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Prophylactic Treatment Pattern Among the Patient's Diagnosed with Migraine – An Overview

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ABSTRACT

Background: Migraine is a paroxysmal headache disorder that are characterized by an unilateral p91ain on the head which usually begins at puberty and are much common between 35 to 45 years. The major objective of this review study is to assess the prophylactic treatment pattern among the patients diagnosed with migraine and to provide healthcare professionals with the updated guidance in the use of novel preventive therapy for migraine.

Methods: In this systemic review, we identified 89 articles, among which 40 articles was selected, we rejected articles which are not relevant to the study. Search was conducted with no date limits, Abstracts were first selected for full text review and the results were screened for relevance to the review topic.

Results: Patients with migraine require prophylactic therapy to reduce the frequency of migraine attacks. Currently available evidence-based prophylactic treatment options for migraine are topiramate, propranolol and, sumatriptan was the predominant triptan used for acute treatment. New biologics have been developed to target a specific substance in the brain calcitonin gene-related peptide, which plays a key role in migraine pathophysiology recently, 3 new calcitonin gene-related peptide (CGRP) receptor antagonists-erenumab, fremanezumab, and galcanezumab were approved by FDA for prophylactic treatment of migraine.

Conclusion: Migraine is the most common neurological disorders. The effective and well tolerated new treatment indicated for prophylaxis may also help for prevention of migraine. A pooled analysis of clinical trial result suggests that, migraine prophylaxis may help to prevent migraine severity, migraine, frequency, migraine chronification, and improve quality of life.

Keywords: "Migraine" "Prophylaxis" "Treatment" "New biologics" "Non pharmacological Therapy".

INTRODUCTION

Migraine is a chronic neurological disease that is characterized by attacks of throbbing pain. It is a unilateral headache that are exacerbated by the physical activity and it is also associated with photophobia, phonophobia, nausea, vomiting.[1] Based on the number of headache days migraine is divided into 2 groups – episodic migraine and chronic migraine. Episodic migraine occurs less than 15 days in a month while chronic migraine occurs more than 15 days.[2]

The prevalence of headache was peak in midlife i.e. low among adolescent and after the age of 60yrs. Migraine rank among the top 20 causes of disease burden as per the YLD criteria. Headache is common in urban areas and it is found to be more frequent in female patients aged more than 21yrs.[3]

The international classification of headache disorders outlines the migraine types as

- migraine with aura
- migraine without aura
- chronic migraine
- Menstrual migraine. [4]

Migraine is a neuronal event that may be caused by a hereditary susceptibility of the brain and various environmental triggers like stress, food habits, sensory overload, sleep pattern, changes in weather. It may occur in patients who have a genetically sensitive nervous system. [5]

The diagnostic methods that are involved in migraine prophylaxis includes recognizing the pattern, recognizing the disease, taking the patient's detailed medical history. [6]

The pathophysiology involves the trigeminovascular system and results in the release of various inflammatory peptides, including calcitonin gene- related peptide (CGRP), substance P, neurokinin A, and nitric oxide. The resultant perivascular inflammatory response influences the trigeminal nucleus caudalis in the brainstem and cervical cord area, transferring pain to the upper areas of the brain. This leads to a state of hyperexcitability or cortical sensitization, resulting in the pain of migraine.[5,7]

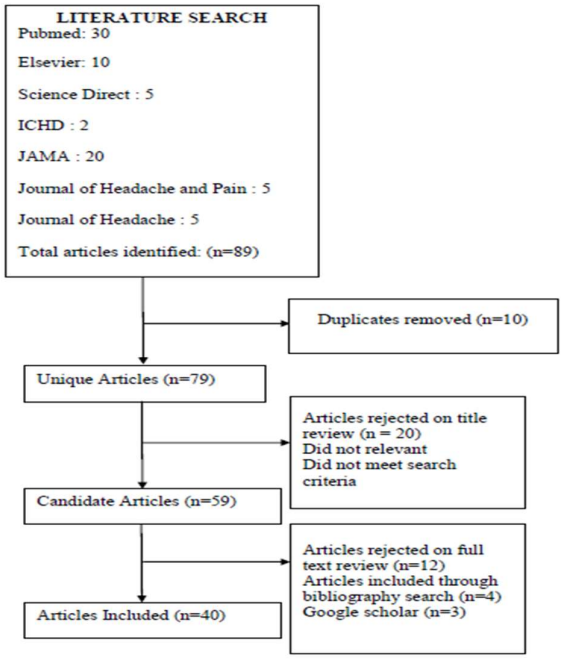
The current prophylactic treatment includes beta blockers, antidepressants, anticonvulsants, angiotensin blockers, calcium channel blockers, non- steroidal anti-inflammatory drugs, neutraceuticals, triptans. New biologics for migraine prophylaxis includes Eerenumab, Fremanezumab, Galcanezumab. The non – pharmacological therapies that can help to prevent migraines are relaxation, acupuncture, massage, cognitive behavior therapy and biofeedback techniques.[8]

The aim of the present review study is to assess the prophylactic treatment pattern among the patients diagnosed with migraine and to provide updated guidelines in the use of novel preventive therapy for migraine in adults.

METHODOLOGY

This is a systematic review that answers a formulated question by collecting and summarizing all the empirical evidences that fits the study. Studies were identified by searching electronic databases including the journal of headache and pain, American academy of neurology, the New England journal of medicine, American Medical Association, Science direct, PubMed, Embase (Elsevier), and Google Scholar [2000-2020]. Observational studies, including randomized double blind study, placebo controlled study, prospective study, non-randomized open label study that address the prophylaxis treatment of migraine. All studies that include the following terms in their keywords as migraine, prophylaxis "treatment" "Monoclonal antibody" "Beta blockers" "Anticonvulsant" were selected. Articles were rejected on abstract review if they were review articles, case studies, or qualitative studies.

Data quality and extraction



Guidelines for migraine prevention

According to Canadian Headache Society Guideline for Migraine Prophylaxis

Migraine prophylactic therapy should be considered

- In patients whose migraine attacks have a significant impact on their lives despite the use of acute medications, trigger management or the lifestyle modification strategies.
- For patients with greater than three moderate or severe headache days in a month, when acute medications are not reliably effective.
- For patients with greater than eight headache days in a month even when acute medications are optimally effective because of the risk of medication overuse headache.[9]

Table 1: Canadian headache-society guideline for migragaine prophylasis [9]

Drug	Recommendation Strength	Quality of Evidence
Topiramate	Strong	High
Propranolol	Strong	High
Metoprolol	Strong	High
Amitriptyline	Strong	High
Nadolol	Strong	Moderate
Gabapentin	Strong	Moderate
Candesartan	Strong	Moderate
Butterbur	Strong	Moderate
Riboflavin	Strong	Low
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low
Divalproex	Weak	High

#Source: https://www.guidelinecentral.com/summaries/canadian-headache-society-guideline-for-migraine-prophylaxis/#section-420

According to the Guidelines by the German Migraine and Headache Society and the German Society of Neurology

The purpose of this guideline is to optimize the treatment of acute migraine attacks and the prevention of migraine.

The duration of the attacks, according to the definition of the International Headache Society (IHS), is between 4 and 72 hours. In children, the attacks are shorter and may manifest without headache, but only with severe nausea, vomiting and dizziness. The localization of the head pain is more often bilateral.[10]

An updated AHS Guidance on Preventive treatment of Migraine

Consider preventive treatment for migraine patients in any of the following situations

- Migraine attacks are frequent (≥4 migraine headache days per month) and/or the attacks interfere with patients' daily routines even with acute treatment
- There is a contradiction to failure, or overuse of acute treatments
- Acute treatments lead to adverse events
- The presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine,
- Migraine with prolonged aura or migrainous infarction (to prevent neurologic damage, as based on expert consensus. [11]

The American Migraine Prevalence and Prevention Study outlined recommendations when daily pharmacological treatment should be initiated

- Prevention should be initiated: At least six headache days per month; at least four headache days with at least some impairment; at least three headache days with severe impairment or requiring bed rest.
- Prevention should be considered with: Four to five migraine days per month with normal functioning;
- Two to three migraine days per month with some impairment; two migraine days with severe impairment.
- Prevention is not indicated with: Less than four headache days per month and no impairment; zero or one headache day per month regardless of impairment. [12]

Analysis of the Evidence On Preventive Therapy

U.S. Headache Consortium migraine guidelines have developed preventive therapy after analysis of data from hundreds of clinical trials on the prevention of migraine. The members of U.S. Headache Consortium, based on the data from clinical trials, categorized the individual drugs in five groups.

Table 2: Strength of the Evidence for Clinical Benefits of Specific Drugs Used in the Prevention of Migraine [13]

Drug Categories	Preventive Medicines	Clinical Benefits
GROUP 1	Amitriptyline, Divalproex sodium, Propranolol, Timolol	Medium to high efficacy, good strength of evidence, mild to moderate side effects and infrequent to frequent side effects
GROUP 2	Aspirin alone, Atenolol, Fenoprofen, Magnesium, Mefenamic acid, Metoprolol, Metoprolol, Nadolol, Naproxen, Nimodipine, Verapamil, Vitamin B_2	Lower efficacy than group 1 drugs or limited strength of the evidence and mild to moderate side effects.
GROUP 3	Bupropion, Cyproheptadine, Diltiazem, Doxepin, Fluvoxamine, buprofen, Imipramine, Nortriptyline, Sertraline, Protriptyline, Tiagabine, Topiramate, Trazodone, Venlafaxine, Phenelzine	Clinically efficacious based on consensus and clinical experience but no scientific evidence of efficacy. (Mild to moderate side effects
GROUP 4	Methysergide	Medium to high efficacy, good strength of evidence but there are concerns about side effects
GROUP 5	Acebutolol, Carbamazepine, Clomipramine, Lamotrigine, Nabumetone, Nicardipine	Evidence indicates no efficacy over placebo
GROUP 6	Erenumab, galcanezumb,fermanezumab	Medium to high efficacy, good strength of evidence, mild to moderate side effects, highly efficacious when compared with placebo

RESULTS

The literature search was performed and around 89 articles were selected, out of which 10 articles was eliminated due to duplication and the 79 unique articles was taken into account, and then 20 articles was rejected based on the title review and that did not met the study criteria. 59 candidate articles was considered, out of which 12 article were rejected based on full text review, 4 rejected based on the bibliography search and 3 on google scholar and Finally, about 40 articles were included for the study.

Table 3: List of articles included for the study

S.No	Author name	Year of publishing	Sample size	Methodology	Conclusion
1.	Peter j. goadsby *et al.,*	2020	955 patients	Randomized controlled trial	Erenumab administered subcutaneously at a monthly dose of 70mg or 140 mg significantly reduced migraine frequently.
2.	Diener HC., Forder reuther,s., Gaul, c.*et*	2020	1671 patients	Cohort study	Monoclonal antibodies against CGRP (Fremanezumab and galcanezumab) are superior to placebo.

	al.,				
3.	Richard B. Lipton *et al*.,	2019	677 patients	Double-blind, placebo controlled study	Erenumab-treated patients with CM experienced clinically relevant improvements across a broad range of patient-reported outcomes.
4.	Jeffrey L. Jackson *et al.,*	2019	108 trails	Randomized controlled trials, placebo-controlled	Propranolol is better than placebo for episodic migraine headache
5.	Tao gut *et al.,*	2018	45 patients	Meta analysis	The data demonstrated brain biochemical changes underlying the effect of acupuncture treatment of migraine
6.	Stephen D Silberstein, *et al.,*	2017	1130 patients	Randomized , double blind , placebo controlled pilot study	Fremanezumab as a preventive treatment for chronic migraine resulted in a lower frequency of headache than placebo in this 12-week trial.
7.	Omid Hesam *et al.,*	2017	140 patients	Randomized double-blinded study	Pregabalin, has comparable efficacy with valproate sodium in reducing migraine frequency, intensity, and duration of attacks.
8.	Macrio cavalcarte salmito, *et al.,*	2016	88 records	An observational longitudinal retrospective study	Prophylactic medications used to treat VM improve the symptoms of the disease.
9.	Chris Cameron *et al.,*	2015	133 trials	Randomized controlled trials	Standardized dose triptans are associated with better outcomes.
10.	Marcelo E. Bigal *etal.,*	2008	24,000 patients	Longitudinal population based study	EM sufferers develop TM at the rate of 2.5% per year. Any use of barbiturates and opiates was associated with increased risk of TM after adjusting for covariates, while triptans were not.
11	Bianca Raffaelli et al.,	2019	16 patients	Retrospective pooled analysis	In this small, self-selected cohort, the results indicate a therapeutic effect of monoclonal antibodies targeting the CRGP pathway in chronic migraine prevention after treatment termination up to 12 weeks.
12	Jeffrey L. Jackson et al.,	2019	108	randomized controlled trials, placebo-controlled	propranolol is better than placebo for episodic migraine headache.
13	Richard B. Lipton et al.,	2019	667	double-blind, placebo controlled study	Erenumab-treated patients with CM experienced clinically relevant improvements across a broad range of patient-reported outcomes.
14	Janet H. Ford, et al.,	2019		Randomized trial	Patients with episodic migraine treated with galcanezumab reported significant and clinically meaningful improvements in daily functioning and decreased disability compared with patients who received placebo.
15	Wildete Carvalho Mayrink et al.,	2018	34	Randomised, placebo controlled double blinded study	Acupuncture can be considered an auxiliary treatment for chronic headache,reducing the intensity of pain, and improving the quality of life in patients with this painful condition.

16	Tao Gu et al.,	2018	45	Meta analysis	The data demonstrate brain biochemical changes underlying the effect of acupuncture treatment of migraine.
17	Juliana VanderPluym, et al.,	2018	1170 patients	post hoc analysis of data	There was an increased number of headache-free days with normal functional performance on all measures for the patients with EM and some measures for patients with CM in the fremanezumab-treated groups.
18	Holland C. Detke, et al.,	2018	1903 patients	Randomized, double-blind, placebo-controlled REGAIN study	Both doses of galcanezumab were superior to placebo in reducing the number of monthly MHDs. Galcanezumab appears efficacious, safe, and well tolerated for the preventive treatment of chronic migraine.
19	Emily Shao et al.,	2017	2228	Descriptive exploratory study	Migraine is an increasingly common presentation to the Emergency department. The medications that are prescribed in the ED for migraine is varied and are not always in line with current evidence for the treatment of migraine
20	Amy A. Gelfand et al.,	2017	30	randomized, double-blind, placebo controlled pilot study	Migraine days in the Final 4weekswere lower in the melatonin group compared with the placebo group, which could be due to chance.
21	Stephen D. Silberstein, et al.,	2017	1130 patients	randomized, double-blind, placebo controlled, parallel-group trial	Fremanezumab as a preventive treatment for chronic migraine resulted in a lower frequency of headache than placebo in this 12-week trial.
22	Kai Le, Dafan Yu, Jiamin Wang, et al.,	2017	465 patients	A meta-analysis of randomized controlled trials	Topiramate may not achieve a more effective clinical trial endpoint than placebo in the prevention of migraines in patients less than 18 years of age, and topiramate may lead to more side effects or adverse vents in the included patients.
23	Omid Hesam et al.,	2017	140	randomized, double-blinded study	pregabalin, has comparable efficacy with valproate sodium in reducing migraine frequency, intensity, and duration of attacks
24	Marcio Cavalcante Salmito et al.,	2016	88 records	An observational, longitudinal, retrospective study	Prophylactic medications used to treat VM improve the symptoms of this disease,but there is no statistically significant difference between the responses of prophylactic drugs.The time of vestibular symptom seems to increase the benefit with prophylactic treatment.
25	Chris Cameron et al.,	2015	133	randomized controlled trials	Standard dose triptans are associated with better outcomes than ergots, and most triptans are associated with equal or better outcomes

					compared with NSAIDs, ASA, and acetaminophen.
26	Márcio Cavalcante Salmito et al.,	2015	87.7% patients met 2001 criteria & 77.8% met 2012 criteria	cross-sectional historical cohort study	The 2012 diagnostic criteria for VM limited the diagnosis of the disease to a smaller number of patients, mainly because of the type, intensity, and duration of dizziness. Patients diagnosed with migraine and associated dizziness demonstrated improvement after prophylactic treatment of VM, even when they did not meet diagnostic criteria.
27	Jeffrey L. Jackson et al.,	2015	4789	Randomised controlled trial	The current practice of tailoring prophylactic medication according to patient characteristics and expected side effects is a good approach
28	Srinish Gopalakrishnan et al.,	2014	82	comparative, double-blinded, randomized controlled study	A minimum dose of 10 mg may be safely used without any increased risk of adverse effects.
29	Dorota Talarska,et al.,	2014	125 females	multivariate analysis	Headache frequency emerging The identification of factors that trigger the onset of migraines
30	Francesco Raudino et al.,	2014	75	Meta analysis	a significant number of patients require longer prophylaxis than usually advised by the guidelines. Besides, in a significant number of patients, one drug previously effective became ineffective if prescribed again after suspension.
31	Karin Meissner, MD et al.,	2013	9278	Randomized placebo contol trail	Sham acupuncture and sham surgery are associated with higher responder ratios than oral pharmacological placebos
32	Raffaella Pizzolato et al.,	2011	47	uncontrolled, open-label, observational, prospective study	pregabalin may represent an efficacious and safe anti migraine agent in both episodic and chronic migraine patients.
33	Carolina Lemos, PhD; et al.,	2010	188	Case control study	confirmed the involvement of syntaxin 1A in migraine susceptibility regarding rs941298.
34	Ahmed M. Ali et al.,	2010	40	randomized open-label study,	effective and better tolerated than topiramate monotherapy, we recommend the use of this combination in migraine prophylaxis.
35	WilliamJ. Mullally et al.,	2009	64	Randomized, prospective, single blind, single center controlled trial.	Biofeedback is an extremely costly and time-consuming treatment modality that, in our study, provided no additional benefit when compared to simple relaxation techniques alone, in the treatment of migraine and tension type headaches in adults.

36	Marcelo E. Bigal et al.,	2008	24000	Longitudinal Population-Based Study	EM sufferers develop TM at the rate of 2.5% per year. NSAIDs were protective depending on the headache frequency.
37	Jan Lewis Brandes, MD et al.,	2007	1461	Two replicate, randomized, double-blind, single attack, parallel-group studies	Sumatriptan, 85 mg, plus naproxen sodium, 500 mg, as a single tablet foracute treatment of migraine resulted in more favorable clinical benefits compared with either monotherapy, with an acceptable and well-tolerated adverse effect profile.
38	Jan Lewis Brandes, MD et al.,	2000	483	Randomised controlled trial	Topiramate showed significant efficacy in migraine prevention withinthe first month of treatment, an effect maintained for the duration of the doubleblind phase.
39	Ninan T. Mathew et al.,	2004	143	4-week, single-blind, placebo baseline period was followed by a 12-week,double-blind, treatment period	Gabapentin is an effective prophylactic agent for patients with migraine. In addition, gabapentin appears generally well tolerated with mild to moderate somnolence and dizziness
40	James D. Gomersall And Alice Stuart	1973	26	A double-blind controlled clinical trial of crossover design	Amitriptyline was found to have the greatest effect in reducing attacks with a short warning and in which no specific cause could be recognized. It had least effect in attacks with a long warning and recognized as due to fatigue. The drug was effective only in reducing those attacks with shorter duration and its effect was irrespective of severity. A dosage of between 10 and 60 mg, usually taken at night, was found to be adequate.

DISCUSSION

The current options for migraine prophylaxis are, the majority of prophylactic treatments are adopted from alternate indications, including propranolol (β-blocker), amitriptyline (antidepressant), valproate and topiramate (both anticonvulsants). Stephen D. Silberstein, *et al., (*2021) and Ahmed M. Ali*et al., (*2010) were also stated the above finding in their study on migraine prophylaxis.

Diener, HC., Förderreuther, S., Gaul, C. *et al.* (2020) in their study demonstrated that monoclonal antibodies are very effective prophylaxis in the treatment of chronic migraine. Current prophylactic therapies can suffer from a lack of specificity, poor tolerability, potential side effects and limited efficacy, leading to dissatisfaction in a large proportion of patients. On a more positive note and borne from the clinical success of the gepant small molecule CGRP receptor antagonists, several monoclonal antibodies (mAbs) have been developed that target either CGRP or its receptor. As reviewed all phase III clinical trials for CGRP targeted mABs ―umabs‖ have proven successful with first to market compounds eagerly awaited. In parallel to the development of novel therapeutics for migraine, there is a growing literature on the use of neuro modulatory approaches. These non-pharmacological approaches are reviewed and represent an ever-increasing area of clinical practice.

The identification of a potential 5-HT1F action for the triptans has led to the development of specific 5-HT1F agonists termed the ditans. Jan Lewis Brandes, MD *et al* (2007), in their found that, sumatriptan resulted in more favorable clinical benefits compared with either monotherapy, with an acceptable and well-tolerated adverse effect profile. Lasmiditan is currently the most advanced molecule that has

successfully completed phase III clinical trials for migraine with no indication of any cardiovascular contraindications that limit the utility of the triptans.

Similarly, bench-to-bedside approaches identified increased circulating calcitonin gene-related peptide (CGRP) levels in animal and human experimental migraine models as well as during spontaneous attacks As such, CGRP has emerged as a key neuropeptide target for migraine therapy.48 Richard B. Lipton *et al* (2019) and Antonio Russo *et al.,* (2020) were observed in their study that Erenumab-treated patients with CM experienced clinically relevant improvements across a broad range of patient-reported outcomes.

The initial attempts to develop small molecule antagonists for the CGRP receptor gepants are documented from the initial positive results with Olcegepantto the detrimental identification of potential hepatotoxicity following their testing for migraine prophylaxis. Despite this off-target class effect on liver enzymes, two small molecule antagonists, Ubrogepant and Rimegepant, remain in development for acute migraine therapy. Unfortunately, a single clinical trial exploring a dual orexin receptor antagonist failed to show any effect in migraine prophylaxis; however, several limitations likely explain this negative result. In conjunction with orexinergic research, the hypothalamic oxytocin, PACAP and Neuropeptide Y pathways along with their clinical potential are discussed. One key mechanism that remains under investigation is the inhibition of nitric oxide synthase.

Clinical studies have demonstrated that the triptans (eg. Almotriptan, eletriptan, frovatripan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) as well as an aspirin/acetaminophen/caffeine combination are effective for the abortive treatment of menstrual migraine. Efficacy rates of these therapies for the treatment of menstrual migraine are similar to those observed for non-menstrually related attacks.

Valproic acid, an anticonvulsant drug is a simple 8-carbon, 2-chain fatty acid. Several subsequent randomized placebo controlled studies have confirmed its efficacy, with responder rates ranging between 43% and 48% with dosages ranging from 500 mg per day to 1500 mg per day. Extended-release (ER) Divalproex sodium has also been shown to be effective for migraine prevention, and compliance and side effect profile may be more favorable with this formulation.

Clinical trials with the TCA amitriptyline have reported a 50% to 70% reduction in the number and in intensity of migraine attacks, with doses ranging from 10 to 100mg daily. Trials comparing amitriptyline with the beta blocker propranolol have reported similar efficacy. The selective serotonin reuptake inhibitors (SSRIs) have not shown consistent benefits in migraine prophylaxis. A few small, short-term trials with fluoxetine reported benefits.

A U.S. Headache Consortium meta-analysis concluded that relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive behavior therapy may be considered as treatment options for the prevention of migraine. Additionally, behavioral therapy (i.e., relaxation, biofeedback) may be combined with preventive drug therapy (i.e., propranolol, amitriptyline) for patients to achieve additional clinical improvement for migraine relief.

CONCLUSION

There is an array of options for the acute and prophylactic management of migraine. Significant advances are currently being made in the prophylactic treatment of migraine, which open the new and promising scenarios in migraine management. Neurologists, general practitioners, pharmacists and patients all need to be well informed about migraine and the new treatment options for migraine prophylaxis. A pooled analysis of clinical trial results suggests that, migraine prophylaxis may help to prevent migraine severity, migraine, frequency, migraine chronification, and improve quality of life. The choice of a prophylactic agent should be tailored to the patient‘s needs and expectations. Along with pharmacological agents, patient education, lifestyle factors, overuse of acute medication, and co-morbidities all need to addressed in a multidisciplinary treatment plan to ensure optimal management of migraine. Only flunarizine has sufficient evidence to be considered probably effective for migraine prevention in children. Agents commonly prescribed for children, such as propranolol and topiramate, have conflicting results in studies. Other agents, including cyproheptadine, amitriptyline, valproic acid, and levetiracetam, have insufficient data in children. More quality randomized controlled trials are needed in this population.

Large clinical trials are especially needed in this field and will hopefully allow a better understanding of headache disorders, as well as a more individual-based approach to treatment in the future.

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