Chapter 57

# Antiepileptic Drugs in Migraine Prophylaxis

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Migraine and epilepsy are both chronic, believed to result from brain hyperexcitability, and the therapeutic agents effective for each disorder overlap (1). These disorders are linked by their symptom profiles, comorbidity, and treatment (1,34,41). Each disorder provides a rationale for using drugs that suppress neuronal excitability in migraine prevention.

Antiepileptic medication is recommended for migraine prevention because placebo-controlled, double-blind trials prove them effective (22,25,37,46,58). Despite the earlier belief that they are more effective in children who have paroxysmal electroencephalograms (44), they are effective regardless of the electroencephalogram (43). With the exception of valproic acid and topiramate, many anticonvulsants interfere with the efficacy of oral contraceptives (7,19).

## ANTIEPILEPTIC DRUGS

### Carbamazepine

Carbamazepine was used in migraine prophylaxis based on its efficacy against trigeminal neuralgia. One placebo-controlled, randomized, double-blind, crossover trial suggested a significant benefit: either marked or complete improvement was reported by 26 of 45 (58%) patients on carbamazepine and by 5 of 48 (10%) on placebo. However, this trial was inadequately described in several important respects (46). Another trial, comparing carbamazepine with clonidine and pindolol, suggested that carbamazepine had a weaker effect on headache frequency than either comparator treatment, although differences from clonidine were not statistically significant (2). Significantly more patients reported adverse events (AEs) with carbamazepine than with placebo or pindolol; there was no significant difference in this respect between carbamazepine and clonidine.

#### *Therapeutic Use*

Carbamazepine (Tegretol), 600 to 1200 mg a day (beginning at 100 mg twice a day), is occasionally used, particularly for patients who have coexisting mania or hypomania, especially if there is rapid cycling. Monitor carbamazepine plasma levels and white blood counts.

### Clonazepam

Clonazepam was studied in one placebo-controlled crossover trial (58) of 34 patients. Those completing 4 weeks' treatment (1 mg daily) had their mean headache days per month reduced by 50% compared with an 8% reduction for patients receiving placebo ($p < 0.05$). The effect was less at 2 mg daily. Drowsiness was a problem.

### Gabapentin

Gabapentin's mode of action in migraine is unclear (66). It interacts with the $\alpha_2\delta$-subunit of the calcium channel and increases the concentration and probably the synthesis of brain $\gamma$-aminobutyric acid (GABA). Gabapentin binds to gabapentin-binding protein—a novel, membrane-associated protein in the outer layers of the cerebral cortex (61). It penetrates the blood-brain barrier but does not interact with GABA receptors (17). Gabapentin (600 to 1800 mg) was effective in both episodic and chronic migraine in a 12-week open-label study (35). Gabapentin was not effective in one placebo-controlled double-blind study (65). In a second randomized, placebo-controlled, double-blind trial (36), gabapentin 1800 to 2400 mg was superior to placebo in reducing the frequency of migraine attacks. The responder rate was 36% for gabapentin and 14% for placebo ($p = 0.02$). The most common AEs were dizziness or giddiness and drowsiness. Some trials reported relatively high patient withdrawal rates due to AEs associated with gabapentin (18).

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### Therapeutic Use

Gabapentin is used in doses of 600 to 3200 mg/day.

## Lamotrigine

Lamotrigine blocks voltage-sensitive sodium channels, inhibiting neuronal release of glutamate (31,32,64), essential to the propagation of spreading depression (49). In an open study, 10 patients with migraine with aura responded to lamotrigine. Lamotrigine as combination therapy was studied in one prospective, open-label trial of 65 patients, most of whom had chronic migraine (67). Only 35 patients were sufficiently compliant with treatment to warrant inclusion in the analysis; 12 dropped out because of AEs. The primary endpoint was reduction in severe headache frequency; 17 (48.6%) responded, at a mean dose of 55 mg/day. Those with migraine with aura had a better response rate (12/18 or 67%), including 4 of 8 whose headaches were chronic. Another open-label study found that lamotrigine significantly reduced both the frequency and duration of aura (67).

Chen et al. (5) reported two patients with migraine with persistent auralike visual phenomena for months to years. After lamotrigine treatment for 2 weeks, both had resolution of the visual symptoms.

Steiner et al. (57) compared lamotrigine to placebo in a double-blind, randomized, parallel-group migraine prophylaxis trial. Lamotrigine was initially begun at the full dose of 200 mg/day, but, following a high incidence of skin rashes, a slow dose-escalation was introduced: 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, and then 200 mg/day. Attack rates were reduced from baseline means of 3.6 per month on lamotrigine and 4.4 on placebo to 3.2 and 3.0, respectively, during the last month of treatment. In this study lamotrigine was ineffective for migraine prophylaxis. There were more AEs on lamotrigine than on placebo, most commonly rash.

## Tiagabine

Tiagabine was effective (14) in an open-label clinical trial of 41 patients who had been previously treated with divalproex sodium and who discontinued for AEs or lack of efficacy. Tiagabine was started at 4 mg at bedtime for 1 week and then increased to 4 mg twice a day. Five patients experienced a remission, and 33 of 41 patients had at least a 50% reduction in their attacks. The mean dose of tiagabine was 10 mg/day. Fourteen AEs were reported by 12 patients. No placebo-controlled, double-blind trials are available.

## Topiramate

Topiramate is a structurally unique anticonvulsant that is a derivative of the naturally occurring monosaccharide D-fructose and contains a sulfamate functionality. Topiramate is rapidly and almost completely absorbed. The blood plasma concentration increases linearly as a function of dose over the pharmacologically relevant range (13,60). It is not extensively metabolized and is eliminated predominantly unchanged in the urine. The average elimination half-life is approximately 21 hours (13). Topiramate readily enters the central nervous system parenchyma; in rats, the concentration in whole brain was approximately one-third that in blood plasma 1 hour after oral dosing.

Topiramate influences the activity of some types of voltage-activated $Na^+$ and $Ca^{2+}$ channels, $GABA_A$ receptors, and the $\alpha$-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate subtype of glutamate receptors. Topiramate also inhibits some isozymes of carbonic anhydrase (CA) and exhibits selectivity for CA II and CA IV (11,50).

The effects of topiramate on voltage-activated $NA^+$ channels, voltage-activated calcium channels, $GABA_A$ receptors, and AMPA/kainate receptors are unique. They are all regulated by protein phosphorylation (29,45,51,64). One or more subunit of each complex is phosphorylated by protein kinase A, protein kinase C, and possibly $CA^{2+}$/CaM-activated kinases. Topiramate may bind to the membrane channel complexes at phosphorylation sites in the inner loop and thereby allosterically modulate ionic conductance through the channels.

Storer and Goadsby (59) found that topiramate inhibited the activation of trigeminocervical neurons in response to stimulation of the superior sagittal sinus. Its inhibition is a plausible mechanism of the action of migraine or cluster headache preventive medicines.

### Clinical Trials (Table 57-1)

The first pivotal placebo-controlled migraine clinical trial (54) (MIGR-001) compared topiramate at doses of 50, 100, and 200 mg/day to placebo. In the topiramate 100 mg/day group, there was a mean reduction of 2.1 monthly migraine episodes (5.4 to 3.3), compared with 0.8 for placebo. The responder rate ($\geq$50% reduction in monthly migraine frequency) was 54% for topiramate 100 mg and 23% with placebo. Efficacy was observed by the end of the first month of treatment. The 200-mg dose was not significantly more effective than the 100-mg dose. The most common AEs were paresthesias, fatigue, nausea, anorexia, and abnormal taste. Cognitive AEs occurred in 19% of patients in the 100-mg group, but led to withdrawal in only 4%. Body weight was reduced an average of 3.8% in the 100-mg and 200-mg groups.

The second pivotal trial (4) (MIGR-002), of identical design, found that topiramate (100 or 200 mg/day) was associated with significant improvements in each efficacy measure. The mean monthly number of migraine periods decreased significantly for those patients on 100 mg/day of topiramate (from 5.8 to 3.5, $p = .008$) or 200 mg/day of

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**TABLE 57-1 Topiramate Clinical Trials**

| *Study* | *Patient Population (Diagnostic Criteria)* | *No.* | *Design* | *Dosage (mg/day)/ Other Medication* | *Duration* | *Results* |
|---|---|---|---|---|---|---|
| Silberstein et al. (2004) | Migraine with and without aura | 487 | Double-blind/ placebo-controlled crossover | 50 mg (25 BID)<br>100 mg (50 BID)<br>200 mg (50 BID) | 4-week baseline;<br>8 weeks titration<br>18 weeks maintenance | Placebo: 23%<br>Topiramate 50 mg: 36%<br>Topiramate 100 mg: 54%<br>Topiramate 200 mg: 49% |
| Brandes et al. (2004) | Migraine with or without aura | 483 | Double-blind/ placebo-controlled | 50 mg (25 BID)<br>100 mg (50 BID)<br>200 mg (50 BID) | 4-week baseline;<br>8 weeks titration<br>18 weeks maintenance | Placebo: 23%<br>Topiramate 50 mg: 39%<br>Topiramate 100 mg: 49%<br>Topiramate 200 mg: 49%? |
| Diener et al. (2004) | Migraine with or without aura | 176 | Double-blind/ placebo- and propranolol-controlled | | 4-week baseline;<br>8 weeks titration<br>18 weeks maintenance | Placebo: 23%<br>Topiramate 100 mg: 37%<br>Topiramate 200 mg: 35%<br>Propranolol 160 mg: 43% |

topiramate (from 5.1 to 2.9, $p = .001$) vs. placebo (from 5.6 to 4.5). Significant reductions were evident as early as the first month of treatment. The responder rate was 39% for 50 mg/day ($p = .009$) and 49% for 100 and 200 mg/day ($p = <.001$). Patients treated with 200 mg/day of topiramate lost an average of 4.8% of body weight. In the topiramate groups, the most common AEs (resulting in discontinuation) included paresthesias, fatigue, nausea, and abdominal pain.

A third study (10) compared two doses of topiramate to placebo or propranolol in a randomized, double-blind, parallel-group, multicenter trial. Subjects assigned to receive topiramate received an initial daily dose of 25 mg/day, while subjects assigned to receive propranolol received an initial daily dose of 20 mg/day. The dose of study medication was titrated upwards in weekly increments of 25 mg/day for topiramate and 20 mg/day for propranolol until either the assigned dose or the maximum tolerated dose was achieved.

Topiramate 100 mg/day was superior to placebo as measured by average monthly migraine period rate, average monthly migraine days, rate of rescue medication use, and percent of patients with a 50% or greater decrease in average monthly migraine period rate (responder rate 37%). The topiramate 100 mg/day and propranolol groups were similar in change from baseline to the core double-blind phase in average monthly migraine period rate and other secondary efficacy variables. Topiramate 200 mg/day failed in the primary endpoint compared with placebo but had a significantly higher responder rate (35% vs. placebo 22%). Topiramate 100 mg/day (responder rate 37%) was better tolerated than topiramate 200 mg/day and was comparable to propranolol (responder rate 43%). A major shortcoming was the high dropout rate of patients in the topiramate 200-mg group due to AEs, which resulted in the nonsuperiority of topiramate 200 mg over placebo.

### *Therapeutic Use*

Topiramate is effective for migraine prophylaxis and is a first-line drug. Topiramate is available as 25-, 50-, 100-, or 200-mg tablets and as a 15-mg spansule. The 100-mg dose seems to have the best efficacy/tolerability ratio. Cognitive side effects are of less concern with doses of 100 mg or less. The following guidelines should be followed: Start at a dose of 15 to 25 mg at bedtime. Increase by a dose of 15 to 25 mg/week. Do not increase the dose if bothersome AEs develop; wait until they resolve. If they do not resolve, decrease the drug to the last tolerable dose, then increase by a lower dose more slowly. Attempt to reach a dose of 50 to 100 mg/day given twice a day. Patients who tolerate the lower doses with only partial improvement often have increased benefit with higher doses. The dose can be increased to 600 mg/day or higher.

The more common AEs include paresthesia and weight loss. Cognitive effects, particularly word-finding difficulties, occur as with other antiepileptic drugs. Paresthesia, the most common AE, can be managed with patient education and attention to dosing. Potassium supplementation can be used to control paresthesias when they continue to be bothersome (52). Renal calculi can occur; the reported incidence is about 1.5%, representing a two- to fourfold increase over the estimated occurrence in the general population (28,48).

Acute myopia associated with secondary angle closure glaucoma has been reported infrequently in patients receiving topiramate. Symptoms include the acute onset of bilateral decreased visual acuity and/or ocular pain. Oligohidrosis (decreased sweating), infrequently resulting in

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-57 Olesen- 2057G GRBT050-Olesen-v6.cls July 25, 2005 16:28



hospitalization, has been reported in association with an elevation in body temperature.

### *Contraindications*

Allergy to topiramate.

## Valproate/Valproic Acid

### *Pharmacology*

#### *Valproic Acid*

Valproic acid is a simple eight-carbon, two-chain fatty acid with 80% bioavailability after oral administration. It is highly protein bound, with an elimination half-life between 8 and 17 hours. Valproate at high concentrations increases GABA levels in synaptosomes, perhaps by inhibiting its degradation; it enhances the postsynaptic response to GABA, and at lower concentrations, it increases potassium conductance, producing neuronal hyperpolarization. Valproate turns off the firing of the 5-HT neurons of the dorsal raphe, which are implicated in controlling head pain. Valproate blocks c-*fos* expression and neurogenic inflammation through $GABA_A$ receptor–mediated mechanisms in a putative animal model of acute migraine (8,9,33).

Five studies provided strong and consistent support for the efficacy of divalproex sodium (15,26,37) and sodium valproate (20,23). Two placebo-controlled trials of each of these agents showed them to be significantly better than placebo at reducing headache frequency (20,23,26,37). Divalproex sodium was more effective than placebo, but not significantly different from propranolol, in migraine patients without aura (24). An extended-release form of divalproex sodium demonstrated comparable efficacy to the tablet formulation (15), but had AE rates identical to placebo.

### *Pharmacokinetics of Valproate*

Valproate exhibits dose-dependent pharmacokinetics: As concentrations approach 70 to 80 mg/L, albumin binding sites become saturated and the unbound plasma fraction increases (62). Its half-life is 10 to 20 hours (69); active metabolites have longer half-lives. Steady plasma levels are not developed for a week or longer after dose titration. An absence of interactions between valproate and other drugs used in migraine therapy has been claimed (62), but a significant pharmacokinetic interaction between valproate and amitriptyline was found in one study (68): The area under the curve for amitriptyline was increased by 31% in male volunteers receiving divalproex 500 mg every 12 hours. Summed peak plasma concentrations of amitriptyline and its active metabolite, nortriptyline, were 19% higher.

### *Clinical Trials (Table 57-2)*

Sorenson (56) performed the first prospective open trial of valproate. The dose was 600 mg twice a day, adjusted upward to a serum level of about 700 $\mu$mol/L. Follow-up in 3 to 12 months revealed that 11 patients were migraine free, 6 had had a significant reduction in frequency, 1 had had no change, and 4 had dropped out.

Hering and Kuritzky (20) performed the first controlled crossover trial of valproate in migraine treatment. Thirty-two patients were divided into two groups and given either 800 mg of sodium valproate a day or placebo for 8 weeks. Sodium valproate was effective in preventing migraine or reducing the frequency, severity, and duration of attacks

**TABLE 57-2 Divalproex/Valproate Clinical Trials**

| *Study* | *Patient Population (Diagnostic Criteria)* | *No.* | *Design* | *Dosage (mg/day)/ Other Medication* | *Plasma Levels* | *Duration* | *Results* |
|---|---|---|---|---|---|---|---|
| Hering and Kuritzky (1992) | Migraine | 29 | Double-blind/ placebo-controlled crossover | 800 mg (400 mg BID) | 31.1 to 91.9 $\mu$g/mL | 8 weeks each; total of 16 weeks | 86.2% of patients responded better to valproate |
| Jensen et al. (1994) | Migraine without aura | 43 | Double-blind/ placebo-controlled crossover | 1000 to 1500 mg/ sodium valproate | Mean 73.4 $\mu$g/mL | 32 weeks | 50% valproate 18% placebo |
| Mathew et al. (1995) | Migraine with or without aura | 107 | Double-blind/ placebo-controlled | 500 to 1500 mg/ divalproex | 70 to 120 $\mu$g/mL | 16 weeks | 48% divalproex 14% placebo |
| Klapper (1997) | Migraine with or without aura | 176 | Double-blind/ placebo-controlled | 500 to 1600 or 1500 mg/ divalproex | | 10 weeks | 43% divalproex 21% placebo |
| Freitag et al. (2003) | Migraine with or without aura | 234 | Double-blind/ placebo-controlled | 500 to 1000 mg/ divalproex | | 12 weeks | 30% divalproex 24% placebo |

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-57 Olesen- 2057G GRBT050-Olesen-v6.cls July 25, 2005 16:28



in 86.2% of the remaining 29 patients, whose attacks were reduced from 15.6 to 8.8 a month.

Jensen et al., in 1994 (22), studied 43 patients with migraine without aura in a triple-blind, placebo- and dose-controlled, crossover study of slow-release sodium valproate. Patients randomized to valproate received 1000 mg/day for the first week. Patients with serum levels below 50 $\mu$g/mL were blindly adjusted to 1500 mg of sodium valproate a day, and those with serum levels above 50 $\mu$g/mL were continued on 1000 mg a day. Fifty percent of the patients had a reduction in migraine frequency to 50% or less for the valproate group compared with 18% for placebo. During the last 4 weeks of valproate treatment, 65% of patients responded. The most common AEs (33% valproate, 16% placebo) were usually mild or moderate and included intensified nausea and dyspepsia, tiredness, increased appetite, and weight gain. Fifty-eight percent of the patients had no AEs.

A multicenter, double-blind, randomized, placebo-controlled investigation (37) compared divalproex sodium with placebo. Divalproex sodium and placebo dosages were titrated in blinded fashion during the 4-week dose-adjustment period to achieve actual/sham trough valproate sodium concentrations of approximately 70 to 120 $\mu$g/mL. During the 12-week treatment phase, the mean migraine headache frequency per 4 weeks was 3.5 in the divalproex sodium group and 5.7 in the placebo group ($p \leq .001$), compared with 6.0 and 6.4, respectively, during the baseline phase. The responder rate was 48% in the divalproex sodium–treated patients and 14% in the placebo-treated patients ($p < .001$). Treatment was stopped in 13% of the divalproex sodium–treated patients and 5% of the placebo-treated patients because of intolerance ($p$, not significant).

In a second multicenter, double-blind, randomized, placebo-controlled study (26), patients were randomized to a daily divalproex sodium dose of 500 mg, 1000 mg, or 1500 mg, or placebo (4 weeks for titration, 8 weeks maintenance). The responder rate was 43% for divalproex sodium–treated patients, compared with 21% for placebo-treated patients. A statistically significant ($p \leq 0.05$) dose-response effect across the dose range (placebo, 500 mg, 1000 mg, 1500 mg) was observed for both overall reduction in attack frequency and a greater than or equal to 50% reduction in attack frequency. Except for nausea, AEs were similar in all groups (divalproex sodium 24%, placebo 7%, $p = 0.015$) and were mild or moderate in severity.

An open-label follow-up study (55) evaluated the long-term safety of divalproex sodium. The most frequent AEs were nausea (42%), infection (39%), alopecia (31%), tremor (28%), asthenia (25%), dyspepsia (25%), and somnolence (25%). A subset of patients who were treated for at least 12 months was analyzed. Patients who discontinued divalproex after 1 year failed to show this improvement up to days 361 to 500 in contrast to patients who remained in the study.

Extended-release divalproex sodium was compared with placebo in a double-blind, randomized, placebo-controlled, parallel-group study (4 weeks baseline, 12 weeks treatment) (15). The mean reductions in 4-week migraine headache rate were 1.2 (baseline mean of 4.4) in the extended-release divalproex sodium group and 0.6 (baseline mean of 4.2) in the placebo group ($p = 0.006$); reductions with divalproex sodium were significantly greater than with placebo in all three 4-week segments of the treatment period. Overall 8% of subjects treated with divalproex sodium and 9% of those treated with placebo discontinued for AEs. The proportion of subjects achieving at least 50% reduction in their experimental phase migraine headache rate was higher in the extended-release divalproex sodium group (36/119; 30%) than in the placebo group (28/115; 24%), but the difference was not significant ($p = 0.251$).

Nausea, vomiting, and gastrointestinal distress are the most common AEs of valproate therapy. These are generally self-limited and are slightly less common with divalproex sodium than with sodium valproate. Their incidence decreases with time, particularly after 6 months.

Valproate has little effect on cognitive function and it rarely causes sedation. On rare occasions, it is associated with idiosyncratic severe AEs, such as hepatitis or pancreatitis. The frequency varies with the number of concomitant medications used, the patient's age and general state of health, and the presence of genetic and metabolic disorders (42).

Valproate is potentially teratogenic and should not be used by women who are pregnant or considering pregnancy (53). Hyperandrogenism (resulting from elevated testosterone levels), ovarian cysts, and obesity are of concern when young women with epilepsy take valproate (63). It is uncertain if valproate can cause these symptoms in young women with migraine or mania.

### *Comparative Trials*

No randomized double-blind, placebo-controlled trials have compared valproate or divalproex with other antimigraine drugs. In open or single-blind trials, valproate had similar efficacy to propranolol (27) and flunarizine (40), and divalproex to propranolol (24).

### *Therapeutic Use*

Valproate is effective in migraine prevention and is a first-line drug. Valproic acid is available as 250-mg capsules and as a syrup (250 mg/5 mL). Divalproex sodium is a stable coordination complex of sodium valproate and valproic acid in a 1:1 molar ratio. Depakote is an enteric-coated form of divalproex sodium available as 125-, 250-, and 500-mg capsules and a sprinkle formulation. The starting dose

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-57 Olesen- 2057G GRBT050-Olesen-v6.cls July 25, 2005 16:28



is 250 to 500 mg a day in divided doses; this can be slowly increased, monitoring serum levels if there is a question of toxicity or compliance. (The usual therapeutic level is from 50 to 100 mg/mL.) The maximum recommended dose is 60 mg/kg/day.

Valproate has a potential idiosyncratic interaction with barbiturates (severe sedation, coma). Migraine patients taking valproate should use barbiturate-containing combination analgesics cautiously if at all.

Patients can experience gastrointestinal AEs (39,47); these can be reduced by enteric coating (53). Other AEs are weight gain, hair loss, and tremor. Fulminant hepatitis, not consistently preceded by abnormal liver function tests, occurs rarely with valproate monotherapy in epilepsy (39). In some countries, routine hematologic screening and biochemical tests of liver function are considered necessary before starting and occasionally during valproate or divalproex treatment.

#### *Contraindications*

Valproate is associated with an increased incidence of neural tube defects (21) and other fetal abnormalities. Absolute contraindications are pregnancy and a history of pancreatitis or a hepatic disorder such as chronic hepatitis or cirrhosis of the liver. Other important contraindications are hematologic disorders, including thrombocytopenia, pancytopenia, and bleeding disorders.

### Vigabatrin

Vigabatrin (39) is a selective irreversible inhibitor of GABA transaminase. It was compared with placebo in a 12-week double-blind crossover study in drug-resistant migraineurs (16) at a dose of 1000 to 2000 mg/day. Three patients were withdrawn for poor compliance and four dropped out. Treated patients had a 40 to 90% reduction in their migraine attack frequency. Analysis of variance indicated a significant reduction in migraine attack frequency in women but not in men.

### Zonisamide

There are two retrospective, open-label studies in migraine prevention (12,30). Drake et al. treated 34 patients with migraine adjunctively with zonisamide at doses as high as 400 mg/day (12). A 40% reduction in headache severity, a 50% reduction in headache duration, and a 25% decrease in headache frequency were found at 3 months. Krusz reported improvement in 14 of 33 patients (42%), with four dropouts due to AEs (30). Zonisamide was used as monotherapy in a small, prospective, open-label study of nine patients of episodic migraine (6). It was effective or very effective in 6 of 9 patients (67%). Placebo-controlled, double-blind trials are in progress.

## CONCLUSION

The antiepileptic drugs used to treat migraine can be divided into four major categories: (1) drugs with documented high efficacy and mild to moderate AEs (topiramate, divalproex); (2) drugs with lower documented efficacy and mild to moderate AEs (gabapentin); (3) drugs with unproven efficacy (zonisamide, levetiracetam); and (4) drugs with proven limited or no efficacy (lamotrigine, carbamazepine). For the patient with migraine and epilepsy (20,38) or migraine and bipolar illness (3,53), divalproex sodium, topiramate, and the other AEDs are useful choices.

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