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## Anticonvulsant drugs for pediatric migraine prevention: an evidence-based review

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### CRD summary

This review found that the use of anticonvulsants to prevent migraine in children and adolescents was not well supported by the current evidence and more research was needed. The review methods were not clearly reported and there appeared to be some risk of publication bias, but the limitations of the included evidence suggest that the authors' conclusions are justified.

### Authors' objectives

To evaluate the efficacy and safety of anticonvulsants for the prevention of migraine in children and adolescents.

### Searching

PubMed (1966 to September 2008), EMBASE (1980 to 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2008, issue 1) were searched for published studies, without language restriction. The reference lists of included studies and other relevant articles were checked and the search terms were reported.

### Study selection

Randomised and non-randomised controlled trials, and prospective and retrospective case series were eligible for inclusion if they were of children and adolescents (aged under 18 years) with migraine diagnosed by established diagnostic criteria (specified in the review). Acceptable comparators (where relevant) were placebo or another drug treatment. Studies were required to have at least eight participants and at least one study arm in which anticonvulsants were given regularly to prevent migraine or reduce its severity. The efficacy outcomes included frequency, intensity, and duration of migraine attacks. Studies including both adults and children were excluded unless they included children below the age of 14 years and reported data separately for these children. Studies that did not distinguish between migraine and other childhood headaches (e.g. tension or cluster headaches) were also excluded.

The age range of participants in the included studies ranged from three to 17 years. The intervention groups received topiramate, sodium valproate (or divalproex sodium), levetiracetam, and zonisamide, in varying doses. Controls received propranolol, placebo, no intervention, or a different dose of anticonvulsant. The primary outcome in most studies was the monthly migraine frequency, reported as migraine days per month, or the response rate (greater than 50% reduction in monthly migraine frequency). The tools for outcome measurement varied, and included headache diaries, questionnaires, and a quality of life scale. The treatment duration ranged from one to 18 months (where reported).

The authors did not state how the papers were selected for the review nor how many reviewers performed the selection.

### Assessment of study quality

The quality of randomised controlled trials (RCTs) was evaluated using the Jadad scale, which assesses the adequacy of randomisation, double blinding, and withdrawals or dropouts. Each RCT was awarded a score out of a maximum of five points.

The authors did not state how many reviewers conducted this validity assessment. The quality of uncontrolled trials was not assessed.

### Data extraction

Data were extracted on event rates in the two groups for each study, with p values for the differences between the groups. Studies were classified by their level of evidence based on the study design, using published criteria (Agency for Healthcare Research and Quality, 2008).

Data were extracted independently by two reviewers and checked by a third, with disagreements resolved by consensus.

## Methods of synthesis

Studies were combined in a narrative synthesis, organised by intervention, level of evidence, and outcome (efficacy or safety).

## Results of the review

Fourteen studies were included in the review (n=939 children, range eight to 305); five were RCTs (n=645), one was a meta-analysis of paediatric subgroups in three RCTs (n=51), four were prospective non-consecutive case series (n=151), and four were retrospective chart reviews (n=92). Six studies were assessed on the Jadad scale; four scored five out of five points (high quality), one scored three points (acceptable quality), and one scored two points (low quality).

Topiramate versus placebo (three RCTs and one meta-analysis): One high-quality RCT (n=44) reported that the intervention group had a statistically significant reduction in mean monthly migraine frequency (11.9 days versus 5.9 days for control,  $p=0.025$ ), as well as statistically significant benefits in response rate (95% versus 52% for control,  $p=0.002$ ), quality of life ( $p=0.003$ ), and school absenteeism ( $p=0.002$ ); the severity of migraine attacks did not differ significantly between the two groups. The meta-analysis of data from three high-quality RCTs, comparing topiramate at various doses with placebo, found a statistically significant median percentage reduction in the monthly migraine frequency in children receiving 100mg (63%,  $p=0.02$ ) to 200mg (65%,  $p=0.04$ ) of topiramate per day (placebo 16%). Two other RCTs, one of high quality (n=162) and one of acceptable quality (n=14) found no statistically significant difference between the groups in migraine days per month. A range of adverse effects were reported to occur more frequently in the topiramate groups and these included upper respiratory tract infection, anorexia, weight loss, gastroenteritis, paraesthesia, and somnolence (statistical significance not reported). Serious adverse events (infection, severe migraine, and suicidal ideation) occurred in four children in the topiramate group in one study.

Valproate versus comparators (two RCTs): One high-quality RCT (n=305) found no statistically significant differences in efficacy or adverse event rates between divalproex sodium and placebo. A low-quality RCT (n=120) reported no statistically significant difference between valproate sodium and propranolol in efficacy nor adverse events.

The findings of the case series were also reported.

## Authors' conclusions

The use of anticonvulsants to prevent migraine in children and adolescents was not well supported by the current evidence and more research was needed.

## CRD commentary

The objectives and inclusion criteria of the review were clear and relevant sources were searched, without language restriction. The apparent restriction to published studies meant that publication bias might have been present. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently extract the study data, but it is unclear whether such precautions were taken with study selection or validity assessment. Some relevant aspects of the quality of the RCTs were assessed, but no details were given of some important aspects of quality in individual RCTs (e.g. allocation concealment, and drop-out rates). Many of the studies used poor quality designs and their data might not be reliable; the validity of these studies was not assessed. The authors suggested that some of the data in their review might be suitable for meta-analysis and it is unclear why one was not reported. The narrative synthesis was clearly organised and prioritised the better quality data, but heterogeneity between the studies was not explored. The statement that all drugs were well tolerated with no serious events did not appear to be entirely consistent with the reported results.

The review methods were not clearly reported and there appeared to be some risk of publication bias, but the limitations of the included evidence suggest that the authors' conclusions are justified.

## Implications of the review for practice and research

Practice: The authors stated that valproate should not be used for the prevention of migraine in children and

adolescents. Topiramate appeared to be promising for this use and its tolerability appeared to be adequate, but no firm conclusions could be made. The use of levetiracetam and zonisamide should be considered to be experimental.

**Research:** The authors stated that there was a need for more RCTs to assess the safety and efficacy of specific drugs to prevent paediatric migraine. The use of anticonvulsants (especially topiramate) should be investigated further. More epidemiological studies on paediatric migraine were also needed and they should use revised diagnostic criteria.

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