

FROM THE FAMILY PRACTICE INQUIRIES NETWORK

What medication best prevents migraine in children?

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■ EVIDENCE-BASED ANSWER

Propranolol, valproic acid, and amitriptyline are effective prophylaxis for migraine in children to varying degrees, are widely available, and have a reasonable safety profile (strength of recommendation [SOR]: **B**, based on either single randomized controlled trial, prospective or retrospective cohort studies, or trials with conflicting evidence).

Flunarizine and nimodipine have the best evidence of benefit in children; however, availability, cost, and side effects limit their usefulness (SOR: **B**, based on multiple small randomized controlled trials).

■ EVIDENCE SUMMARY

Amitriptyline was moderately efficacious in 3 small nonblinded trials.^{1,2} The largest and best-designed prospective cohort trial studied 192 children. Of the 146 patients available for the first follow-up visit, 84% noted subjective improvement of symptoms. Headache frequency decreased from 17.1 ± 10.1 to 9.2 ± 10.0 days/month ($P < .001$).¹

Propranolol, although widely used in children, has conflicting evidence regarding effectiveness. One small randomized controlled trial showed reduced headache frequency in children when compared with placebo.³ However, these results were not duplicated in a larger randomized controlled trial using slightly smaller doses.⁴

A comparative randomized controlled trial with multiple crossovers involving 33 children found that a self-hypnosis placebo decreased mean headache frequency from 13.3 per 3-month interval to 5.8 ($P = .045$), but found propranolol no different than placebo.⁵ Propranolol was also studied in a 3-armed randomized controlled trial in comparison with flunarizine—a drug likely to be efficacious—and placebo. Both drugs were equally efficacious and superior to placebo according to reviews; however, these results were not published in English and could not be critiqued by this author.²

In 2 small retrospective case studies, *valproic acid* demonstrated >50% improvement in symptoms in 65%⁶ and 78%⁷ of subjects. A single uncontrolled interventional trial of valproic acid in 10 children showed a significant trend of improvement in frequency (mean of 6 attacks/month to 0.8 attacks/month) and duration (mean 5.5 hours per attack to 1.1 hour).⁸

Two similar vasodilatory calcium channel blockers, *flunarizine* and *nimodipine*, have the best evidence as migraine prophylactics in children. Flunarizine was found to be effective in multiple well-designed randomized controlled trials and case series, as well as in multiple comparative trials with other agents.²

In a double-blinded, placebo-controlled randomized controlled trial of 48 children, flunarizine decreased mean headache frequency (3.0 attacks/3 months vs 6.5 [$P<.001$]).⁹ A repeat randomized controlled trial in 70 children had similar outcomes.¹⁰

Nimodipine, in a single randomized controlled trial with crossover design in 37 children decreased headache frequency from a mean of ~2.7 attacks/month to ~1.9 vs. no change for placebo ($P<.05$).¹¹ A small, prospective, nonblinded comparative trial found that nimodipine and flunarizine have similar efficacy and are superior to placebo.¹²

Cyproheptadine is widely used in children but is not as effective as amitriptyline and propranolol.² In adults it is not considered a first-line agent due to lack of evidence of efficacy.¹³ Nonsteroidal anti-inflammatory drugs have insufficient data to recommend them as prophylactic medications in children.²

■ RECOMMENDATIONS FROM OTHERS

Nelson Textbook of Pediatrics recommends propranolol as a first-line agent for prevention.¹⁴

A recent review article¹⁵ recommends cyproheptadine as an initial agent in children <10 years of age. This article also has a patient handout discussing nonpharmacologic prophylactics such as regular sleep, exercise, stress reduction, and avoiding certain foods.

UpToDate recommends propranolol, cyproheptadine, valproate, and amitriptyline as prophylactic options based on patient parameters such as age, sex, and comorbid conditions.¹⁶

CLINICAL COMMENTARY

Propranolol has fewest side effects

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Migraines in children are not as well studied as the same problem in adults. I like to stick with older medications known to have fewer side effects. Propranolol is my first choice for any age, since it has been well studied and has very few side effects. Amitriptyline would be second because it is well known, but it does have a sedating effect. If both of these fail

to control the migraines, I would consider calcium channel blockers, which are newer in the prevention of migraines.

REFERENCES

1. Hershey AD, Powers SW, Vockell AL, et al. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000;40:539–549.
2. Evers S. Drug treatment of migraine in children. *Paediatr Drugs* 1999;1:7–18.
3. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. *Acta Neurol Scand* 1974;50:109–115.
4. Forsythe W, Gillies D, Sills M. Propranolol ('Inderal') in the treatment of childhood migraine. *Dev Med Child Neurol* 1984;26:737–741.
5. Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. *Pediatrics* 1987;79:593–597.
6. Pakalnis A, Greenburg G, Drake ME Jr, Paolichi J. Pediatric migraine prophylaxis with divalproex. *J Child Neurol* 2001;16:731–734.
7. Caruso JM, Brown WD, Exil G, Gascon GG. The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache* 2000;40:672–676.
8. Serdaroglu G, Erhan E, Tekgul H, et al. Sodium valproate prophylaxis in childhood migraine. *Headache* 2002;42:819–822.
9. Sorge F, Marano E, Flunarizine v. placebo in childhood migraine. A double-blind study. *Cephalalgia*. 1985;5(suppl 2):145–148.
10. Sorge F, De Simone R, Marano E, Nolana M, Orefice G, Carrieri P. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. *Cephalalgia* 1988;8:1–6.
11. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. *Headache* 1990;30:264–268.
12. Castellana M, Carini U, Capirci G, Mazzocchi B. Calcium entry blockers in the treatment of primary headache in children: our experience with flunarizine and nimodipine. In: Lanzi G, Balottin U, Cernibori A, eds. *Headache in children and adolescents*. Amsterdam: Elsevier; 1989;349–352.
13. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. American College of Neurology, April 2000. Available at: www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed on August 7, 2003.
14. Behrman RE, Kliegman R, Jenson HB. *Nelson Textbook of Pediatrics*. 16th ed. Philadelphia: W.B. Saunders; 2000;16:1832–1834.
15. Lewis DW. Headaches in children and adolescents. *Am Fam Physician* 2002;65:625–632.
16. Cruse RP. Management of migraine headache in children. UpToDate. Last update October 15, 2002. Available at: www.uptodate.com. Accessed on July 22, 2003.

