = average dose 30–40 mg.
[b] = 46 patients dropped out during placebo run-in.
[c] = Hamilton depression scale and Zung self-rating depression scale.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

BOTULINUM TOXIN

In addition to its use in the treatment of dystonic movement disorders and of increased muscle tonus, botulinum toxin has been extensively discussed for the treatment of pain, particularly in headache. Several reviews (88–93) have presented conflicting results and conflicting interpretations regarding the use of botulinum toxin in idiopathic headache disorders.

For the explanation of a possibly successful treatment of idiopathic headaches with botulinum toxin, different hypotheses with different pathophysiologic concepts have been proposed covering peripheral myogenic as well as central antinociceptive mechanisms. The concept of a peripheral mode of action is supported by the effect of botulinum toxin on muscle spindles in experimental animal studies (93). A direct effect on intra- and extrafusal γ-fibers was demonstrated resulting in a reduced activity of α-motoneurons and a decreased muscle tonus. Experimental studies on the central effects of botulinum toxin were able to show that the toxin is internalized in neurons and can be transported afferently, and that its uptake is possible in cultures of hippocampal neurons and astrocytes (94). This uptake in nociceptive neurons leads to a decreased release of neuropeptides (e.g., substance P) in cell or animal models (95), and to a blockade of glutamate release in an in vivo model (96). An increased release of neuropeptides, as well as sensitization of trigeminal nociceptors of the first branch, are well-known mechanisms in idiopathic headaches. An attenuation of peripheral neuropeptide release by botulinum toxin has also been shown in human in vivo studies (97). This attenuation was, however, without any analgesic effect.

A summary of three controlled double-blind, randomized trials on the efficacy of botulinum toxin injections in migraine prophylaxis as well as an open controlled randomized trial is given in Table 58-3. In one double-blind study, the low-dose group of botulinum toxin (25 U) was significantly superior to placebo in reducing migraine attacks after 3 months; the high dose (75 U), however, did not result in a significant improvement of migraine (98). The other two double-blind studies showed no significant reduction of migraine frequency (99,100), although one reported a significant reduction of pain intensity by botulinum toxin (100). The open trial found that botulinum toxin, but not placebo, significantly reduced migraine frequency (101).

All other open studies on migraine prophylaxis with botulinum toxin showed positive results, with a majority of patients experiencing improvement by the injections (93). These studies, however, were in part with mixed patient groups and only retrospective chart analyses. Furthermore, the improvement was based in some studies only on the impression of the patient but not on diary measures. Thus, there is no convincing and consistent evidence that botulinum toxin is effective in migraine prophylaxis.

HERBAL REMEDIES

Herbal remedies have been suggested for migraine treatment ever since antiquity. However, there have been very few modern controlled trials. Systematic evaluations have been performed for feverfew (Tanacetum parthenium) and for butterbur root extract (Petasites hybridus).

The first clinical trial of feverfew in migraine prophylaxis (102) was initiated after a marked increase in self-medication with this herb when the health food industry responded to demand and marketed a variety of formulations containing dried feverfew. The active ingredient is thought to be in the sesquiterpene lactone content of the leaves, the principal one being parthenolide. This double-blind, placebo-controlled pilot trial was completed in 17 patients in a parallel-group comparison design. All patients had been using fresh feverfew leaves daily for at least 3 months before commencement of the trial; they then received capsules containing a standard equivalent daily dose of freeze-dried feverfew leaves or placebo for 24 weeks. The conclusion that feverfew is of benefit in migraine relied on the indirect finding that migraine frequency and intensity remained unchanged in the feverfew group but increased significantly in the placebo group. A larger and more valid double-blind, placebo-controlled trial confirmed that feverfew reduced migraine attack frequency but not its duration and severity (103). This trial design was a crossover study of treatment with feverfew and placebo (4 months in each case) following a 1-month run-in with placebo, completed in 59 patients. Capsules contained dried feverfew leaves standardized for parthenolide content. Only 23% of the trial subjects had previously used feverfew, and all migraine-related treatments were stopped at the beginning of the run-in period but without washout. Although feverfew was clearly superior to placebo in some respects, the overall 24% reduction in the frequency of attacks with feverfew use relative to the frequency in the placebo group appears to be a modest improvement. However, a subsequent placebo-controlled crossover study with 50 subjects receiving 143 mg of granulated feverfew for 4 months did not show any significant effect of the drug (104); likewise, an earlier small crossover study (20 patients) had not shown any effect (105). Pain intensity and accompanying symptoms (but not frequency) was reduced by 100 mg of powdered feverfew given for 1 month to 57 patients (106); however, this trial had several limitations such as no washout period and too short duration. The largest trial completed so far was a placebo-controlled, parallel group study with 147 patients treated with placebo or one of three different doses of feverfew (107). There was no significant efficacy and no dose-dependent effect of

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GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

TABLE 58-3 Randomized Clinical Trials Comparing Botulinum Toxin A (all Trials: Botox®) with Placebo in the Prophylaxis of Migraine

Trial	No. of Patients	Duration	Methods	Treatment	Results
(98)	123	1 mo baseline	r, db, pc	Group 1: placebo	Significant reduction of migraine frequency in group with 25 U (month 3) compared to the placebo group
		3 mo treatment		Group 2: 25 U	
				Group 3: 75 U	No significant results in 75 U group
(100)	56 12	4 mo treatment	r, db, pc	4 groups: Temporal and frontal injection either placebo or verum	No significant reduction of migraine frequency and duration; significant reduction of pain intensity in week 12
(99)	60	1 mo baseline 3 mo treatment	r, db, pc	Group 1: placebo Group 2: 16 U Group 3: 100 U	No significant results
(101)	30	1 year treatment	r, pc, open	Group 1: placebo Group 2: verum	Significant reduction of migraine frequency in botulinum toxin group but not in placebo group

r = randomized; db = double-blind; pc = placebo-controlled; mo = month(s).

feverfew. Only a small group of patients with at least four migraine attacks per month showed a significant benefit with the medium (but not the high) dose of feverfew. Critical reviews including a Cochrane Review of all trials using feverfew for migraine prophylaxis concluded that the use of feverfew is very safe but that sufficient scientific evidence of efficacy has not been established to date (108,109).

The first double-blind randomized placebo-controlled trial of a special butterbur root extract (Petasites hybridus or Petasites rhizoma) in migraine prophylaxis in 60 patients had been performed in the early 1990s (110). The initial publication of this trial had major shortcomings; thus, a new and appropriate statistical analysis of the data has recently been published (111). This reanalysis showed that a daily dose of 100 mg of butterbur was significantly superior to placebo in reducing migraine frequency, days with headache, and headache severity, and in improving the responder rate. No significant adverse events or changes of laboratory values were observed in this study. The efficacy of a butterbur root extract has been confirmed in a recent larger double-blind, placebo-controlled study with 202 evaluated patients (112); in this study, 75 mg but not 50 mg daily was superior to placebo during a 4-month treatment period for all efficacy parameters.

OTHER MISCELLANEOUS DRUGS

In recent years, some agents that have not been regarded as orthodox drug therapy for migraine have been subjected to clinical trials. Those considered here are magnesium, riboflavin, and coenzyme Q10.

Magnesium has been tested in four double-blind, placebo-controlled trials using a parallel-group comparison design, on the basis of reductions in Mg^{2+} levels in blood, saliva, cerebrospinal fluid, and cortex cells in association with migraine. The first trial (113) included patients with menstrual migraine in whom magnesium was found to be effective in reducing the total index of pain and days with migraine when administered in a total daily oral dose of 360 mg of Mg^{2+} (from day 15 to onset of menses for two menstrual cycles). A larger trial (114) also showed some efficacy in migraine (with or without aura) patients who took a total daily oral dose of 600 mg of Mg^{2+} for 12 weeks. Attack frequency was reduced by 42% compared with 16% in the placebo group; comparable reductions in days with migraine also were reported. The number of responders (>50% reduction in attack frequency), however, was not significantly higher after magnesium (39%) than after placebo (21%). Another trial, however, concluded that magnesium at a total daily oral dose of 243 mg of Mg^{2+} for 12 weeks had no significant effect on intensity or total duration of migraine attacks in patients who had migraine without aura (115). Only 29% of each group achieved the study's primary endpoint of a 50% or better reduction in attack intensity or total duration. The lower dose used in this trial might account for the apparent lack of efficacy of magnesium, but given the very low absorption of magnesium following oral administration, the range of oral doses used might not be a critical factor in producing increases in extracellular and intracellular Mg^{2+} levels. A recent double-blind trial on migraine in children showed a significant reduction of migraine in the magnesium group (9 mg/kg per day) but not in the placebo group; direct comparison of reductions in headache frequency, however, revealed

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GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

no significant difference between magnesium and placebo (116). In one of these magnesium trials (113), blood levels in the migraine patients at the commencement of the trial were lower in lymphocytes and polymorphonucleated cells but were not lower in erythrocytes or plasma, compared with nonmigrainous controls. The magnesium treatment produced generally greater increases in lymphocyte and polymorphonucleated cell Mg^{2+} levels compared with those in the placebo group, but erythrocyte and plasma levels remained unchanged. Diarrhea and gastric irritation were the most commonly reported adverse effects of magnesium in these trials; the only other adverse effect was palpitations (in three patients). The results of these trials suggest that magnesium may prove to be of benefit, but further controlled trials are needed because of the relatively small number of patients recruited into trials thus far.

Riboflavin for migraine prophylaxis has been studied in only one placebo-controlled trial (117). The stimulus for this trial was the identification of impaired oxygen metabolism resulting from mitochondrial dysfunction as a possible pathogenic factor in migraine, the beneficial effect of riboflavin in some other rare mitochondriopathies, and encouraging results from a small open pilot study (118). The controlled trial was a double-blind, parallel-group comparison design, with results from migraine patients treated for 3 months with riboflavin (400 mg/day) or placebo. Riboflavin was superior to placebo in reducing attack frequency, intensity, and duration, as well as days with migraine and migraine index. A 50% or greater reduction in attack frequency, days with migraine, and migraine index was achieved by 56%, 59%, and 41% of the riboflavin group, respectively, compared with 19%, 15%, and 8% of the placebo group. The high dose of riboflavin used resulted in only two minor adverse events (diarrhea, polyuria). These findings justify further controlled trials to define a possible role for riboflavin in migraine prophylaxis.

Coenzyme Q10 is, like riboflavin, an essential element of the mitochondrial electron transport chain. It has, therefore, also been studied in migraine prophylaxis. An open trial with 32 migraine patients showed a greater than 50% reduction in migraine frequency for 61.3% of the patients taking 150 mg of coenzyme Q10 per day, and a reduction of mean migraine frequency from 4.9 at baseline to 2.8 after 3 months of treatment (119). A recent double-blind, placebo-controlled study with 42 patients confirmed the efficacy of coenzyme Q10 in migraine prophylaxis (120). A 50% reduction of migraine frequency after 3 months was obtained for 47.6% of the coenzyme Q10 group (300 mg/day) and for 14.3% of the placebo group.

Finally, those substances for which negative modern randomized, placebo-controlled, double-blind trials are available and which are not mentioned above or in other chapters are listed as follows: no efficacy at all in migraine prophylaxis has been shown for homeopathic remedies (121–124); for the antagonist of the cysteinyl-leukotriene receptor antagonist montelukast (125); for acetazolamide 500 mg/day (126); and for the neurokinin-1 receptor antagonist lanepitant (127).

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GRBT050-58 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 17:56

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