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Q/ What are the best prophylactic drugs for migraine?

Propranolol and timolol have consistently demonstrated efficacy for preventing episodic migraine.

EVIDENCE-BASED ANSWER

A/ **BETA-BLOCKERS** without intrinsic sympathomimetic activity, amitriptyline, divalproex sodium/sodium valproate, and topiramate are the most effective drugs for preventing episodic migraine (strength of recommendation: **A**, multiple, well-designed, randomized controlled trials [RCTs]).

Evidence summary

Many medications have been evaluated for migraine prophylaxis. However, very few head-to-head trials of more than 2 drugs have been published, and no recent meta-analyses of available drug classes have been performed. The most commonly evaluated outcome is a 50% reduction in headache frequency.

Propranolol and timolol offer consistent prevention

Propranolol and timolol have consistently demonstrated efficacy for preventing episodic migraine. In a 1991 meta-analysis, propranolol resulted in a 44% reduction in the headache index—a composite score that takes into account both intensity and duration—compared with a 14% reduction for placebo.[1]

Less evidence supports other beta-blockers

Atenolol, metoprolol, and nadolol have demonstrated a moderate effect, but less evidence exists to support their use.[2] A recent trial comparing metoprolol and nebivolol demonstrated a positive response—defined as a 50% reduction in headache frequency—to each drug at 14 weeks (57% of metoprolol-treated and 50% of nebivolol-treated patients), but noted that nebivolol was better tolerated.[3]

Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) appear to be ineffective for migraine prevention.[4]

Amitriptyline works better than propranolol for some migraines

Amitriptyline is the most often studied antidepressant and the only one with consistent support for efficacy in preventing migraine. A 1981 trial found amitriptyline to be more effective than propranolol in mixed migraine-tension-type headache, whereas propranolol was more effective for migraine alone.[5]

Some support for fluoxetine, none for similar drugs

Limited evidence exists for the use of fluoxetine, 20 mg daily. A small 1999 study of patients with migraine without aura found a 57% reduction in total pain index—a value based on pain intensity and hours of headache per month—with fluoxetine compared with an insignificant 31% reduction with placebo.[6]

No evidence from controlled trials supports the use of fluvoxamine, paroxetine, sertraline, phenelzine, venlafaxine, mirtazapine, trazodone, or bupropion.[4]

Divalproex sodium, sodium valproate are effective

Divalproex sodium and sodium valproate show strong, consistent evidence of efficacy; they may be particularly useful for patients with prolonged or atypical migraine aura.[4] Initial studies of delayed-release divalproex at doses ranging from 500 to 1500 mg daily found

TABLE

Recommended drugs for migraine prophylaxis[13]

Drug	Dose	Comments
Propranolol	80-240 mg/d	May cause fatigue. When used in combination with rizatriptan, give a lower dose of rizatriptan.
Timolol	20-30 mg/d	As with propranolol, may cause fatigue. Avoid β-blockers in patients with asthma or Raynaud's disease.
Amitriptyline	25-150 mg/d	Drowsiness, weight gain, and significant anticholinergic adverse events are common.
Divalproex sodium; **Sodium valproate**	500-1500 mg/d; 800-1500 mg/d	Side effects include nausea, drowsiness, weight gain, hair loss, and tremor. Hepatotoxicity, pancreatitis, and hyperammonemia have been reported rarely. Pregnancy category D.
Topiramate	100-200 mg/d	Paresthesia is the most common adverse event; fatigue, nausea, anorexia, and cognitive symptoms are less common. Carbonic anhydrase inhibition may cause metabolic acidosis. Acute myopia and angle closure glaucoma are rare events.

that 44% of divalproex-treated patients reported a 50% reduction in migraine frequency, compared with 21% in the placebo group (number needed to treat [NNT]=4).[7]

A more recent study of the extended-release form of divalproex sodium demonstrated a 4-week reduction in headache rate to 1.2 from a baseline of 4.4, compared with a decrease of 0.6 for placebo (95% confidence interval [CI] of treatment difference, 0.2-1.2).[8]

Topiramate may decrease frequency as much as propranolol

Topiramate has significantly reduced the mean frequency of episodic migraine at doses of 100 to 200 mg daily and also improved secondary end points, including number of migraine days per month, use of acute medication, and daily activity.[9] One study found that topiramate 100 mg daily had comparable efficacy to propranolol 160 mg daily; both drugs decreased monthly migraine frequency to 1.6 from a baseline of 4.9 with topiramate and 5.1 with propranolol (95% CI for the pair-wise difference of topiramate minus propranolol, –0.58 to 0.60).[10]

Anticonvulsants also reduce migraine frequency

A 2004 Cochrane review of anticonvulsant drugs for migraine prophylaxis found that anticonvulsants, as a class, reduce migraine frequency by about 1.3 attacks per 28 days when compared with placebo (based on 10 trials [N=902]). When analyzing data on relative frequency of migraines, data from 13 trials (N=1773) were combined and showed that anticonvulsants more than doubled the number of patients with a 50% or greater decrease in migraine frequency relative to placebo (relative risk=2.25; 95% CI, 1.79-2.84; NNT=3.9; 95% CI, 3.4-4.7).[11]

Other drugs to keep on your radar

Agents available in the United States that have at least limited evidence supporting their use to prevent episodic migraine include gabapentin, lisinopril, candesartan, memantine, riboflavin, magnesium, feverfew, coenzyme Q10, butterbur, and melatonin.

Drugs so far proved ineffective in preventing episodic migraine include clonidine, carbamazepine, clonazepam, vigabatrin, oxcarbazepine, zonisamide, lamotrigine, nifedipine, and acetazolamide. Botulinum toxin type A given by intramuscular injection in the head and neck region has demonstrated limited efficacy in chronic headache disorders, but doesn't prevent episodic migraine.[12]

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Amitriptyline is more effective than propranolol for mixed migraine-tension-type headache, whereas propranolol works better for migraine alone.

Recommendations

The 2000 guidelines of the American Association of Neurology address Group 1 (first-line) drugs and Group 2 drugs:

- **Group 1 drugs** (medium to high efficacy, good strength of evidence, and a range of severity [mild to moderate] and frequency [infrequent to frequent] of side effects) include amitriptyline, divalproex sodium, propranolol, and timolol.
- **Group 2 drugs** (lower efficacy than Group 1, or limited strength of evidence, and mild to moderate side effects) include aspirin (but not combination products), atenolol, fenoprofen, feverfew, flurbiprofen, fluoxetine, gabapentin, guanfacine, ketoprofen, magnesium, mefenamic acid, metoprolol, nadolol, naproxen, nimodipine, verapamil, and vitamin B_2.[13]

Topiramate was still under study when the guidelines were released and wasn't approved by the US Food and Drug Administration for migraine prophylaxis until 2004. The 2000 guidelines are undergoing revision. JFP

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