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Treating migraines: It's different for kids

Certain medications used for migraine prevention in adults do not perform the same way in children and adolescents and can actually cause harm.

PRACTICE CHANGER

Do not prescribe amitriptyline or topiramate as preventive therapy for migraine in children; both drugs are no better than placebo for this population and are associated with increased rates of adverse events.^{1,2}

STRENGTH OF RECOMMENDATION

A: Based on a single double-blind randomized control trial (RCT) and supported by a meta-analysis of 4 RCTs.

1. Powers SW, Coffey CS, Chamberlin LA, et al; for the CHAMP Investigators. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *N Engl J Med.* 2017;376:115-124.

2. Le K, Yu D, Wang J, et al. Is topiramate effective for migraine prevention in patients less than 18 years of age? A meta-analysis of randomized controlled trials. *J Headache Pain.* 2017;18:69.

ILLUSTRATIVE CASE

A 15-year-old girl presents to your clinic with poorly controlled chronic migraines that are preventing her from attending school 3 to 4 days per month. As part of her treatment regimen, you are considering migraine prevention strategies.

Should you prescribe amitriptyline or topiramate for preventive migraine therapy?

Migraine headaches are the most common reason for headache presentation in pediatric neurology outpatient clinics, affecting 5% to 10% of the pediatric population worldwide.² Current recommendations regarding prophylactic migraine therapy in childhood are based on consensus opinions.^{3,4} And the US Food and

Drug Administration (FDA) has not approved any medications for preventing migraines in children younger than 12 years of age. However, surveys of pediatric headache specialists suggest that amitriptyline and topiramate are among the most commonly prescribed medications for childhood migraine prophylaxis.^{3,4}

There is low-quality evidence from individual randomized controlled trials (RCTs) about the effectiveness of topiramate. A meta-analysis by El-Chammas and colleagues included 3 RCTs comparing topiramate to placebo for the prevention of episodic migraines (migraine headaches that occur <15 times/month) in a combined total of 283 children younger than 18 years of age.⁵ Topiramate demonstrated a nonclinically significant, but statistically significant, reduction of less than one headache per month (-0.71; 95% confidence interval [CI], -1.19 to -0.24). This is based on moderate quality evidence due to a high placebo response rate and study durations of only 12 weeks.⁵ The FDA has approved topiramate for migraine prevention in children ages 12 to 17 years.⁶

Adult guidelines. The findings described above are consistent with the most recent adult guidelines from the American Academy of Neurology and the American Headache Society.⁷ In a joint publication from 2012, these societies recommended both topiramate and amitriptyline for the prevention of migraines in adults based on high-quality (Level A evidence)



INSTANT POLL

Do you prescribe
amitriptyline or
topiramate to prevent migraines in
patients younger than 18 years of
age?

Yes

No

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and medium-quality evidence (Level B), respectively.⁷

STUDY SUMMARY

Both drugs are no better than placebo in children

A multicenter, double-blind RCT by Powers and colleagues compared the effectiveness of amitriptyline, topiramate, and placebo in the prevention of pediatric migraines.¹ Target dosing for amitriptyline and topiramate was set at 1 mg/kg/d and 2 mg/kg/d, respectively. Titration toward these doses occurred over an 8-week period based on reported adverse effects. Patients then continued their maximum tolerated dose for an additional 16 weeks.

Patients were predominantly white (70%), female (68%), and 8 to 17 years of age. They had at least 4 headache days over a prospective 28-day pre-treatment period and a Pediatric Migraine Disability Assessment Scale (PedMIDAS) score of 11 to 139 (mild to moderate disability=11-50; severe disability >50).^{1,8} The primary endpoint consisted of at least a 50% relative reduction (RR) in the number of headache days over the 28-day pre-therapy (baseline) period compared with the final 28 days of the trial.¹

The authors of the study included 328 patients in the primary efficacy analysis and randomly assigned them in a 2:2:1 ratio to receive either amitriptyline (132 patients), topiramate (130 patients), or placebo (66 patients), respectively. After 24 weeks of therapy, there was no significant difference between the amitriptyline, topiramate, and placebo groups in the primary endpoint (52% amitriptyline, 55% topiramate, 61% placebo; adjusted odds ratio [OR]=0.71; 98% CI, 0.34-1.48; $P=.26$ between amitriptyline and placebo; OR=0.81; 98% CI, 0.39-1.68; $P=.48$ between topiramate and placebo; OR=0.88; 98% CI, 0.49-1.59; $P=.49$ between amitriptyline and topiramate).

There was also no difference in the secondary outcomes of absolute reduction in headache days and headache-related disability as determined by PedMIDAS. The study was stopped early for futility. Compared with placebo, amitriptyline significantly increased

fatigue (number needed to harm [NNH]=8) and dry mouth (NNH=9) and was associated with 3 serious adverse events of altered mood. Compared with placebo, topiramate significantly increased paresthesia (NNH=4) and weight loss (NNH=13) and was associated with one serious adverse event—a suicide attempt.¹

WHAT'S NEW?

Higher-level evidence demonstrates lack of efficacy

This RCT provides new, higher-level evidence that demonstrates the lack of efficacy of amitriptyline and topiramate in the prevention of pediatric migraines. It also highlights the risk of increased adverse events with topiramate and amitriptyline.

Two of the 3 topiramate trials used in the older meta-analysis by El-Chammas and colleagues⁵ and this new RCT¹ were included in an updated meta-analysis by Le and colleagues (total participants 465) published in 2017.² This newer meta-analysis found no statistical benefit associated with the use of topiramate over placebo. It demonstrated a nonsignificant decrease in the number of patients with at least a 50% relative reduction in headache frequency (risk ratio = 1.26; 95% CI, 0.94-1.67) and in the overall number of headache days (mean difference = -0.77; 95% CI, -2.31 to 0.76) in patients younger than 18 years of age.² Both meta-analyses, however, showed an increase in the rate of adverse events in patients using topiramate vs placebo.^{2,5}

CAVEATS

Is there a gender predominance?

El-Chammas and colleagues⁵ describe male pediatric patients as being the predominant pediatric gender with migraines. However, they do not quote an incidence rate or cite the reference for this statement. No other reference to gender predominance was noted in the literature. The current study,¹ in addition to the total population of the meta-analysis by Le and colleagues,² included women as the predominant patient population. Hope-



After 24 weeks of therapy, there was no significant difference between amitriptyline, topiramate, and placebo in the primary or secondary outcomes.

fully, future studies will help to delineate if there is a gender predominance and, if so, whether the current treatment data apply to both genders.

CHALLENGES TO IMPLEMENTATION

None to speak of

There are no barriers to implementing this recommendation immediately in all primary care settings.

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ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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