Review: anticonvulsants are better than placebo for reducing the frequency of migraine attacks

Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;(3):CD003226.

Clinical impact ratings GP/FP/Primary care ★★★★★☆☆IM/Ambulatory care ★★★★★★☆ Neurology ★★★★★☆☆

Q In patients with migraine, are anticonvulsants more effective than placebo for preventing or reducing the intensity of migraine attacks?

METHODS

Data sources: Medline (up to April 2003); the Cochrane Central Register of Controlled Trials (up to April 2003); review article references; books on headache; contact with drug companies, authors, and experts; and hand searches of *Headache* and *Cephalalgia*.

Study selection and assessment: randomised controlled trials (RCTs) that compared anticonvulsants given regularly during headache free intervals in adults >18 years of age with placebo, no intervention, other drug treatments, or behavioural or physical therapies. Methodological quality was assessed using the Jadad 5 point scale.

Outcomes: headache frequency (number of migraine attacks measured at 28 d), headache index measures (frequency and intensity or duration), and adverse events.

MAIN RESULTS

15 RCTs met the selection criteria. Anticonvulsants investigated were divalproex sodium (500–1500 mg daily [4 RCTs]), topiramate (50–200 mg daily [3 RCTs]), sodium valproate (800–1500 mg daily [2 RCTs]), gabapentin (1200–2400 mg daily [2 RCTs]), carbamazepine (dose not reported [1 RCT]), clonazepam (1 mg daily [1 RCT]), and lamotrigine (200 mg daily [1 RCT]). Mean duration of the maintenance phase of trials was 9.6 weeks (range 4–18 wk). The median quality score of studies was 4 (range 1–5). Compared with placebo, anticonvulsants as a class reduced mean migraine frequency by 1.4 attacks per 28 days (8 RCTs, weighted mean difference [WMD] −1.43, 95% CI −2.2 to −0.65) and increased the number of patients in whom migraine frequency is reduced by ⩾50% (10 RCTs) (table). For individual anticonvulsants compared with placebo, migraine frequency was reduced by sodium valproate (2 RCTs, WMD –4.31, CI –8.32 to –0.30), topiramate (3 RCTs, WMD –1.27, CI –1.74 to –0.79), and gabapentin (1 RCT, WMD –1.89, CI –2.35 to –1.43). The results of individual anticonvulsants for the number of patients in whom migraine frequency is reduced by ⩾50% are in the table. Lamotrigine or clonazepam did not differ from placebo for reducing migraine frequency. The most common adverse events were nausea (number needed to harm [NNH] 6.6, CI 5.0 to 9.8), asthaenia or fatigue (NNH 12.3, CI 7.6 to 31.8), tremor (NNH 12.4, CI 8.9 to 20.1), weight gain (NNH 16.0, CI 8.5 to 154.4), and dizziness or vertigo (NNH 16.3, CI 9.5 to 57.9).

CONCLUSIONS

In patients with migraine, anticonvulsants as a class reduced the frequency of migraine attacks.

Abstract and commentary also appear in ACP Journal Club.

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Commentary

The review by Chronicle and Mulleners supports the use of anticonvulsant medications to prevent migraine attacks. However, it is unclear how to incorporate antiepileptic medication into the care of patients with frequent migraine attacks. Few studies have compared medications directly, and none has combined medications for prophylaxis.

Any meta-analysis risks combining studies that are too heterogeneous to be "lumped" together. The underlying assumption of this Cochrane review is that all antiepileptic medications can logically be considered together as a class. However, the mechanisms of action of antiepileptic drugs are either typically unclear or vary if known. In addition, the studies described different rules for administering rescue medication.

Many patients in studies come from such specialised study settings as headache or neurology clinics. Patients presenting to these centres might have headaches that are more difficult to treat. However, this bias should strengthen any findings that support antiepileptic treatment.

Although the benefit of anticonvulsant drugs appears worth the risk, cost may be prohibitive (eg, topiramate is much more expensive than propranolol), and the rates of side effects and discontinuation of medication were high.

Antiepileptic medications have shown similar results to other classes of drugs commonly used for prophylaxis in reducing the frequency and intensity of migraines by about 40%.[1] Only 2 studies compared antiepileptic medications with other medications used for such migraine prophylaxis as propranolol or amitryptiline.[2] It would be interesting for future research to investigate the synergistic effect of combining 2 medications (eg, β blockers and antiepilectic drugs) to improve outcomes.

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1 Brandes JL, Saper JR, Diamond M, *et al*. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004;**291**:965–73.
2 Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database Syst Rev 2004(2):CD003225.

Anticonvulsants *v* placebo for number of patients who responded with ⩾50% reduction in migraine frequency at mean 9.6 weeks*

Number of trials (n)	Comparisons	Weighted event rates	RBI (95% CI)	NNT (CI)
10 (1341)	Anticonvulsants as a class *v* placebo	49% *v* 20%	71% (63 to 80)	4 (3 to 5)
4 (579)	Divalproex sodium *v* placebo	47% *v* 21%	74% (57 to 91)	4 (3 to 12)
1 (68)	Sodium valproate *v* placebo	29% *v* 18%	68% (47 to 89)	4 (2 to 10)
3 (498)	Topiramate *v* placebo	48% *v* 22%	74% (66 to 82)	4 (3 to 6)

*Abbreviations defined in glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a random effects model.