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# Is Amitriptyline Effective in Reducing Headache Days in Pediatric Patients with Migraines and Chronic Headaches Compared to Topiramate, Propranolol, or No Treatment?

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**Is amitriptyline effective in reducing headache days in pediatric patients with migraines and chronic headaches compared to topiramate, propranolol, or no treatment?**

Megan N. Hall, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

December 14, 2018

## **Abstract**

**Objective:** The objective of this selective EBM review is to determine whether or not “Is amitriptyline effective in reducing headache days in pediatric patients with migraines and chronic headaches compared to topiramate, propranolol, or no treatment?”

**Study design:** Systematic review of two randomized control trials (RCTs) and one case series published in peer-reviewed journals in English after 2007.

**Data Sources:** Two RCTs and one case series were found using PubMed.

**Outcome(s) Measured:** Headache frequency was measured using a headache diary or calendar. A secondary objective included headache severity that was measured using a ten-point scale or the Pediatric Migraine Disability Assessment (PedMIDAS).

**Results:** Powers et al. found that headache frequency did not vary significantly between amitriptyline, topiramate, or placebo.<sup>2</sup> It was also recorded that there was no significant variation among reduction in scores on the PedMIDAS.<sup>2</sup> Eidlitz-Markus et al. stated that this trial showed no significant difference between amitriptyline and propranolol (p-value=0.8).<sup>4</sup> Sezer et al. found that 31% of patients in the topiramate group and 28% of patients in the amitriptyline group “reported freedom from headache.”<sup>5</sup> It was also recorded that the severity of headaches also decreased 4.5 points on a visual analog scale in both treatment groups.

**Conclusions:** Amitriptyline in these three trials is less effective in reducing the frequency of chronic headaches and migraines when compared to topiramate, propranolol, or a placebo.<sup>2,4,5</sup> These results could be affected by subjectivity, drug adherence, or misunderstanding between younger subjects and their parents. The safety of amitriptyline should always be in question because the FDA warns that antidepressants can cause suicidal thoughts or actions in children under eighteen years old.

**Key Words:** pediatric, migraine, headache, amitriptyline

## **Introduction**

Migraines are primary throbbing headaches of moderate or severe intensity that are worsened by activity and associated with photophobia and/or phonophobia. These can be accompanied by vomiting and abdominal pain. The pathophysiology is unclear. The most studied and most recent theory is migraines are caused by cortical spreading depolarization across the brain which can be associated with the aura before a migraine. This depolarization leads to trigeminovascular system activation, causing increased activity in pain pathways. Migraines can affect patients of all ages but studies show most children with migraines will have them lifelong.<sup>1,2</sup> They are more common in males in younger populations but more common in females overall.<sup>1,2</sup> Less than 25% of boys and 15% of girls have migraines before reaching age fourteen.<sup>1</sup> Altogether, more than 6 million children in the U.S. have migraines.<sup>2,3</sup> These costs for all patients of all ages are approximately \$36 billion.<sup>2</sup> Unfortunately, there is no way, other than clinically, to diagnose migraines in any population. Acute treatment of migraines includes analgesics (such as acetaminophen, ibuprofen, and naproxen), migraine-specific medications commonly called “triptans” (such as sumatriptans, almotriptan, zolmitriptan or rizatriptan), or IV dihydroergotamine. Preventative treatment of migraines includes antiepileptics (such as topiramate or valproic acid), antihypertensives (such as flunarizine or propranolol), antihistamines (such as cyproheptadine), and antidepressants (such as amitriptyline or nortriptyline).

Chronic headaches are primary headaches that occur fifteen or more days each month for three or more consecutive months. These headaches have different characteristics than migraines. Chronic headaches are not throbbing and are not associated with photophobia or phonophobia but they can be just as incapacitating as migraines. There may be overlap in

patients with chronic headaches who also have a history of migraines.<sup>5</sup> Both types of headaches affect school performance but migraines alone are associated with higher deficiencies and absences.<sup>3,4</sup> Studies and practitioners use the Pediatric Migraine Disability Assessment Scale (PedMIDAS) to measure the debilitating effects of headaches on “school, home, play, and social activities.”<sup>2</sup>

There is no single pharmacologic therapy suggested for the prevention of chronic headaches or migraines in patients under eighteen. As with most diagnoses, pediatric patients are tried on lower doses of treatments shown to provide relief in adults. These treatments are complicated even more by the dosing difference in patients under twelve. Children older than twelve should be treated with adult dosing. Most pediatric treatment strategies are based on studies in adults. Amitriptyline is an oral tricyclic antidepressant used frequently for migraine and chronic headache prevention in adults. Children older than twelve can take adult dosing but younger children should take 1mg/kg/day (max 200mg/day). Amitriptyline inhibits serotonin reuptake throughout the central nervous system. The theory behind this preventative strategy is to prevent the low serotonin conditions that lead to an increase in pain receptor pathways during trigeminovascular activation.

This paper evaluates two double-blind, RCTs and one case series comparing the efficacy of amitriptyline with either topiramate, propranolol, or no treatment for reducing headache days in pediatric patients diagnosed with chronic headaches or migraines.

## **Objective**

The objective of this selective EBM review is to determine whether or not “Is amitriptyline effective in reducing headache days in pediatric patients with migraines and chronic headaches compared to topiramate, propranolol, or no treatment?”

## Methods

The author concluded all research by reviewing studies that analyzed the effectiveness of amitriptyline. Two double-blinded RCTs and one case series surrounding female and male participants younger than nineteen diagnosed with chronic headaches or migraines were chosen for this selective review.

Amitriptyline was compared to different interventions, such as topiramate, propranolol, or no treatment, in efficacy of reducing the frequency of headache days during each specified trial period. Trial periods varied from 4 months to 24 weeks.<sup>2,5</sup> The frequency of headache days throughout each study was measured using a headache calendar or diary. A secondary goal was to reduce headache severity. This was recorded via a ten-point scale or the PedMIDAS.

All articles were found via PubMed using the key words: pediatric, migraine, headache, and amitriptyline. The author conducted all research for this review and carefully selected articles that were both relevant and patient-oriented. The inclusion criteria for this review encompassed articles that were primary research studies published between 2007 and the present, all subjects were diagnosed with chronic headaches or migraines, and one trial group must be treated with amitriptyline. Exclusion criteria for this review omitted articles that were not in English, not peer-reviewed, and articles with subjects older than eighteen. Statistics were reported using p-values and CI. After narrowing down studies with inclusion and exclusion criteria, the author evaluated the relevance and validity of all articles.

Table 1: Demographics of included studies

Study	Type	#of Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Powers (2017) <sup>2</sup>	Double blinded RCT	361	8-17	Diagnosis of migraine with/without aura or chronic migraine without continuous headache as defined by the International Classification of Headache Disorders, 2 <sup>nd</sup> edition A score on the PedMIDAS from 11 to 139 A headache frequency of >4 days from a prospective headache diary over a baseline period of 28 days	No exclusion criteria listed	64	Amitriptyline 1mg/kg/day PO  Topiramate 2mg/kg/day PO  Placebo
Eidlitz-Markus (2012) <sup>4</sup>	Case series	118	4-18	Pediatric patients ages 4.4 to 18 with either chronic or episodic migraine headaches making non-pharmacological lifestyle changes	Inability to verbally communicate pain Failure to adhere to full instructions for treatment Failure to maintain regular follow-up Overusing prescribed medication Parental refusal of pharmacologic treatment	N/a	Amitriptyline 10-25 mg/day PO QHS  Propranolol 5-80 mg/day PO BID
Sezer (2013) <sup>5</sup>	Double blinded RCT	60	12-16	Pediatric patients with chronic daily headache including chronic migraines	Symptoms of increased intracranial pressure, neurological abnormalities as revealed by clinical examination or brain MRI The presence of systemic diseases and major psychiatric disorders (depression) The current use of high-dose analgesics Previously used amitriptyline or topiramate	3	Amitriptyline 0.5 mg/kg PO  Topiramate 100 mg/day PO

## Outcomes measured

The frequency of headache days in all three studies was recorded by way of individual calendar or diary entries by subjects or their parents. An outcome of greater than 50% reduction in headache frequency was presented in all studies and is seen in Table 2. The secondary objective noted in two studies was to reduce headache baseline severity. Powers et al. measured severity using the PedMIDAS.<sup>2</sup> Sezer et al. measured headache severity using a ten-point visual analog scale (VAS) in which 10 indicates most severe and 1 indicates least severe.<sup>5</sup>

## Results

This review compares the efficacy of amitriptyline to similar migraine prevention methods in three different studies. Powers et al. compared 1mg/kg/d of amitriptyline to 2mg/kg/d of topiramate or placebo.<sup>2</sup> Patients were included in the study if they had a previous diagnosis of any type of migraine with or without aura except continuous migraine as defined by the *International Classification of Headache Disorders, 2<sup>nd</sup> edition*, a PedMIDAS score 11-139 or a headache frequency more than four days during the baseline period (twenty-eight days) before the study.<sup>2</sup> In this twenty-four week trial the reduction in headache days from baseline to the end of the trial was -6.7 days (95% CI, -7.9 to -5.5) with amitriptyline and -6.7 days (95% CI, -7.6 to -5.7) with topiramate. The placebo had very similar results causing an early end to the trial due to the ineffectiveness of the trial's pharmacologic interventions (Table 2).<sup>2</sup> Reduction of headache severity was calculated by comparing the PedMIDAS score during the baseline period and the post-treatment score. There was no significant difference in reduction of disability scores when comparing any two treatment methods (Table 3).<sup>2</sup>



Table 2: Greater than 50% reduction in headache frequency

Study	Amitriptyline	Comparison group(s)
Powers (2017) <sup>2</sup>	52%	55% topiramate 61% placebo
Eidlitz-Markus (2012) <sup>4</sup>	82.2%	85% propranolol
Sezer (2013) <sup>5</sup>	55%	61% topiramate

Table 3: PedMIDAS scores<sup>2</sup>

	Treatment comparison	Difference in score pre-treatment to post-treatment	P-value
Amitriptyline	Topiramate	4.5	0.10
	Placebo	-0.4	0.91
Topiramate	Placebo	-4.8	0.13

Eidlitz-Markus et al. compared 0.266-0.4mg/kg/d of amitriptyline to 0.47-0.81mg/kg/d of propranolol.<sup>4</sup> Patients were included in the study if they were under age eighteen, were diagnosed chronic or episodic migraine headaches, and were making “non-pharmacologic lifestyle changes.”<sup>4</sup> Children were excluded from the study if they were unable to verbally express their pain to parents or staff, if caregivers or subjects were unable to follow instructions for treatment or follow-up, if subjects overused treatment methods of any type of medication, or if parents refused treatments for the subjects.<sup>4</sup> The results of this trial showed no significant difference between the different treatment options (p-value=0.8) (Table 2).<sup>4</sup> The dosage of each medication was titrated throughout the trial to attempt to increase drug effectiveness. After subjects’ dosage of propranolol had reached 0.81mg/kg/d without efficacy, treatment was switched from propranolol to amitriptyline.<sup>4</sup> In the propranolol treatment group, 72% of subjects without aura saw 75% or more decrease in headache frequency as compared to 28% of subjects with aura (p-value=0.02).<sup>4</sup> The same association was not seen in the amitriptyline group.

Sezer et al. compared 0.5mg/kg of amitriptyline to 100mg/d of topiramate.<sup>5</sup> Children were selected for this trial if they were age 12-16 with chronic daily headache.<sup>5</sup> This

encompasses patients with chronic migraine. Sezer et al. stated children were excluded from the trial if they had “symptoms of increased intracranial pressure, neurological abnormalities as revealed by clinical examination or brain MRI, the presence of systemic diseases, major psychiatric disorders including depression, and the current use of high-dose analgesics or previously used amitriptyline or topiramate.”<sup>5</sup> This article reports after four months of treatment, 28% of patients treated with amitriptyline “reported freedom from headache.”<sup>5</sup> Which was less than the 31% of patients treated with topiramate who reported the same (p-value>0.05).<sup>5</sup> The severity of headaches decreased 4.5 points on the VAS after treatment for both amitriptyline and topiramate (p-value>0.05).<sup>5</sup>

As seen in Table 2, the reduction in headache frequency is evident. In a final analysis, the reduction in frequency is slightly higher in comparison groups. According to the numbers needed to treat (NNT) in Table 3 for all three articles, patients would see benefits with other trial medications or placebos than with amitriptyline. The NNT for each article was below zero. From the study by Powers et al. amitriptyline is compared to placebo in Table 3.<sup>2</sup>

Table 4: Number Needed to Treat (NNT) or Harm (NNH)

Study	RRR	ARR	NNT	RRI	ARI	NNH
Powers (2017) <sup>2</sup>	-0.15	-0.09	-11.11→-11			
				N/a	0.01	100
Eidlitz-Markus (2012) <sup>4</sup>	-0.04	-0.028	-35.7→-35			
Sezer (2013) <sup>5</sup>	-0.10	-0.06	-16.66→-16			

The safety of amitriptyline will come into question for all pediatric patients. Unfortunately, amitriptyline was associated with significant adverse events in four patients such as altered mood, and syncope (Table 4).<sup>2</sup> The FDA has always cautioned against using antidepressants in patients under eighteen years old for risk of suicidal thoughts or actions.

## **Discussion**

There are a significant amount of studies covering of the benefits and risks of amitriptyline in adult populations.<sup>6</sup> Studies in pediatric populations regarding any treatment method are scarce. This became a limitation of the author's searching. Future studies should encompass more pediatric double-blind, randomized control trials.

One limitation of most studies was the lack of investigation into compliance. Only one study checked compliance of patients and their parents by testing serum drug levels.<sup>2</sup> The outcomes of these studies could vary significantly if families were reporting use but were not following dosing or other directions.

Powers et al. concluded the study early due to futility.<sup>2</sup> There is a significant amount of evidence from the 24 week trial and continuing the study would not have produced new information on the benefits or risks of amitriptyline, topiramate, or placebo.<sup>2</sup> Powers et al. has shown to be very thorough due to its baseline survey over 28 days and the comparison of this baseline to the last 28 days of the study.

Every medication has side effects on the body. Amitriptyline's primary side effects are changes in behavior or thinking, dry mouth, and fatigue. All of these mental and anticholinergic side effects were reported in the study by Powers et al.<sup>2</sup> It is primarily prescribed for major depressive disorder but has many off-label uses in adults. In children, the only uses are for the treatment of depression, chronic pain management, and migraine prophylaxis.

## **Conclusion**

Tricyclic antidepressants such as amitriptyline is effective in treating adults with chronic headaches and migraines but it appears to be ineffective in children.<sup>6</sup> Amitriptyline, in all three trials, was less effective in reducing the frequency of chronic headaches and migraines when

compared to topiramate, propranolol, or a placebo.<sup>2,4,5</sup> These outcomes may be affected by the subjectivity of results collection. The documentation on headache calendars or diaries was recorded at home by pediatric patients or their parents which may have been affected by improper documentation. These outcomes may also have been affected by patient drug adherence. Fortunately, this was combatted by close follow up during the trials and serum-drug level testing by Powers et al. Future studies should include more testing for adherence. Some documentation was by parents whose children had limited communication skills.<sup>4</sup> These parents may have misinterpreted their child's signs further skewing results of the trial. Further studies should be conducted comparing different dosages of amitriptyline due to the variation amongst the studies selected for this review. Overall, more studies are required to decrease the instance and severity of migraines and headaches in pediatric populations.

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