Medicine by the Numbers

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The NNT Group rating system:

Green:	Benefits greater than harms
Yellow:	Unclear benefits
Red:	No benefits
Black:	Harms greater than benefits

Valproate for Adult Migraine Prophylaxis

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VALPROATE FOR ADULT MIGRAINE PROPHYLAXIS

Benefits	*Harms*
1 in 5 experienced 50% or greater reduction in migraines	1 in 7 experienced adverse effects such as nausea, tremor, or vertigo

Details for This Review

Study Population: Patients 16 years or older with episodes of migraine headache on at least 15 days of every month

Efficacy End Points: 50% or greater reduction in migraines after one month of treatment

Harm End Points: Adverse effects such as fatigue, vertigo, nausea, tremor, and weight gain

Narrative: Migraines are the sixth most common cause of disability worldwide and affect more than 10 million U.S. adults annually.[1,2] Daily antiepileptic medications are commonly used to prevent migraine headaches. A 2013 Cochrane review assessed evidence on the efficacy and tolerability of valproate medications (valproic acid [Depakene] or divalproex sodium [Depakote], or a combination of both) in migraine prophylaxis. Ten randomized trials enrolled 2,296 patients 16 years or older with migraines occurring on at least 15 days per month. The studies compared valproate to a placebo or other medications. The analysis demonstrated that significantly more patients treated with divalproex sodium met their definition of success compared with those receiving placebo, with a number needed to treat (NNT) of 5 (95% confidence interval [CI], 4 to 8). Vertigo, nausea, and tremor were increased compared with placebo, whereas the frequency of other adverse effects (fatigue, weight gain, cumulative adverse effects) were not significantly different.[3]

Caveats: The 10 small trials in this review were judged overall to be at some risk of bias, often missing critical methodological elements such as allocation concealment (eight out of 10), double blinding (three out of 10), or complete reporting of outcomes (six out of 10). In addition, studies using varying forms of valproate and comparators were included and, in some cases, combined. The meta-analysis demonstrated superiority of valproate over placebo for migraine prevention. Similar to divalproex sodium, sodium valproate was found to have an NNT of 3 (95% CI, 2 to 9) for at least 50% reduction in migraine frequency compared with placebo. In two studies (one comparing divalproex sodium vs. propranolol and another evaluating sodium valproate vs. flunarizine) no significant differences in the proportion of responders were identified. Two small trials (n = 88) studying sodium valproate vs. topiramate (Topamax) found the latter medication to be slightly more effective, corresponding to a reduction of approximately one headache per 28 days with topiramate.[3]

Adverse effects are difficult to assess from these small studies. However, when assessed individually, statistically significant differences were identified for vertigo, nausea, and tremor (number to need to harm = 14, 7, and 14, respectively).[3] Because migraine headaches tend to be more debilitating than these adverse effects, the data suggest good clinical tolerance with valproate and a favorable benefits-to-harms profile for migraine prevention. Of note, valproate medications

are well-classified teratogens and physicians should consider this factor when treating women of reproductive age with these types of medications.[4]

Although further study is needed to better define the utility of this treatment compared with other medication options, the evidence suggests valproate medications are likely effective for preventing migraine, which agrees with current guideline recommendations.[5] Therefore, we have classified this treatment as green, suggesting overall benefits outweigh harms. However, physicians should evaluate experienced adverse effects compared with prevention benefits for individual patients, because the data pertaining to adverse events are limited.

This series is coordinated by Dean A. Seehusen, MD, MPH, *AFP* Contributing Editor, and Daniel Runde, MD, from the NNT Group.

A collection of Medicine by the Numbers published in *AFP* is available at http://www.aafp.org/afp/mbtn.

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