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Title:
The Pharmacologic Prophylaxis of Pediatric Migraine: A Systematic Review, Survey and Design of a Randomized Controlled Trial

(*A thesis submitted in partial fulfillment of the requirements for the degree of MSc Epidemiology*)

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LEGEND

χ^2: Chi square
AHS: American Headache Society
ANOVA: Analysis of variance
CAM: Complimentary and alternative medicine
CANTAB: Cambridge Neuropsychological Test Automated Battery
CBT: Cognitive behavior therapy
CHS: Canadian Headache Society
CI: Confidence interval
DSMB: Data and Safety Monitoring Board
FDA: Food and Drug Administration
ICHD: International Classification of Headache Disorders
IHS: International Headache Society
Kg: Kilograms
MCID: Minimal clinically important difference
MedDRA: Medical Dictionary for Regulatory Activity
Mcg: Micrograms

Mg: Milligrams
N: Number
NIH: National Institutes of Health
NIMM: Non-Inferiority Margins in Migraine Research
OHSN-REB: Ottawa Health Science Network Research Ethics Board
OR: Odds ratio
PDF: Portable Document Format
PedMIDAS: Pediatric Migraine Disability Assessment Scale
PRN: Pro re nata (as needed)
qAM: Quaque die ante meridiem (every day before noon)
qHS: Quaque hora somne (every night at bedtime)
REDCap: Research Electronic Data Capture
RevMan: Review Manager
RCT: Randomized controlled trial
SAS: Statistical Analysis System
SD: Standard deviation
WHO: World Health Organization

ENGLISH THESIS ABSTRACT

Objectives: 1) To describe the state of the evidence for interventions in pediatric migraine, 2) to survey experts regarding non-inferiority margins in migraine research and 3) to design a clinical trial in this area of research.

Methods: A systematic review was carried out to identify randomized, placebo-controlled trials of pharmaceutical and nutraceutical interventions used to prevent migraine in children and adolescents, using Cochrane methods. Secondly, neurologists with expertise in Headache Medicine were invited to participate in a survey regarding their opinions on non-inferiority margins for outcomes used in clinical trials of migraine interventions. Thirdly, a protocol was written for a three-arm, parallel-group, randomized trial comparing the efficacy and safety of topiramate, levetiracetam and placebo for the prophylaxis of pediatric migraine.

Results: The systematic review identified 19 articles of 12 interventions for pediatric migraine. The quality of the evidence was poor and few conclusions could be made. Ninety-nine eligible respondents completed the survey and non-inferiority margins for six outcomes were determined. A randomized controlled trial protocol was developed to determine if topiramate and levetiracetam are superior to placebo, and if levetiracetam is non-inferior to topiramate for the prevention of migraines in children and adolescents.

Conclusions: It is hoped that the results of this thesis can be applied to further the evidence in this area of clinical research.

FRENCH THESIS ABSTRACT

Objectifs: 1) Décrire l'état de la recherche sur la migraine chez les enfants, 2) faire un sondage parmi les experts par rapport aux seuils de non-infériorité pour les essais cliniques sur la migraine and 3) faire la conception d'un essai clinique sur des interventions préventifs pour la migraine chez les enfants.

Méthodes: Une revue systématique a été executée afin d'identifier des essais cliniques sur le sujet d'interventions pharmaceutiques et nutraceutiques pour prévenir la migraine chez les enfants, en utilisant les méthodes Cochrane. Des neurologues avec expertise par rapport aux maux de têtes ont été invités à participer dans un sondage sur le sujet des seuils de non-infériorité utilisés pour la recherche sur la migraine. Un protocol a été developpé pour décrire un essai clinique qui comparera l'efficacité et la tolérabilité de topiramate, levetiracetam et d'un placebo pour la prévention des migraines chez les enfants.

Résultats: La revue systématique a identifiée 19 articles sur le sujet de 12 interventions pour la migraine chez les enfants. La qualité de la recherche était faible et peu de conclusions étaient possibles. Quatre-vingt-dix-neuf répondents ont completés le sondage et six seuils de non-infériorité ont été specifiés. Un essai clinique a été développé afin de determiner si topiramate et levetiracetam sont supérieurs au placebo, et si levetiracetam est non-inférieur à topiramate pour la prévention des migraines chez les enfants.

Conclusions: Les résultats de cette thèse peuvent être appliqués pour améliorer la qualité de la recherche dans ce domaine.

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- Serena Orr: Conceptualized the survey, designed the survey, wrote the protocol, submitted the protocol to the OHSN-REB, carried out the analyses and wrote the manuscript.
- Dariush Dowlatshahi: Helped Dr. Orr in designing the survey, planning survey distribution and reviewed the protocol and manuscript.
- Suzanne N. Christie: Helped Dr. Orr in designing the survey, planning survey distribution and reviewed the protocol and manuscript.
- Timothy Ramsay: Helped Dr. Orr in designing the survey, planning survey distribution and reviewed the protocol and manuscript.
- Jonathan Gladstone: Helped Dr. Orr in planning survey distribution, distributed the survey to members of the Canadian Headache Society, reviewed the protocol and manuscript.
- David Dodick: Helped Dr. Orr in planning survey distribution and reviewed the protocol and manuscript.

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THESIS PART I: SYSTEMATIC REVIEW

1. Background

1.1. The prevalence and impact of pediatric migraine

Migraine is one of the most common diagnoses encountered by the pediatric neurologist. It has been estimated that the worldwide prevalence of migraine is 7.7% in the pediatric age group, with considerable variation with age, whereby the prevalence increases significantly in adolescence[1]. Not only is migraine common, but it also has an important impact on the individual and society in terms of disability. In the 2010 Global Burden of Diseases, Injuries and Risk Factors Study, migraine was the eighth most common cause of global years of life lived with disability amongst the most commonly reported diseases and injuries[2]. A multitude of studies have found that children and adolescents with migraine suffer from impaired health-related quality of life[3–5]. Furthermore, children and adolescents with migraine experience a significant amount of disability related to their headaches[6–8], which engenders important functional consequences on their day-to-day lives. For example, children and adolescents with migraine have inferior academic performance as compared to their peers[9,10]. Therefore, migraine is not only common in the pediatric age group but has important consequences for day-to-day functioning and quality of life.

1.2. The pathophysiology of migraine

Migraine is most often conceptualized as a neurovascular disorder, although its pathophysiology is not completely understood. The pain arising from migraine originates in the trigeminovascular system: nociceptors residing in meningeal blood vessels, cranial sinuses and proximal cerebral blood vessels become activated and send afferent pain signals to the spinal trigeminal nucleus in the brainstem and to the upper cervical spinal cord[11]. It is unclear how these nociceptors become activated at the onset of migraine, although a leading theory implicates

peripheral sensitization provoked by sterile meningeal inflammation. It is thought that a pro-inflammatory state exists in the meninges during migraine and that this state causes a lower threshold for nociceptor activation or perhaps even sustained activation of the nociceptors[12].

From the spinal trigeminal nucleus, second order neurons project to a multitude of brain areas, including the parabrachial nucleus, and several thalamic and hypothalamic nuclei. The second order neurons located in the upper cervical spinal cord also project to several targets in the thalamus and hypothalamus as well as targets in brainstem including the periaquedual gray in the midbrain, the reticular formation and the superior salivatory nucleus[12]. These projections from second order spinal trigeminal and upper cervical neurons are thought to play a role in generating some of the symptoms associated with migraine (eg. nausea, anorexia and fatigue)[11].

As is described above, many of the second order neurons from the spinal trigeminal nucleus and upper cervical spinal cord project to thalamic nuclei. In turn, third order neurons in the thalamus send projections to various cortical areas, with individual nuclei projecting to specific cortical regions (eg. dura-sensitive neurons in the ventroposteromedial nucleus of the thalamus project to the primary somatosensory and insular cortices). These third order thalamic neurons are thought to modulate cortical activity in their respective target regions, and some of the higher order symptoms associated with migraine, such as allodynia and difficulty concentrating, may be explained by activation of these pathways[11].

In addition to these ascending pathways, there are also numerous descending pathways that act to modulate the experience of pain and that may play a role in central sensitization. Various cortical and brainstem regions have a descending influence on the trigeminovascular system, and recent evidence suggests that the hypothalamus also has a modulatory effect on trigeminal nociception[11]. Migraineurs are thought to have altered excitability at the level of the cortex and perhaps also dysfunction of modulatory brainstem regions such as the periaqueducal gray area of the midbrain[11].

Because of the complexity of migraine pathophysiology, migraine interventions are numerous, varied, and have diverse theoretical mechanisms of action.

1.3. General approach to the treatment of pediatric migraine

Given the impact they have not only on patients' lives, but on society as a whole, the optimal treatment of migraines is vital. Treatment requires a multipronged approach. There are two broad classes of interventions for migraines: pharmacological and non-pharmacological. There is also a series of interventions that fall under the umbrella of complimentary and alternative medicines (CAM). A variety of non-pharmacological interventions have been studied for migraine.

1.4. Education and lifestyle changes for the management of pediatric migraine

Firstly, patient education is necessary. Many factors under the patient's control can influence the frequency of migraines. Lifestyle factors appear to have an important impact on primary headaches. Adolescents with low physical activity are more likely to report recurrent headaches[13,14], and amongst those with migraine, low physical activity is associated with higher levels of migraine-related disability[15]. Other lifestyle factors including diet[14,16] and sleep-related problems[17–22] have been shown to have an important relationship with migraine in the pediatric age group. In addition, studies amongst adult migraineurs have shown that dysfunctional coping with stress is prevalent in this population[23–25]. One study amongst children with primary headaches, including migraine, found that poor coping skills were associated with lower quality of life scores[26].

In addition to research documenting the associations above, a few studies have explored the efficacy of lifestyle interventions for pediatric migraine prevention. A randomized trial carried out amongst pediatric migraine patients with known sleep hygiene problems demonstrated that education about sleep hygiene guidelines significantly improved their migraines in regards to several parameters as compared to the control condition[27]. A couple of studies have also tried to assess the effect of removing dietary migraine triggers on migraine parameters in the pediatric

population. One randomized trial compared a high fiber diet to a high fiber diet plus elimination of foods high in vasoactive amines in a sample of children with migraines and found no difference between intervention arms[28]. However, a non-randomized, uncontrolled study found that elimination of a variety of common trigger foods from the diets of children with migraines resulted in 93% of participants reporting significant improvement in their migraines[29]. Therefore, in addressing the treatment of migraines, it is crucial to counsel the patient on lifestyle factors that can impact their headaches, prior to any discussions of active interventions for the migraines.

1.5. Psychological interventions for pediatric migraine

There are several other classes of non-pharmacologic interventions to consider in this patient population, which fall under the umbrella of psychological interventions. Given the fact that children and adolescents with migraine are thought to have issues with stress coping, relaxation therapy has been studied as a prophylactic therapy for migraine. A systematic review published in 2006 identified three studies on relaxation therapy for this indication. The results of the studies were inconsistent, and the reviewers concluded that relaxation therapy might be superior to a wait list condition[30]. Since publication of this review, two studies have explored relaxation therapy techniques in this population and have shown promising preliminary results in regards to the potential of relaxation therapy for pediatric migraine prophylaxis[31,32]. The same 2006 systematic review also pooled the evidence for biofeedback, and found that it did not differ significantly from placebo for the prevention of migraines in children and adolescents[30]. One small study published since then found that biofeedback was effective in yielding a reduction in migraine frequency and severity in a group of children with migraine without aura[33]. Despite the scarce evidence, biofeedback is used frequently in certain pediatric headache practices and has been recommended for select patients in pediatric migraine management guidelines[34]. Cognitive behavior therapy (CBT) has also been assessed for prevention of migraines in children and adolescents. Prior to 2006, two studies had assessed CBT in this population and found no significant differences in its

efficacy as compared to placebo, additional pain behavioral management or a progressive relaxation technique[30]. In 2013, a randomized controlled trial comparing amitriptyline plus headache education to amitriptyline plus CBT in a group of children and adolescents with chronic migraine showed that the arm receiving CBT had significantly greater improvement in the frequency of their migraines and in their migraine-related disability scores[35]. A 2009 Cochrane review carried out a pooled analysis of all psychological treatments for pediatric headache, which included studies on relaxation therapy, biofeedback and CBT and also included children with non-migrainous primary headaches. In total, 15 studies assessed the efficacy of psychological interventions for pediatric headache immediately after treatment, and found a strong effect on immediate pain reduction (OR=5.51, 95% CI: 3.28-9.24). Six of the studies assessed pain at follow-up, and results were also very promising in regards to the efficacy of psychological interventions in reducing headache-related pain (OR=9.91, 95% CI: 3.73-26.33)[36]. A 2006 meta-analysis of psychological interventions for recurrent headaches in children and adolescents came to similar conclusions about the efficacy of these interventions as the 2009 Cochrane review[37]. Thus, there are several non-pharmacologic interventions with varying degrees of evidence for efficacy in the treatment of pediatric migraine.

1.6. Complimentary and alternative medicine for pediatric migraine

The next category of interventions for pediatric migraine pertains to complimentary and alternative therapies (CAM). The National Institutes of Health has defined CAM as a: "group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine"[38]. The use of CAM is increasing[39], and it is currently a multibillion-dollar per year industry in the US[40]. In the pediatric world, headache is the most common reason for CAM use, along with pain[41]. A couple of studies have highlighted the prevalence of CAM use amongst pediatric headache patients. A study carried out in an Italian headache clinic found that 76% of the children with headaches, most of whom had migraines, reported using CAM,

with the most common modalities being herbal remedies or vitamin and mineral supplements[42]. This study may have overestimated the use of CAM given the highly selected population, but a study amongst a population-based sample of US children found that 30% of the children reporting headaches were also using CAM[43]. Therefore, it indeed appears that CAM use for headaches is common in children and adolescents, though an accurate estimate of the prevalence is not currently available. A variety of CAM modalities have been studied for pediatric headache: acupuncture, homeopathy, nutritional supplements, vitamins, herbal preparations and manual therapies including osteopathy and chiropractic techniques[44]. Two studies have found acupuncture to be effective in pediatric migraine prophylaxis. In one study, a small group of children with migraine were randomized to acupuncture or sham acupuncture. The acupuncture group had significantly greater reductions in the frequency and intensity of their migraines[45]. The second study was a more recent randomized trial comparing laser acupuncture to sham laser acupuncture in a group of children and adolescents with primary headaches. Those randomized to laser acupuncture had significantly greater decreases in migraine frequency and intensity as compared to the sham group[46]. Homeopathy has only been studied for this indication in one instance. A multicenter, open-label, non-randomized, prospective study assessed a variety of individualized homeopathic remedies for the prevention of migraines in children aged 5 to 15 years[47]. Although 209 participants were recruited, only 168 were included in the analyses and no intention-to-treat analyses were attempted. During the first three months of treatment, all outcomes changed favorably. Migraine frequency, intensity and duration decreased significantly over time and the percentage of children with absenteeism from school was significantly reduced. However, the lack of a control group and the diversity of treatments used makes it difficult to draw conclusions about the efficacy of homeopathy for this indication from this study. Although osteopathy has been assessed for cervicogenic headache in children, no studies have examined its potential efficacy for pediatric migraine[44]. Thus, some evidence exists in relation to the efficacy of acupuncture and

homeopathy for pediatric migraine prophylaxis, but other CAM modalities such as osteopathy and energy medicine have not yet been explored for this indication.

1.7. Nutraceuticals for pediatric migraine

Nutraceuticals, defined as "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease"[48], comprise nutritional supplements, vitamins and herbal preparations. A variety of nutraceuticals have been assessed for the prophylaxis of pediatric migraine. In this systematic review, evidence derived from eligible randomized controlled trials on the efficacy of nutraceuticals for this indication will be reviewed. However, the magnitude of evidence from non-randomized studies is not negligible. The main nutraceuticals that have been studied for pediatric migraine prophylaxis are: butterbur, riboflavin, magnesium, coenzyme Q_{10}, fish oils and combination therapies[49].

1.7.1. Butterbur

One open-label study amongst a sample of children and adolescents with migraine found Petadolex®, a formulation of butterbur, to be effective for migraine prevention, with results showing that after 4 months of treatment the frequency of migraines was significantly reduced, with no major adverse events reported[50].

1.7.2. Riboflavin

Two non-randomized studies have explored the potential for riboflavin as an intervention in pediatric migraine prevention. In a retrospective chart review involving a small series of children with a variety of headache disorders, the majority of whom had migraine, riboflavin was found to significantly decrease migraine frequency in the first 4 months of treatment, but not beyond that initial treatment period[51]. Riboflavin was also studied retrospectively in a group of adolescents with chronic headaches, most of whom had chronic migraine, and was found to yield improvement in 73% of the subset of participants with chronic migraine[52]. Thus, based on non-randomized

evidence, it appears that riboflavin is a promising prophylactic therapy for migraine in children and adolescents.

1.7.3. Magnesium

Only one non-randomized study has evaluated magnesium for the prophylaxis of pediatric migraine. This small open-label study assessed magnesium in a variety of childhood periodic syndromes including migraine. Overall, 77.5% of the participants, of whom most had migraine, had a good clinical response whereby their attacks were eliminated or reduced to less than one third of the baseline frequency[53]. The size of the study and heterogeneity of the participants renders it low quality evidence for the question of interest.

1.7.4. Coenzyme Q_{10}

One non-randomized study evaluated the use of coenzyme Q_{10} for migraine prophylaxis in a relatively large sample of children and adolescents who were found to be deficient in coenzyme Q_{10}. After variable treatment periods, participants benefited from a statistically significant reduction in migraine frequency and migraine disability scores[54]. This study therefore shows promise for coenzyme Q_{10} as a targeted intervention in pediatric migraine prevention.

1.7.5. Fish Oils

In children and adolescents, only one study assessed the efficacy of fish oils in migraine prevention and it was randomized by design[55]. Therefore, it will not be summarized here.

1.7.6. L-5-Hydroxytryptophan

L-5-hydroxytryptophan is a naturally occurring amino acid with antidepressant properties that has also been studied for migraine, but there is only one study that was carried out in the pediatric population and it was randomized[56]. Therefore, it will not be reviewed here.

1.7.7. Combination Therapies

There are three non-randomized studies on the efficacy of combination nutraceutical therapies for migraine in the pediatric population. Each of these studies assessed the efficacy of the same combination of ginkgolide B, coenzyme Q_{10}, magnesium and riboflavin over time[57–59], with only one of the studies having a comparison intervention[59]: a combination of L-tryptophan, 5-hydroxytryptophan, vitamin PP and vitamin B_6. All three studies demonstrated that the combination therapy yielded statistically significant decreases in migraine frequency over time, and the study with a comparison group demonstrated that the ginkgolide-containing combination therapy was superior to the alternate therapy. Therefore, this combination of ginkgolide B, coenzyme Q_{10}, magnesium and riboflavin may be effective for the prevention of migraines in children and adolescents based on non-randomized preliminary findings.

1.8. Pharmaceuticals for Pediatric Migraine

A host of pharmaceutical medications have been studied for pediatric migraine prophylaxis. In this systematic review, we will summarize the evidence from eligible randomized controlled trials for pharmaceutical agents in pediatric migraine prophylaxis. However, many non-randomized studies also exist. Here, a brief overview of the non-randomized literature in this area will be provided.

1.8.1. Antiepileptic Medications

Topiramate is one of the best-studied medications for migraine prophylaxis in both adults and children. The efficacy and safety of topiramate for the prevention of migraines in children and adolescents has been assessed in four non-randomized studies. Three retrospective chart reviews have been carried out. Two of the chart reviews did not have a comparison group, and found that over time, topiramate yielded significant reductions in migraine frequency and other headache parameters[60,61]. The other retrospective study compared topiramate prophylaxis to flunarizine prophylaxis in a relatively large group of pediatric patients, and found that both interventions

resulted in reductions in migraine frequency, with no significant group differences noted[62]. One prospective open-label study evaluated the efficacy of topiramate in the prevention of migraines for children with migraines refractory to other treatments. This small study, which included only 24 participants, did not yield any significant differences in migraine frequency over time, though migraine severity and associated symptoms did significantly abate with topiramate[63]. Adverse events rates varied between 10% and 33% in these four studies, with the most common side effects reported being weight changes, anorexia, cognitive side effects, paresthesias and drowsiness[60–63]. Evidence from non-randomized studies therefore supports the efficacy and tolerability of topiramate for the prophylaxis of pediatric migraine.

Valproic acid has also been frequently studied as a potential intervention for the prevention of migraines in this age group. The non-randomized literature on valproic acid as a prophylactic agent for pediatric migraine is comprised of five studies. Two of these studies were retrospective chart reviews, encompassing a total of only 67 patients[64,65]. Both of these studies hinted at a favorable response to divalproex, which is the enteric-coated counterpart of valproic acid. The other three non-randomized valproic acid studies had open-label prospective designs, with a much larger number of participants: in total, 368 children and adolescents with migraine were included in these studies[66–68]. One of the studies did not assess efficacy, but only safety and tolerability of divalproex for this indication[67]. The two studies that reported on efficacy found that divalproex and sodium valproate both significantly decreased migraine frequency over time and lead to improvement in other clinical outcomes[66,68]. The safety study uncovered a high rate of side effects: 88% of the participants reported at least one side effect, with the most common being weight gain, nausea, somnolence and upper respiratory tract infections. Five serious adverse events were reported, of which only one, hyperammonemia, was deemed related to divalproex sodium extended-release. The investigators also found that, overall, ammonia levels increased during treatment[66]. The other studies reported similar side effect profiles and overall rates of side effects between 48 and 84%[64–

[66,68]. Based on this non-randomized data, it is evident that valproic acid might be effective for pediatric migraine prophylaxis, but that it is associated with a significant rate of side effects, not to mention its questionable use in teenaged females given its known teratogenic effects, which has lead to recommendations to avoid its use in women of childbearing potential whenever possible[69].

Although traditionally, the only two antiepileptic medications that have been commonly used clinically and studied for pediatric migraine prophylaxis are topiramate and valproic acid, interest in the potential use of levetiracetam for this indication is emerging. Two very small studies prospectively assessed the efficacy and safety of levetiracetam for pediatric migraine[70,71]. Migraine frequency decreased significantly over time in both studies and tolerability was favorable. In each study, approximately 10% of the patients experienced behavioral or psychiatric adverse events, which have been well documented with this medication. More evidence is required prior to drawing conclusions about the efficacy and safety of levetiracetam for the prevention of migraines in pediatrics, but the preliminary, very limited data is promising.

1.8.2. Calcium-Channel Blockers and Beta-Blockers

Three medications classified as calcium-channel blockers, flunarizine, nimodipine and cinnarizine, and two medications classified as beta-adrenergic blockers, propranolol and timolol, have been studied in this population. In fact, propranolol was the most commonly prescribed migraine prophylactic medication amongst a group of US pediatricians based in Michigan in a survey on pediatric migraine management patterns[72].

Three non-randomized studies have looked at flunarizine as a prophylactic agent for pediatric migraine. One of the studies was a relatively large retrospective chart review[62], and two of the studies were small, prospective-open label studies[73,74]. The retrospective study compared the efficacy of flunarizine to that of topiramate in 261 children and adolescents with migraine and found no difference in responder rates comparing the two medications; both groups had favorable responses[62]. Both of the prospective studies found preliminary evidence for the efficacy of

flunarizine in pediatric migraine prophylaxis: in one study, 66% of the patients improved[74], and in the other study, all patients had some response to flunarizine[73]. In two of the studies, no adverse events were reported[73,74]. In the retrospective study, 6% of the participants taking flunarizine reported adverse events, with weight gain, drowsiness and dizziness being the most common. Thus, flunarizine does appear to have some potential for pediatric migraine prophylaxis based on non-randomized evidence. Nimodipine and cinnarize have not been assessed in any non-randomized studies in this population.

The literature is devoid of evidence from non-randomized studies for the use of timolol in pediatric migraine prophylaxis. One non-randomized study, with a retrospective chart review design, assessed the efficacy of propranolol for the prevention of migraines in a sample of children and adolescents. In this study, both propranolol and amitriptyline yielded significant responder rates, with no differences between the groups except for higher rates of side effects reported in the amitriptyline group[75]. This one study therefore supports the use of propranolol in this population.

1.8.3. Antidepressants

Amitriptyline and trazadone are the two antidepressants that have been commonly used and studied for the prevention of migraines in the pediatric age group. In fact, in many centers, practitioners use amitriptyline as a first line pharmacologic prophylactic agent for this indication[76].

Two retrospective chart reviews[75,76] and one prospective, open-label study[77] have explored the efficacy and safety of amitriptyline for prevention of migraines in children and adolescents. Both retrospective studies found favorable efficacy results for amitriptyline: one of the studies demonstrated that 89% of participants had a positive response to amitriptyline with a significant decrease in migraine frequency[76] and the other found that both amitriptyline and propranolol yielded significant decreases in migraine frequency over time[75]. Migraine frequency decreased significantly and 84.2% of children demonstrated improvement in their headaches with amitriptyline prophylaxis in the prospective study[77]. Although two of these studies did not report

on side effects, one of the studies found that amitriptyline resulted in higher adverse event rates than propranolol, with weight gain, fainting, drowsiness and tremor being the most commonly reported side effects[75]. Evidence from non-randomized trials supports the current widespread use of amitriptyline to prevent migraines in children and adolescents. There are no non-randomized studies that have explored the efficacy of trazadone for this indication.

1.8.4. Antiemetics

Several antiemetics might be useful in pediatric migraine prophylaxis: domperidone, metoclopramide and cyproheptadine. Domperidone and metoclopramide have not been assessed in any non-randomized studies. The efficacy of cyproheptadine for pediatric migraine prophylaxis has only been tested in one non-randomized study. A retrospective chart review showed that cyproheptadine significantly reduced migraine frequency and was associated with an 83% response rate in a small sample of pediatric migraineurs[76]. Cyproheptadine was associated with sedation and increased appetite, though the proportion of patients with side effects was not specified. Thus, there is little evidence from non-randomized studies to assess the use of antiemetics in pediatric migraine prophylaxis.

1.8.5. Others

There are several other pharmacologic agents used in this context beyond those described in the classes above: Botox, clonidine, papaverine and pizotifen. Two chart reviews retrospectively evaluated the efficacy and safety of Onabotulinumtoxin A (Botox) for the prevention of chronic headaches, including chronic migraine. One small retrospective case series of 6 adolescents with chronic headaches found that all patients responded to Botox injections given every 3 months, with three patients reporting transient side effects: ptosis, neck injection site hematoma and burning at injection sites[78]. The second retrospective study assessed the efficacy of Botox in 45 children and adolescents with chronic headaches. There was a statistically significant decrease in migraine

frequency with the injections. Seven patients had adverse events, including pain at the injection sites, eyelid inflammation, eyelid pain and neck and shoulder myalgias[79]. In addition to these studies, there is a randomized controlled trial currently underway that aims to assess the efficacy and safety of Botox for migraine prevention in adolescents with chronic migraine (clinicaltrials.gov identifier: NCT01662492)[80]. Based on this limited retrospective evidence, there is promise for Botox in pediatric chronic migraine prevention and results from the randomized study will aid in assessing its efficacy more definitively.

Clonidine has been used for migraine prophylaxis in the past, but has fallen out of favor both in the clinical and research communities in the last couple of decades. It has only been assessed in one non-randomized study in the pediatric population. A prospective open-label pilot study amongst children with migraine revealed that 50% of participants had meaningful reductions in their migraine frequencies, with 40% benefiting from complete and lasting remission from their headaches[81]. In this group of 50 children, six developed side effects: three rashes were reported, two children had drowsiness and one child had continuous headaches. There is little evidence to support the use of clonidine for pediatric migraine prophylaxis, though this one study does suggest some potential.

Papaverine and pizotifen have not been assessed in non-randomized studies this indication.

1.9. Conclusions

As is evidenced from the overview above, there is a wide range of therapeutic options for pediatric migraine, none of which have been particularly rigorously or well studied. Most of the evidence for pediatric migraine interventions is derived from low quality, non-randomized studies. Pharmaceuticals remain the mainstay of allopathic medical treatments offered by practitioners looking after children and adolescents with migraine. However, nutraceuticals are an important part of the growing CAM movement, which currently represents a multibillion dollar per year industry in the US[40]. In one Italian study, 76% of children and adolescents in a tertiary care

headache clinic were using herbal therapies and 40% were using vitamin and mineral supplements for their headaches[42]. In the US, 30% of children with headaches reported using CAM therapies, including nutraceuticals, in to a nationally representative survey[82]. Thus, nutraceuticals are increasingly popular, and this is compelling practitioners of allopathic medicine to educate themselves about nutraceutical options.

In this systematic review, we will aim to summarize the evidence from the highest quality randomized studies for the efficacy and safety of pharmaceutical and nutraceutical options in the prophylaxis of pediatric migraine.

2. METHODS

2.1. Objectives

The primary objective of this systematic review is to summarize, evaluate and quantify the evidence for the efficacy of nutraceutical and pharmaceutical interventions in the prophylaxis of pediatric migraine.

The secondary objective of this systematic review is to summarize, evaluate and quantify the evidence for the safety and tolerability of nutraceutical and pharmaceutical interventions in the prophylaxis of pediatric migraine.

2.2. Study Design

The methodology followed in this systematic review adheres to the guidelines set out in the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions[83]. This methodological approach is complimented by consideration of the Guidelines for Controlled Trials of Drugs in Migraine, which were developed in 2012 by the International Headache Society, the leading authority on primary headaches[84]. Stipulations in these guidelines were used to refine the eligibility criteria for studies in this systematic review. The goal of using the guidelines to establish eligibility

criteria was to ensure that only the most methodologically rigorous randomized studies would be included in this review, so as to maintain a summary of the highest quality of evidence.

In addition to the systematic review, meta-analyses were carried out on bodies of evidence that were amenable to pooling. Again, the methodology laid out in the Cochrane Handbook is adhered to for the purposes of the meta-analyses.

2.3. Criteria for Considering Studies for this Review

2.3.1 Types of Studies

The aim of this systematic review is to summarize the highest quality evidence for the efficacy and safety of prophylactic nutraceutical and pharmaceutical pediatric migraine interventions. In order to limit included studies to those of high methodological quality, only randomized, placebo-controlled trials were considered. Parallel-group and cross-over designs were eligible. In order to comply with the recommendations set forth in the International Headache Society Guidelines for Controlled Trials of Drugs in Migraine[84], cross-over studies were required to have a minimum washout period of 4 weeks between study interventions. The purpose of setting a minimum washout period was to avoid the inclusion of studies with biased results due to carry-over effects. The unit of randomization was required to be the individual and cluster-randomized trials were excluded. Limiting eligible studies to those randomized by individual reduces the chance of selection bias, which is often a significant problem with cluster randomized trials[85].

In order to minimize performance bias, included studies were required to blind participants, such that either single-blind or double-blind trials were eligible. Unblinded studies were excluded.

2.3.2 Types of Participants

Only studies limited to pediatric patients, aged 18 years and under, were included. Studies that included adults were considered only if results of a subgroup analysis on patients under the age of 18 years were available. Participants were required to have migraine or a subtype of migraine (eg.

migraine with aura, chronic migraine, probable migraine) as per a set of validated criteria. The three most commonly used migraine criteria in the pediatric literature are the International Classification of Headache Disorders (ICHD) criteria, now in their third iteration[86], the Ad Hoc criteria[87] and the Vahlquist criteria[88]; the latter two sets of criteria were mostly used prior to the first iteration of the ICHD criteria in 1988. Currently, the ICHD criteria are considered the gold standard for the diagnosis of migraine. The ICHD and Vahlquist criteria have both been shown to be valid[89] and the two sets of criteria are consistent with an overall kappa of 0.57 reported in one pediatric study[90]. The Ad Hoc criteria were created in 1962 and are considered to be the predecessor of the ICHD criteria[87]. Although they are more vague than the ICHD criteria, one adult study showed that the Ad Hoc criteria agreed with the ICHD criteria 91.7% of the time[91], indicating high consistency between the two classification systems, and supporting the validity of using the Ad Hoc criteria against the gold standard of the ICHD criteria. There has also been a pediatric study published that found remarkable consistency in migraine prevalence rates regardless of whether the ICHD, Ad Hoc or Vahlquist criteria were used for diagnosis, especially in the case of migraine without aura[92]. Therefore, studies using ICHD, Vahlquist or Ad Hoc criteria were eligible, and other criteria had to be validated in order to be considered for inclusion.

2.3.3. Types of Interventions

As is described in detail in the introduction, there is a wide variety of interventions aimed at preventing migraines in children and adolescents. In order to limit the scope of this review, only pharmacologic and nutraceutical interventions were included. Pharmacologic interventions for pediatric migraine prophylaxis are medications used in allopathic medicine that fall into a variety of categories, listed above (ie. antiepileptic medications, antidepressants, etc). As described above, nutraceuticals are food derivatives that are used for medical purposes and have been defined as: "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease"[48]. Interventions falling out of the scope

of pharmaceuticals or nutraceuticals, such as lifestyle interventions and psychological treatments, were excluded.

2.3.4 Types of Comparisons

All included studies were required to have at least one study arm comprising a placebo control. The placebo control is necessary given that none of these interventions have been adequately studied and therefore assay sensitivity must be established. In addition, the International Headache Society Guidelines for Controlled Trials of Drugs in Migraine[84] state that prophylactic trials for migraine should include a placebo control and they specify that even studies with active comparators should include a placebo arm.

No restrictions were placed on active comparators: any type of active comparator was eligible as long as there was also a placebo comparator arm.

2.3.5 Types of Outcomes

Studies were not excluded based on outcomes. The Cochrane Collaboration recommends that priority outcomes be established but states: "reporting of outcomes should rarely determine eligibility of studies"[83]. For the purposes of this review, any trial with an outcome pertaining to migraine prophylaxis was eligible for inclusion. The primary outcome of interest relates to migraine frequency. The International Headache Society Guidelines for Controlled Trials of Drugs in Migraine[84] stipulate that the primary outcome in migraine prophylaxis trials should be the difference between migraine frequency at the end of treatment or throughout treatment and migraine frequency at baseline. Thus, when available, this outcome was highlighted and used for pooling the results in meta-analyses.

2.3.6 Language of Studies

Eligibility of the studies was not restricted by language of publication. Articles deemed potentially eligible and written in languages other than English or French were translated to English and included if they met all eligibility criteria.

Table 1. Eligibility criteria for studies

Component of Study	Inclusion Criteria	Exclusion Criteria
Study type	• Randomized at individual level • Parallel-group design • Crossover design with minimum washout period of 4 weeks • Single blind • Double blind	• Non-randomized • Cluster randomized • Crossover design with washout period less than 4 weeks • Unblinded
Participants	• Aged 18 years or less • Migraine or migraine subtype as per ICHD criteria, Vahlquist criteria or other validated criteria	• Studies with participants over 18 years with no subgroup analysis on those under 18 years • Non-migraine headaches • Migraine diagnosed with unvalidated criteria
Interventions	• Pharmaceutical interventions • Nutraceuticals interventions	• Lifestyle interventions • Psychological interventions • CAM interventions other than nutraceuticals (eg. acupuncture)
Comparisons	• Placebo • Active comparator if placebo arm included	• Active comparator if no placebo arm
Outcomes	• One outcome must pertain to migraine prophylaxis • Primary outcome of interest is change in migraine frequency over treatment period	• No outcomes relating to migraine prophylaxis

2.4. Search Methods for Identification of Studies

The following databases were searched: MEDLINE including In-Process & Other Non-Indexed Citations (1946- May 19, 2015), Embase (1947 to Week 20, 2015) and Cochrane Central Register of Controlled Trials (CENTRAL, April 2015). All were searched using the Ovid interface. The MEDLINE search strategy was developed by a librarian experienced in systematic review searching (Margaret Sampson), and peer reviewed by another librarian (Janet Joyce), using the PRESS standard[93]. The MEDLINE search was then adapted for the other databases. No language limits were applied but the search was limited to randomized controlled trials and the pediatric age group using validated filters. Included reference lists were screened for additional references. The detailed electronic search strategies are presented in Appendix A.

As well, the International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov were searched on July 2nd 2015 for ongoing or recently completed trials. Authors of potentially eligible unpublished trials were contacted in order to inquire about timing of manuscript publication and access to the unpublished data.

2.5. Screening Process

2.5.1 First Screen Methodology

Two screeners (Serena Orr and Suzanne Nadine Christie) completed the first eligibility screen. The search results were uploaded into the Abstrackr software, which was used to facilitate the first screen of studies. Abstrackr is an open-sourced web-based application available to users at no charge[94]. It is designed to assist researchers in the process of screening references for a systematic review. References are uploaded to Abstrackr and multiple screeners can then use the application to rapidly and efficiently screen the titles and abstracts resulting from the search. This tool allows users to keep track of eligibility decisions made during the first screen. Each reference can be assigned a descriptive tag that summarizes why a particular eligibility decision was made about the given study (eg. excluded because not randomized). Abstrackr stores all eligibility decisions and

tags, and the results of the screen can be exported once complete. In addition, the application will automatically identify conflicts between screeners in regards to eligibility decisions and allows users to enter a decision reconciliation mode where conflicts can be resolved. Another feature that allows Abstrackr to maximize screening efficiency is its ability to highlight key words in abstracts and titles. Users can define key words that indicate either weak or strong potential for inclusion or exclusion. Abstrackr will search each subsequent reference's title and abstract for these key words, highlighting words associated with inclusion in green and words associated with exclusion in red.

2.5.2 Second Screen Methodology

After the first screen was complete in Abstrackr, two screeners (Serena Orr and Suzanne Nadine Christie) undertook the second eligibility screen. Mendeley was used to manage the second eligibility screen. Mendeley (www.mendeley.com) is a free reference manager that allows the user to upload references with Portable Document Format (PDF) files into the application, organize the references into folders, highlight and annotate the PDF files and create groups where references can be shared between users.

For the purposes of this review, once the first eligibility screen was complete in Abstrackr, the references were uploaded to Mendeley. Results of the Abstrackr screen were exported into an Excel file. Eligibility decisions and tags in the Excel file were reviewed and used to organize the references into folders in Mendeley. All references that passed the first eligibility screen were included in the second screen and their associated PDF files were uploaded into Mendeley. The PDF files were read during the second screen in order to make final eligibility decisions. Eligibility decisions were recorded by organizing the files into folders (eg. "included after second screen", "excluded after second screen because migraine criteria not validated", etc). Conflicts between the two screeners were resolved in a consensus telephone meeting, held on January 4th 2016, once both screeners had completed the second screen.

2.6. Data Extraction

For each included study, an eligibility screening form was completed in order to ensure that the study indeed met all inclusion criteria and none of the exclusion criteria (see Appendix B).

Data from included studies were extracted using a standardized form called the "Characteristics of Studies Table" (see Appendix C), which was modeled based on the recommended format in the Cochrane Handbook[83]. The "Characteristics of Studies Tables" are organized into five sections designed to comprise the entirety of the most pertinent data from each study: methods, participants, interventions, outcomes and notes. In the "Methods" section, the design of the trial was described, including whether the study was parallel-group or crossover, how many study arms were included, the blinding status of the study and details on recruitment and study duration. The "Participants" section provided details about the number of participants and the most important defining characteristics of the participant population, that is the age of the participants, the migraine definition used in the study, the duration and frequency of the migraines at baseline and whether or not important group differences existed in terms of baseline characteristics in the intervention groups. The active intervention(s) and placebo arm were described in detail in the "Interventions" section of the table, whereby the number of participants assigned to each group was given, in addition to the name, route, dose, frequency, and if available, the appearance and smell of each intervention. The primary and secondary outcomes, as well as the adverse events, were described in detail in the "Outcomes" section, with point estimates, variance estimates, and tests of significance reported for the primary outcome when available. The "Notes" section was used to document particularities about the study in question that may impact interpretation of its results, the quality rating of the study and any other salient details.

Quality ratings were completed on each study. The "Cochrane Risk of Bias Tool" is a tool that was developed by the Cochrane collaboration to make a determination on the internal validity of a particular study[83]. In this systematic review, the "Cochrane Risk of Bias Tool" was used to make

determinations about the risk of bias in six different domains (see Appendix D): selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment for self-reported and objective outcomes), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. Each domain was given a risk of bias rating based on the information in the manuscript: 1) "high risk of bias" when the method used clearly could have led to biased results, 2) "unclear risk of bias" when the method used was inadequately described to make a judgment on the quality rating, 3) "low risk of bias" when the method used was adequate and the risk of bias for that domain was considered to be negligible. In accordance with the Cochrane guidelines[83], a study was given an overall "high risk of bias" if at least one domain was rated as having a "high risk of bias", whereas the quality rating was "unclear risk of bias" if at least one domain was rated as having an "unclear risk of bias" and there were no domains with "high risk of bias", and a study had to have "low risk of bias" throughout all domains in order to be given an overall rating of "low risk of bias".

2.7. Meta-Analyses

When several studies were available for one intervention, the outcomes in each study were reviewed in detail. Where groups of studies had overlap in outcomes with sufficient data available for pooling the results, a meta-analysis was considered. Meta-analyses were carried out if: 1) outcomes overlapped as above, 2) the interventions were the same, 2) the comparators were the same (ie. placebo), 3) the studies were not excessively clinically heterogeneous. If a study within one intervention category was lacking the outcome used to pool the data or lacking components of the data necessary for the meta-analysis, the authors were contacted in order to request the missing data. Up to three attempts were made to contact authors to obtain supplemental data. If the authors did not respond or were unwilling to share the data, then the study in question was excluded from the meta-analysis.

All meta-analyses were carried out using the Cochrane Collaborations' Review Manager 5.3.5 software (RevMan: http://tech.cochrane.org/revman). RevMan is a software package endorsed by the Cochrane Collaboration that has the ability to convert raw data from a group of studies into pooled estimates of effects using a variety of statistical techniques for meta-analysis. The raw data for the meta-analyses were entered directly into RevMan and appropriate analysis options were selected depending on the outcome in question and the characteristics of the studies being pooled.

All outcomes amenable to pooling were continuous and thus point estimates, standard deviations and sample sizes were entered for each study's intervention and comparator. If the scale used to measure the continuous outcome was identical across studies, then an estimate of the mean difference with 95% confidence intervals (CI) was generated. If the scale used to measure the continuous outcome was different across studies, then an estimate of the standardized mean difference with 95% CI was generated. A random effects inverse-variance method was used as the default model to generate estimates of the mean difference or standardized mean difference. In deciding between using a fixed or a random effects model, statistical and clinical heterogeneity of the studies were considered, with clinical heterogeneity being given greater weight in the decision. Statistical heterogeneity was assessed using two statistics: 1) the chi square test of heterogeneity, where the body of evidence was deemed statistically heterogeneous if the p value was lower than 0.1 and, 2) the I^2 statistic, where statistical heterogeneity was defined as an I^2 in excess of 30%. Each of these definitions of statistical heterogeneity was chosen based on recommendations in the Cochrane Handbook for Systematic Reviews of Interventions[83]: 1) the p=0.1 cutoff is recommended for the chi square test of heterogeneity given the lack of power of the test to detect statistical homogeneity with the typical small sample sizes seen in meta-analyses, 2) the 30% cut-off for the I^2 statistic was chosen based on the cut-off for moderate heterogeneity listed in the Handbook. In no case were the data from pooled studies considered clinically homogeneous enough to justify using a fixed effects model.

3. RESULTS

3.1. Characteristics of Included Studies

The PRISMA diagram in Figure 1 illustrates the results of the systematic review through each stage of screening. In total 19 articles were eligible for inclusion, comprising 27 studies. Details on each study are summarized in Table 2. Twelve interventions were reviewed in these studies: butterbur, riboflavin, topiramate, valproic acid, flunarizine, timolol, clonidine, trazadone, nimodipine, cinnarizine, dimethothiazine and papaverine. All of the studies had a placebo comparator, and three of the studies had another arm involving an active comparator. Five of the studies had a crossover design, and the remaining articles reported on parallel-group trials. Two of the articles comprised pooled analyses from groups of trials. Twelve of the articles used ICHD criteria, five used Vahlquist criteria and two used Ad Hoc criteria to diagnose migraine. Outcomes varied significantly between studies, rendering it a challenge to pool data into meta-analyses. Seven of the studies were given a high risk of bias, eight of the studies had an unclear risk of bias and four studies had a low risk of bias. The overall risk of bias for this body of literature is summarized in Figure 2 and the risk of bias results for each individual study are displayed in Figure 3.

Figure 1. PRISMA Diagram

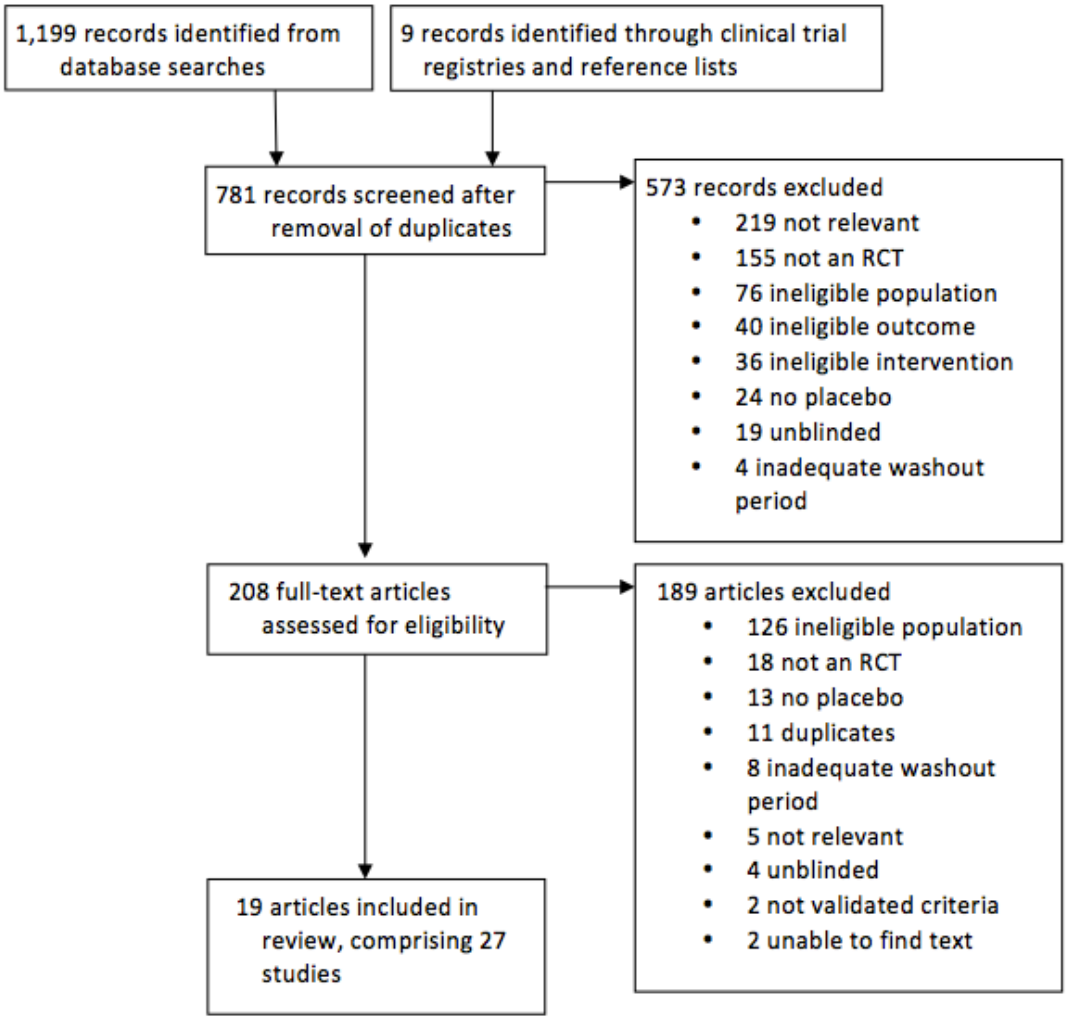


Table 2. Summary of included studies

Intervention	Study	Design	Participants	Interventions	Efficacy	Safety	Risk of Bias
Butterbur	Oelkers-Ax 2008	Randomized, partly double-blind, 3-arm, parallel-group trial with 12 week treatment phase and 8 week follow-up phase	39 children aged 8-12 years with migraine as per ICHD criteria	20 randomized to Petadolex® 50mg/day if 8-9yo or 50mg bid if 10-12yo (dose increased to 75mg/day or 75mg bid respectively PRN at 8 weeks) vs. 19 randomized to	All three groups had a significant reduction in headache frequency with music superior to placebo at post-treatment (p=0.042) and both music and Petadolex® superior to placebo at 6 mth follow-up	Petadolex ® group reported GI symptoms, allergic symptoms and dermal symptoms; no significant differences	High

				placebo vs. 24 randomized to music therapy		comparing the groups	
Riboflavin	Bruijn 2010	Randomized, double-blind, crossover study with 4 week baseline, 12 week treatment, 4 week washout and second 12 week treatment period	42 children aged 6-13 years with migraine as per ICHD criteria	20 randomized to riboflavin 50mg daily for the first period vs. 22 randomized to matched placebo for the first period	No group differences in terms of the change in migraine frequency (p=0.44)	No adverse events in either group	Unclear
	MacLennan 2008	Randomized, double-blind, 2-arm, parallel-group trial with 4 week baseline period and 12 week treatment period	48 children aged 5-15 years with migraine as per ICHD criteria	27 randomized to riboflavin 200mg daily vs. 21 randomized to placebo	No difference in the proportion of participants achieving a 50%+ reduction in migraine frequency: the trial was stopped early due to low likelihood of detecting a difference	One participant on riboflavin had an increase in the number of tension headaches, 4 children taking riboflavin had a change in their urine color	Low
Topiramate	Ford 2014	Pooled analysis of pediatric data from 5 different randomized, double-blind, placebo-controlled, parallel-group trials with treatment periods ranging from 16-26 weeks	309 children aged 6-17 years with migraine as per ICHD criteria	The number of patients randomized to each group is not given: some were randomized to topiramate 2-3 mg/kg/day, 50mg daily, 100mg daily or 200mg daily, some were randomized to placebo and one study had an active comparator arm involving propranolol 160mg daily	In terms of the % reduction in migraines: in TOPMAT-MIG 3006 the topiramate 100mg daily was superior to placebo (p=0.0164); in CAPS-122 the topiramate and placebo groups did not differ; in TOPMAT-MIGR-001/002/003 there was a trend towards topiramate 100mg daily being superior to placebo	Some patients in the topiramate groups reported influenza-like symptoms, language problems and paresthesias	Unclear
	Lakshmi 2007	Randomized, double-blind, placebo-controlled, 2-arm, parallel group study	44 children aged 8-14 years with migraine as per ICHD criteria	22 randomized to topiramate 25mg daily with weekly increases of 25mg to a max	The topiramate group had a greater decrease in migraine frequency from baseline to the end of the study	More adverse events with topiramate with most	Low

		with 4 week titration period and 12 week maintenance period		of 50mg bid vs. 22 randomized to placebo	(from 16.14±9.35 to 4.27±1.95 vs. from 13.38±7.48 to 7.48±5.94, p=0.025)	common being: weight loss, loss of appetite, paresthesias and lack of concentration in school being the most common	
	Lewis 2009	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial with 9 week baseline, 16 week treatment and 6 week taper and exit phase	103 adolescents aged 12-17 years with migraine as per ICHD criteria	35 randomized to low dose topiramate (25mg/day up to a maximum of 25mg bid) vs. 35 randomized to high dose topiramate (25mg/day up to a maximum of 50mg bid) vs. 33 randomized to placebo	High dose topiramate group had a larger decrease in migraine frequency as compared to placebo (72.2% vs. 44.4%, p=0.016), but no significant difference comparing low dose topiramate to placebo (p=0.798)	More adverse events with topiramate (74% vs. 48%) with most common: upper respiratory tract infections, paresthesias and decreased appetite	Low
	Pandina 2010	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial with 9 week baseline, 16 week treatment and 6 week taper and exit phase (analysis of subset of data from Lewis 2009)	103 adolescents aged 12-17 years with migraine as per ICHD criteria	35 randomized to low dose topiramate (25mg/day up to a maximum of 25mg bid) vs. 35 randomized to high dose topiramate (25mg/day up to a maximum of 50mg bid) vs. 33 randomized to placebo	N/A – analysis of subset of the data related to cognitive adverse events	On cognitive testing, high dose topiramate associated with small increases in psychomotor reaction times and decrease in the number of unique words they could generate	Low
	Winner 2005	Randomized, double-blind, placebo-controlled, parallel-group trial with 2:1 assignment to the intervention group and 4	162 children aged 6-15 years with migraine as per ICHD criteria	112 randomized to topiramate 15mg daily titrated up to max of 2-3mg/kg daily or 200mg daily vs. 50 randomized to placebo	Greater reduction in migraine frequency in the topiramate group in per-protocol analysis and trend in intention-to-treat analysis (2.8±2.4 vs. 2.2±2.1, p=0.033 for PP and 2.6±2.6	No difference in side effects overall; 4 serious adverse events with topiramate	Unclear

		week baseline period, 8 week titration period and 12 week maintenance period			days vs. 2.0±3.1 days, p=0.061 for ITT)		
	Winner 2006	Pooled analysis of pediatric data from three randomized, double-blind, placebo-controlled, parallel-group trials with 2 week washout, 4 week baseline, 8 week titration and 18 week maintenance periods	49 adolescents aged 12-18 with migraine as per ICHD criteria	11 randomized to low dose topiramate (50mg daily) vs. 13 randomized to medium dose topiramate (100mg daily) vs. 13 randomized to high dose topiramate (200mg daily) vs. 12 randomized to placebo	Greater reductions in migraine frequency in the medium and high dose topiramate groups as compared to placebo (63% and 65% compared to 13% reductions, p<0.04)	No overall difference in adverse events; more weight loss and cognitive side effects with topiramate ; most common adverse events with topiramate : upper respiratory tract infections, paresthesias and weight loss	Unclear
Valproic acid	Apostol 2008	Randomized, double-blind, placebo-controlled, 4-arm parallel group trial with 2 week washout period, 4 week baseline period, 2 week titration period and 10 week treatment period	305 adolescents aged 12-17 years with migraine as per ICHD criteria	83 randomized to low dose divalproex (250mg daily) vs. 74 randomized to medium dose divalproex (started at 250mg daily and increased to 500mg daily) vs. 75 randomized to high dose divalproex (started at 500mg daily and increased to 1000mg daily)	No difference between any dose of divalproex and placebo in terms of decrease in migraine frequency	No overall differences in adverse events; most common with divalproex: upper respiratory tract infections, somnolence and fatigue	Unclear
Flunarizine	Machín Altueña 1987	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group study with 16 week treatment period	45 children aged 5-13 years with migraine as per Ad Hoc criteria	15 randomized to flunarizine 0.15mg/kg daily vs. 15 randomized to dimethothiazine 1mg/kg daily vs. 15 randomized to	No differences in rates of clinical improvement between the groups (93.3% for dimethothiazine vs. 86.7% for flunarizine vs. 80% for placebo,	23.1% of flunarizine patients gained weight	High

				placebo	p>0.05)		
	Sorge 1985	Randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial with 12 week treatment period	48 children under age 18 years with migraine as per Vahlquist criteria	24 randomized to flunarizine 5mg daily vs. 24 randomized to placbeo	Lower headache frequency at trial completion in the flunarizine group (p<0.001)	Lacking details on adverse events; 3 patients withdrew from the flunarizine group due to side effects (GI symptoms, drowsiness and fatigue)	High
	Sorge 1988	Randomized, double-blind, placebo-controlled, crossover trial with 4 week baseline, 12 week treatment, 4 week washout and second 12 week treatment period	70 children aged 5-11 years with migraine as per Vahlquist criteria	35 randomized to flunarizine 5mg daily for first treatment period vs. 35 randomized to placebo for first treatment period	Greater reduction in migraine frequency during flunarizine treatment period as compared to placebo treatment period (p<0.001)	Most commonly weight gain and drowsiness but group comparisons not made	High
Timolol	Noronha 1985	Randomized, double-blind, placebo-controlled, crossover study with 4 week baseline, 8 week treatment, 4 week washout and 8 week second treatment phase	17 patients aged 5-16 years with migraine as per Vahlquist criteria	9 randomized to timolol 5mg daily for first treatment period and 8 randomized to placebo for first treatment period	There were no group differences in any of the outcomes, including migraine frequency	Lacking detail on adverse events; two patients withdrew from timolol due to headache and vomiting	High
Clonidine	Sillanpää 1977	Randomized, double-blind, placebo-controlled, 2-arm parallel group study with 8 week treatment period	57 children 15 years and under with migraine or vascular headache as per Vahlquist criteria	28 randomized to clonidine 25 micrograms (mcg) daily if under 40kg or and 25mcg bid if over 40kg vs. 29 randomized to placebo	Lack of detail with reporting of results (most hypothesis tests not given): 1/3 of the participants were headache-free during treatment in each group, 57% of clonidine participants and 42% of placebo participants had	Adverse events in 11 clonidine participants vs. 6 placebo; most common with clonidine was fatigue and	High

					only 1 or 2 headaches during the entire study	nausea	
Trazodone	Battistella 1993	Randomized, double-blind, placebo-controlled, crossover study with 12 week treatment, 4 week washout and second 12 week treatment period	40 children aged 7-18 years with migraine as per ICHD criteria	20 randomized to trazadone 1mg/kg daily for first treatment period vs. 20 randomized to placebo for first treatment period	No group differences in the first treatment phase; in the second phase the trazodone group had a greater decrease in migraine frequency (trazadone reduced from 2.1±0.2 attacks/month to 1.8±0.2 vs. placebo increased from 1.8±0.1 to 2.1±0.2, p<0.005)	Lacking details on adverse events; no serious adverse events occurred	Unclear
Nimodipine	Battistella 1990	Randomized, double-blind, placebo-controlled, crossover study with 4 week baseline, 12 week treatment, 4 week washout and second 12 week treatment period	37 patients aged 7-18 years with migraine as per Ad Hoc criteria	18 patients randomized to nimodipine 10-20mg tid for first treatment period vs. 19 randomized to matched placebo for first treatment period	No group differences in the first treatment phase; in the second phase the nimodipine group had a greater decrease in migraine frequency than the placebo group (from 2.7±0.8 attacks/month to 1.9±1.7 vs. from 2.6±0.8 to 2.8±0.6, p<0.01)	Lacking details on adverse events	Unclear
Cinnarizine	Ashrafi 2014	Randomized, double-blind, placebo-controlled, 2-arm parallel group study with 4 week baseline and 12 week treatment period	62 children 5-17 years with migraine as per ICHD criteria	30 randomized to cinnarizine 1.5mg/kg daily if weight less than 30kg and 50mg daily if 30kg or more vs. 32 randomized to placebo	Cinnarizine yielded a higher proportion achieving 50% or greater reduction in migraines (60% vs. 31.3%, p=0.023); no differences in groups for change in migraine frequency	3 cinnarizine participants vs 1 placebo participant had drowsiness; 1 in cinnarizine group had significant weight gain	Unclear
Dimetho-thiazine	Machín Altueña 1987	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group study with 16 week treatment period	45 children aged 5-13 years with migraine as per Ad Hoc criteria	15 randomized to dimethothiazine 1mg/kg daily vs. 15 randomized to flunarizine 0.15mg/kg daily vs. 15 randomized to placebo	No differences in rates of clinical improvement between the groups (93.3% for dimethothiazine vs. 86.7% for flunarizine vs. 80% for placebo, p>0.05)	23.1% of flunarizine patients gained weight	High
Papaverine	Sillanpää	Randomized,	37 children	19 randomized	More patients in	Adverse	High

	1978	double-blind, placebo-controlled, 2-arm parallel-group with	aged 6-15 years with migraine as per Vahlquist criteria	to papaverine 5-10mg/kg daily (started at 5mg/kg daily) vs. 18 randomized to placebo	the papaverine group were pain-free on treatment (6 vs. 0, p<0.001) and headache frequency was lower in the papaverine group (p<0.001)	events not reported	

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

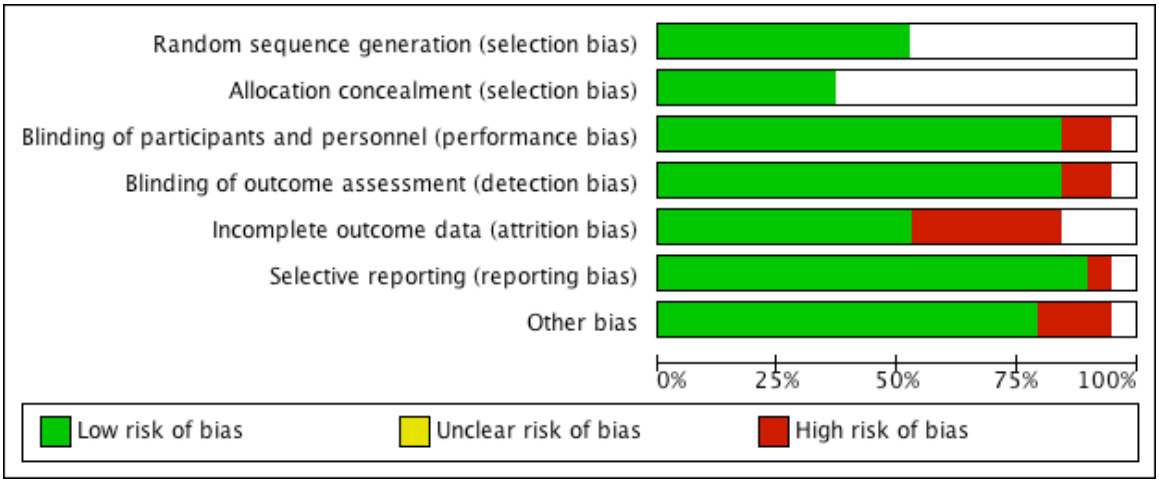
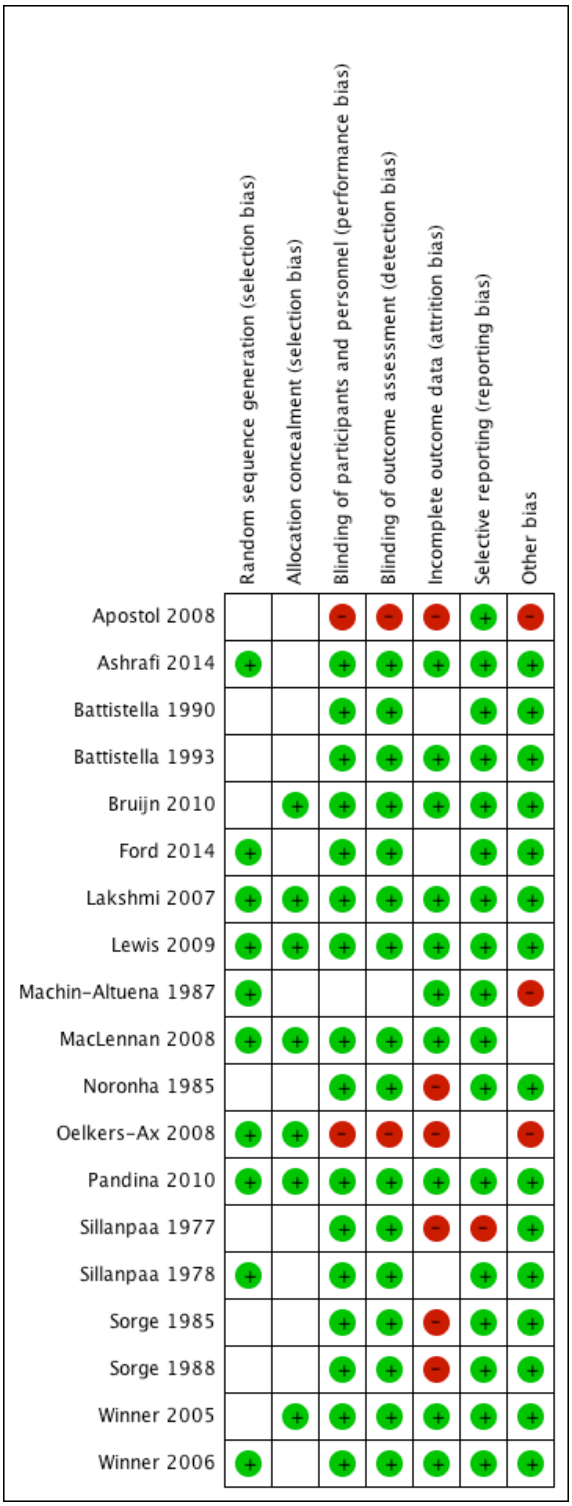


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



**NB. Red circles indicate high risk of bias, green circles indicate low risk of bias and white squares indicate unknown risk of bias*

3.2. Nutraceutical Interventions

3.2.1 Butterbur (Petasites hybridus)

Butterbur (*Petasites hybridus*) is a perennial shrub that grows in several different continents. Its medicinal potential has been recognized for centuries[95]. Although it has had many uses throughout the years, it is currently touted as a remedy for migraines, asthma, rhinitis and chronic cough[95,96]. The mechanism through which it may exert an effect on migraine is unclear. It has been shown to have anti-inflammatory properties through its selective inhibition of the enzyme cyclooxygenase-2[97], and in this way it could relieve migraines with a mechanism similar to that of the non-steroidal anti-inflammatory drugs, which are commonly used in pediatric migraine. Leukotriene production from primed granulocytes also appears to be inhibited by *Petasites*, further contributing to its anti-inflammatory activity[98]. *Petasites* has another property that could render it efficacious in migraine: it has been shown to inhibit L-type voltage-gated calcium channels[99], in a manner analogous to calcium channel blockers like flunarizine, which is recommended for pediatric migraine prophylaxis[100].

Unfortunately, *Petasites* contains pyrrolizidine alkaloids, which are compounds with known hepatotoxicity. A recent study found detectable levels of pyrrolizidine alkaloids in almost half of the samples of *Petasites* commercial products that it assayed[101]. A formulation called Petadolex®, with supposedly undetectable amounts of pyrrolizidine alkaloids, has been developed and was originally found to be safe for human use[102]. However, post-marketing surveillance has identified cases of hepatoxicity linked to Petadolex®. This has prompted regulatory authorities, including the German Federal Institute of Medical Devices and the Swiss Agency for Therapeutic Products, to ban its use in their respective countries[103]. Therefore, although the evidence for the use of Petadolex® from placebo-controlled trials will be reviewed here, it is no longer a viable option for pediatric migraine prophylaxis.

Only one study assessing the efficacy of butterbur for this indication met inclusion criteria. Oelkers-Ax et al carried out a partly double-blind, randomized, 3-arm parallel group trial in a group of 63 children with migraine aged 8 to 12 years[104]. Patients were randomized to receive one of three therapies: butterbur, placebo or music therapy. The butterbur group was given Petadolex®, a regulated formulation of butterbur, at a starting dose of 50mg daily for children aged 8 and 9 years, or 50mg twice daily for children aged 10-12 years. The starting dose was administered for the first 8 weeks. Subsequently, children with a suboptimal response had their dose increased by 50% for the next 4 weeks of treatment. The placebo group was given placebo pills for the first 8 weeks, with a dose adjustment at 8 weeks if necessary. Finally, the music therapy group, who could not be blinded to their assignment given the nature of the treatment, received 12 weekly sessions of music therapy, focused on a variety of techniques including music-aided relaxation training, body awareness techniques and conflict training in a musical role. At the post-treatment assessment, both as-treated and intention-to-treat analyses showed that the groups all had a significant decrease in their migraine frequency as compared to baseline, which was the primary outcome. At this stage, music therapy was superior to placebo with regards to the primary outcome, whereas Petadolex® was not. However, at the 6 month follow-up assessment, both music therapy and Petadolex® were superior to placebo. Furthermore, there were no differences in adverse events between the groups. The butterbur group primarily experienced gastrointestinal, cutaneous and allergic symptoms as side effects. Two patients in the Petadolex® group and and three patients in the placebo group had transient mild transaminitis. This study was deemed to have a high risk of bias based on several key weaknesses. Namely, complete implementation of a double-blind protocol was not possible given that music therapy cannot be blinded to the patients. This posed a high risk for performance bias and detection bias. In addition, randomization did not succeed in making the groups balanced on all baseline characteristics: the Petadolex® group had almost double the baseline migraine frequency as compared to the other groups (9.8$\pm$7.6 vs. 5.5$\pm$4.4 vs.

5.0±2.5, p=0.409), and though this did not reach statistical significance, it is clinically meaningful. Finally, there was a high risk of attrition bias given a higher rate of drop-outs in the music therapy and Petadolex® groups as compared to placebo (29% for music therapy vs. 25% in Petadolex® group vs. 5% in placebo group, p=0.113). Though the differences were not statistically significant, they were clinically significant and therefore likely create bias in the results. Thus, only one study assessed the efficacy of butterbur in children and this study is of inferior methodological quality given several key areas with a high risk of bias. This, coupled with safety concerns about butterbur, precludes recommendations for its use in pediatric migraine prophylaxis.

Therefore, only one small trial with a high risk of bias lends some evidence in favor of Petadolex®. Given this and the evidence suggesting that butterbur compounds may be hepatotoxic, it would be unwise to recommend the use of butterbur for pediatric migraine prophylaxis.

3.2.2 Riboflavin (Vitamin B_2)

Unlike butterbur, riboflavin does not have a long history of medicinal use. It was only isolated in the 1930s and synthesized shortly thereafter. Riboflavin is derived from a multitude of dietary sources. It plays a vital role in mitochondrial energy metabolism through its two active coenzymes: riboflavin 5'-phosphate and flavin adenine dinucleotide. Both of these compounds participate in a multitude of metabolic processes[105]. It is precisely its role in mitochondrial energy metabolism that gives riboflavin some credibility as a potential therapy for migraines. There is an accumulating body of evidence suggesting that migraineurs may be in a state of mitochondrial energy depletion[106–113]. Therefore, compounds like riboflavin, which play a role in mitochondrial energy production, may help to prevent migraines.

Two studies on the efficacy of riboflavin for pediatric migraine prophylaxis were included in the systematic review. The first study, by MacLennon et al, randomized 48 children between the ages of 5 and 15 years to receive either 12 weeks of riboflavin 200mg daily or a matched placebo for their migraines[114]. Efforts were made to maintain blinding amongst both participants and study

personnel. After 12 months of recruitment and attainment of 86% of the planned sample size, the trial was stopped given that an interim data analysis showed that there was a very low probability of finding efficacy for the riboflavin intervention. The exact stopping rule used for the interim analysis is not clear. There were no group differences in the primary outcome, that is, the proportion of participants achieving a 50% or greater reduction in monthly migraine frequency. Also, none of the secondary outcomes favored riboflavin. Overall, however, riboflavin was well tolerated: one child had an increase in their tension-type headaches and four children reported a change in their urine color but otherwise there were no reported adverse events for the treatment group. The study was powered to detect a 40% difference between placebo and riboflavin, which is ambitious and therefore the study was likely underpowered. The study was methodologically sound with a low risk of bias across all of the core domains.

The second study on riboflavin was carried out by Bruijn and colleagues, and involved randomizing 42 children to receive either riboflavin 50mg daily or placebo, consisting of 100mg of carotene, in a double-blind, cross-over design[115]. Each treatment was administered for 16 weeks and there was a 4-week washout period in between the interventions. In the end, intention-to-treat analyses did not uncover any differences between the groups in either the primary or secondary outcomes. The study was only powered to detect a difference of 0.6 standard deviations between the groups relative to the change in migraine frequency. This minimal clinically important difference is likely too large, and the study was therefore arguably underpowered. Also, the dose of riboflavin is much lower than that used in other studies and than the typical dose used clinically. Hence, it is possible that the lack of efficacy was due to under-dosing. Another concern relates to the use of carotene in the placebo; although the rationale for its use was sound (riboflavin colors the urine orange and carotene mimics this side effect), it is possible that the carotene could have a migraine prophylactic effect rendering it an active comparator as opposed to a true placebo. The

study was rated as having an unclear risk of bias given that there were no details available on the method of randomization. Otherwise, the study was methodologically sound.

There are therefore two small trials that have found no difference between placebo and riboflavin for pediatric migraine prophylaxis. Both studies were likely underpowered. The Bruijn et al study had several other methodological shortcomings as well. Hence, it is difficult to make conclusions about riboflavin's efficacy based on the current state of the evidence. Given its favorable tolerability, further high quality studies, involving larger groups of patients, are warranted.

3.3. Pharmaceuticals

3.3.1 Topiramate

Topiramate is a commonly used antiepileptic medication with a broad anticonvulsant profile comprising a multitude of potential mechanisms of action for seizure prophylaxis[116]. It is unclear how it might operate in migraine prevention. The rationale for its use in migraine pertains to the belief that migraine and epilepsy may overlap in their pathophysiologies, and that migraine, like epilepsy, involves a state of brain hyperexcitability[117]. In 2014, topiramate was approved by the Food and Drug Administration (FDA) for the prophylaxis of migraine in adolescents. It is the first and only drug to receive FDA approval for this indication in the pediatric age group[118]. Health Canada currently has not approved any drugs for pediatric migraine prophylaxis, but topiramate is approved for migraine prophylaxis in adults[119].

Six studies on the efficacy of topiramate for migraine prophylaxis in children and adolescents were included. In a double-blind, parallel-group trial, Winner et al randomized children aged 6 to 15 years to receive either topiramate in titrating doses up to 2-3mg/kg/day or titrating doses of placebo in a 2:1 ratio[120]. After the 4-week baseline period, an 8-week titration period was initiated for each group, with the topiramate participants starting at a dose of 15mg daily, followed by a slow

titration up to a maximum of 200mg daily or 2-3mg/kg/day as needed, and the placebo participants having an artificial titration schedule. After the titration, each group entered a 12-week maintenance phase. During 20 weeks of treatment, the topiramate group had a higher mean reduction in their headache frequency in the per-protocol analysis (2.6±2.6 days for the topiramate group vs. 2.0±3.1 days for the placebo group, p=0.033), but the difference between topiramate and placebo only approached significance in the intention-to-treat analysis (2.8±2.4 days for the topiramate group vs. 2.2±2.1 days for the placebo group p=0.061). Because no sample size calculations are reported, it is unclear what minimal clinically important difference the trial was powered to detect. Intention-to-treat analyses for all secondary outcomes favored topiramate in a statistically significant manner except for the analysis comparing the proportion of patients with a 50% or greater reduction in migraine frequency over the treatment period: here, there was no difference when comparing placebo to topiramate (p=0.18). Topiramate was well tolerated with no significant difference in the incidence of adverse events as compared to placebo. There were 4 serious adverse events in the topiramate group. This study was rated as having unclear risk of bias, simply because of a lack of description as to how the randomization code was generated. Otherwise, all other domains of the study had a low risk of bias and overall the methodological quality of the trial was strong.

Lakshmi et al carried out a double-blind, placebo-controlled, parallel-group randomized trial in 44 children aged 8-14 years with migraine[121]. They randomized 22 participants to topiramate, which was initiated at a dose of 25mg daily and titrated up to 50mg bid over 4 weeks followed by maintenance at this dose for 12 weeks, and 22 participants to matched placebo for 16 weeks. Topiramate was significantly better than placebo at reducing the frequency of migraines when comparing baseline to the end of treatment (the topiramate group went from a mean of 16.14±9.35 migraine days/month to 4.27±1.95 days/month vs. the placebo group that went from 13.38±7.48 days/month to 7.48±5.94 days/month, p=0.025). Topiramate was also significantly better than

placebo in terms of the proportion of patients achieving a 50% or greater reduction in migraine frequency, in reducing disability scores on the PedMIDAS and in reducing school absenteeism as compared to placebo, but was no different from placebo in terms of changes in migraine duration or intensity. There were more adverse events with topiramate, with weight loss, reduced appetite, paresthesias and decreased concentration being the most prevalent. Although the trial was small, it was methodologically rigorous, receiving a judgment of low risk of bias for all of the Cochrane risk of bias domains.

Lewis et al randomized a group of 106 adolescents aged 12 to 17 years with migraine to either high dose topiramate, low dose topiramate or placebo in a double-blind, 3-arm, parallel-group trial in a 1:1:1 fashion[122]. The study comprised a 9-week baseline period, during which the first week was dedicated to screening, the next 4 weeks involved a wash-out period for any prophylactic migraine medications in use and the last 4 weeks consisted of the baseline period. After these 9 weeks, the participants entered a 16-week treatment period, which was followed by a 6 week taper and end of study period. The topiramate groups both started at a dose of 25mg daily, and the low dose group was then titrated up to 25mg bid as tolerated, whereas the high dose group was titrated up to 50mg bid as tolerated. The placebo group was given matching placebo pills. Each patient received 4 identical-appearing pills per day, comprised of 25mg of topiramate or placebo, or a combination thereof. The primary outcome, that is, the percent reduction in migraine frequency comparing the last 12 weeks of treatment to baseline, was achieved in significantly more patients taking high dose topiramate as compared to placebo (72.2% vs. 44.4%, p=0.016), whereas there was no difference comparing low dose topiramate to placebo (p=0.798). Most of the secondary outcomes yielded similar results with only the high dose topiramate treatment being favored over placebo. The study was powered to detect a difference of 43% between the topiramate groups and placebo in terms of the primary outcome, that is the percentage reduction in migraine frequency in the last 12 weeks of treatment compared to baseline, at a power of 80% with a probability of type I

error of 5% using a 2-sided Mann-Whitney test. Therefore, it is possible that there was a clinically meaningful difference between low dose topiramate and placebo that was not detected given the relatively low power of the study. This study was methodologically sound with a low risk of bias across all domains of potential bias.

In a subsequent publication, Pandina et al[123] reported on neurocognitive and mood outcomes observed in the Lewis et al study. The same patients had also completed a Cambridge Neuropsychological Test Automated Battery (CANTAB) and a Profile of Mood States. The high dose topiramate group had significant increases in their reaction times on the CANTAB as compared to placebo, but low dose topiramate and placebo did not differ in their reaction times. The low dose topiramate group had a significant reduction in their total number of unique words as compared to placebo. However, changes seen in CANTAB memory, visual information processing and learning scores did not differ significantly between the groups, nor did the Profile of Mood States changes over time.

Winner et al also carried out a pooled analysis on the efficacy and safety of topiramate for adolescent migraine prophylaxis using data from three adult randomized controlled trials[124]. Fourty-nine adolescents were included from the three trials. All three trials had similar methodology where participants were randomized in equal proportions to one of four treatment groups: topiramate 50mg daily or in one trial propranolol, topiramate 100mg daily, topiramate 200mg daily or placebo. Each group underwent a 2-week washout period and then a 4-week baseline period. Subsequently, the groups entered an 8-week titration phase, where patients randomized to topiramate started a dose of 25mg daily, which was subsequently increased by 25mg weekly until the target dose was achieved. Following the titration phase, participants entered an 18-week maintenance phase. The 100mg and 200mg topiramate groups were significantly better than placebo with regards to the primary outcome: they had a greater reduction in migraine frequency during treatment as compared to baseline (63% for topiramate 100mg group and 65%

for topiramate 200mg group compared to 13% reduction for placebo group, p<0.04). However, the treatment groups did not differ from placebo in terms of the secondary outcomes. Overall, topiramate was well tolerated with no serious adverse events and no difference from placebo in terms of the incidence of adverse events. Cognitive side effects were more common with topiramate than with placebo. The most common side effects reported were upper respiratory tract infections, weight loss and paresthesias. The studies that were used for the pooled analysis were methodologically strong, but this analysis was rated as having unclear risk of bias given that it is unclear whether allocation to the random sequence was concealed in any of the studies, even after accessing the original adult trials.

Finally, similarly to Winner et al[124], Ford et al looked at the subset of pediatric patients participating in five large, multicenter RCTs[125]. The trials were all double-blind, placebo-controlled parallel-group designs with treatment periods ranging from 16-26 weeks. Dosing regimens for topiramate varied from 50mg daily to 200mg daily and in one trial the dosing was flexible at 2-3 mg/kg daily. One study had a propranolol 160mg daily active comparator arm in addition to the placebo and topiramate arms. This analysis is only published in conference abstract form and the numbers randomized to each arm are not given, but a total of 309 pediatric participants were included. Two efficacy outcomes were analyzed: the percent change in monthly migraine frequency and the responder rate, that is, the percentage of participants achieving a 50% or greater reduction in migraine frequency. With regards to the percent reduction in migraine frequency, only one trial found a significant difference between topiramate and placebo: in the TOPMAT-MIG-3006 trial, topiramate 100mg daily was superior to placebo for this outcome (p=0.0164). Similarly, only the TOPMAT-MIG-3006 trial yielded a significant difference in responder rates comparing topiramate with placebo, with topiramate 100mg daily outperforming placebo for this outcome (p=0.0048). Side effects are not reported on in detail, but the most common events were flu-like symptoms, language problems and paresthesias. It is important to note that three out of the five trials

comprised both pediatric and adult patients and may not have been powered to detect differences in the outcomes for the pediatric subset of participants. Only the TOPMAT-MIG-3006 and CAPSS-122 trials recruited exclusively pediatric participants and thus only those trials were definitely adequately powered for their primary outcomes. This analysis was only described in conference abstract form and there was unclear risk of bias in terms of allocation concealment and attrition bias. Thus, the analysis had an unclear risk of bias overall. The authors concluded that topiramate 100mg daily was efficacious in adolescents, given that the TOPMAT-MIG-3006 study, which supported the efficacy of topiramate at this dose, recruited only adolescents ages 12 to 17 years.

There is consistent evidence from these six studies that topiramate is effective in preventing migraines in children and adolescents. It also appeared to be well tolerated amongst these patients, though the pooled analysis by Pandina et al[123] confirmed what many clinicians observe anecdotally in their patients: that topiramate has adverse effects on cognition. Because of its side effects, primarily those related to cognition, topiramate must be used judiciously in this population given that cognitive performance is key in the child or adolescent's success in school and in their transition to employment.

3.3.2 Valproic Acid

Valproic acid, like topiramate, is a broad-spectrum antiepileptic drug with multiple mechanisms of action[116] that has been used off-label for pediatric migraine prophylaxis. Valproic acid has FDA approval for use in migraine prophylaxis in adults, whereas Health Canada has not approved it for this indication. Again, the rationale for using valproic acid in migraine pertains to the theory that migraine and epilepsy have similar underlying mechanisms[126].

The efficacy of valproic acid for pediatric migraine prophylaxis has only been assessed in one eligible trial. In a study sponsored by Abbott Pharmaceuticals, Apostol et al randomized 305 adolescents with migraine to either divalproex 250mg daily, divalproex 500mg daily, divalproex 1000mg daily or matched placebo in a double-blind, 4-arm parallel-group trial[127]. Participants first

had a 2-week washout period, followed by a 4-week baseline period. Eligible participants were then randomized to one of the 4 groups and a 2-week titration period started. During titration, those in the 250mg and 500mg divalproex groups started divalproex at dose of 250mg daily, whereas those in the 1000mg divalproex group started divalproex at a dose of 500mg daily. Following the 2-week titration, target doses were started and maintained for 10 weeks. There were no significant differences between the groups in terms of the primary outcome, that is, the change in migraine frequency comparing baseline to the 12-week treatment period. In addition, none of the divalproex groups were significantly different from placebo in any of the secondary outcomes. Overall, there was no difference in the frequency of adverse event rates between the groups. The most common adverse events with divalproex were upper respiratory tract infection, somnolence and fatigue. The effect size used to power the study was based on results of a similar trial in adults. The authors acknowledge that the placebo response was much stronger in their trial than that observed in the adult trial, which is unsurprising given that pediatric studies tend to see higher placebo response rates, especially in parallel-group trials as opposed to cross-over trials[128]. Therefore, it is possible that the trial was underpowered in this setting. The description of how the random sequence was generated lacks detail and it is unclear if the allocation was concealed. Hence, this study was rated as having an overall unclear risk of bias, despite other domains of potential bias having a low risk of bias.

Based on the fact that only one valproate study had enough methodological rigor to be included in this review and given the extensive side effect profile of this medication, valproate certainly does not appear to be a reasonable first line agent for pediatric migraine prophylaxis, although strong conclusions cannot be made given the limited evidence.

3.3.3. Flunarizine

Flunarizine belongs to the class of medications by the name of calcium-channel blockers. Its mechanism of action in migraine is also unknown. One study carried out using patch clamp

recordings in trigeminal ganglion neurons showed that flunarizine inhibited sodium and calcium currents, resulting in hyperpolarizing neuronal membrane potentials[129]. Thus, flunarizine likely inhibits neuronal transmission in the trigeminal ganglion, which plays a crucial role in migraine pathogenesis. Another study showed that flunarizine was able to reduce the degree of cerebral mitochondrial injury that occurs during cortical spreading depression[130], which is believed to be the underlying pathophysiological correlate of migraine aura[131]. Therefore, some preliminary evidence suggests that flunarizine could have plausible mechanisms of action in preventing migraine. In the most current American Academy of Neurology (AAN) practice parameter on the treatment of migraine in children and adolescents, flunarizine is the only medication that received a recommendation to use based on evidence that it is "probably effective" for the prevention of migraines in this population[100].

There were three included studies that assessed the efficacy of flunarizine for the prophylaxis of migraine in children and adolescents, two of which were by the same author group. A double-blind, placebo-controlled, 2-arm, parallel-group trial was carried out by Sorge et al in order to assess the efficacy of flunarizine for the prevention of pediatric migraines[132]. Forty-eight children with migraine were randomized to receive three months of either flunarizine 5mg qHS or placebo. During the treatment period, the participants on flunarizine had a significantly lower mean migraine frequency as compared to placebo ($p<0.001$) and had a significantly lower mean migraine duration ($p<0.05$) as well. However, the latter may have been an artifact of the fact that the flunarizine group had a lower migraine duration at baseline ($p<0.05$). There is little mention of side effects in the manuscript. The authors do state that weight loss and sleepiness were the most common adverse events, but do not report frequencies in each group. Also, three patients withdrew from the flunarizine group due to side effects (gastrointestinal symptoms, drowsiness and fatigue) whereas three patients withdrew from the placebo group due to lack of efficacy. No intention-to-treat analyses were used. The trial overall had a high risk of bias due to this attrition bias, with the

two groups having clearly distinct reasons for drop-outs. There was also unclear risk of bias in relation to the possibility of selection bias, given that randomization and allocation concealment were not described.

A few years later, Sorge et al carried out a double-blind, placebo-controlled, crossover trial in a group of 70 children aged 5 to 11 years with migraine[133]. The timeline of the trial involved a 4-week baseline period, followed by a 12-week treatment period, followed by a 4-week washout period, and finally another 12-week treatment period. Participants randomized to Group A received flunarizine 5mg daily for the first treatment period and then were crossed over to placebo, whereas participants in Group B had the opposite treatment order. During the flunarizine treatment period, both groups had a statistically significant decrease in their migraine frequency ($p<0.001$ in both cases). In addition, during the flunarizine period, both groups had a statistically significant reduction in the duration of their migraines, starting at month 3 of flunarizine in group A and starting at month 2 of flunarizine in group B ($p<0.001$ in both cases). The reporting of side effects is vague and only makes mention of the overall frequency of the most common side effects: 22.2% of participants experienced weight gain and 9.5% experienced drowsiness. It is unclear as to whether there could have been selection bias in the study given the lack of detail given with regards to randomization and allocation concealment. There was a high risk of attrition bias given that 2 patients withdrew from the flunarizine group and 5 patients withdrew from placebo, with no intention-to-treat analyses used. Therefore, the trial was given a high risk of bias overall.

A small study carried out by Machín Altueña et al randomized 45 children aged 5 to 13 years with migraine to either flunarizine, dimethothiazine or placebo in a 4-month double-blind, 3-arm, parallel-group intervention study[134]. There were no group differences in terms of the primary outcome: 93.3% of the dimethothiazine group had clinical improvement vs. 86.7% of the flunarizine group vs. 80% of the placebo group ($p>0.05$). In addition, no group differences were seen in any of the secondary outcomes. Weight gain occurred in 23.1% of the flunarizine group but

no other significant side effects were noted in the manuscript. There was a high risk of bias in this study in that no sample size calculations were given and the study was very likely underpowered to detect clinically important differences in the efficacy of the interventions. There was also unclear risk of bias related to allocation concealment, thus introducing the potential for selection bias. This study was therefore at high risk of bias and it is difficult to draw any conclusions on flunarizine's efficacy from these results.

The two Sorge et al studies[132,133], both of which had high risk of bias, support the use of flunarizine in pediatric migraine prophylaxis and the Machín Altueña is difficult to interpret[134]. Because of the low quality of evidence and the small number of participants in the studies, a strong recommendation for its use should not be made. This is likely why the AAN practice parameter labeled flunarizine as "probably effective" for this indication[100], rather than making a stronger statement about its use in pediatric migraine prophylaxis.

3.3.4 Timolol

Timolol belongs to the class of medications called beta-blockers, which are antihypertensive medications that reduce vascular tone by inhibiting beta-adrenergic receptors. How beta-blockers might work to prevent migraines is unclear. It has been hypothesized that their central inhibition of beta-adrenergic receptors and their interaction with serotonin receptors may mediate their mechanism of action in migraine[135,136]. Timolol is approved for use in adult migraine prophylaxis by Health Canada and the FDA.

One study assessed the efficacy of timolol for pediatric migraine prophylaxis. Noronha described a small double-blind, placebo-controlled, cross-over trial that he carried out, whereby 9 patients were randomized to received timolol 5mg daily for the first treatment period then crossed-over to placebo, and 8 patients were randomized to receive placebo for the first treatment period then crossed-over to timolol 5mg daily[137]. There was a 4-week baseline period in this trial, followed by 8 weeks of treatment, then a 4-week washout period, and then finally another 8-week treatment

period. There are few details given about the results. The author does report that there were no differences between the groups in terms of migraine frequency, severity nor duration. The only mention of adverse events pertains to the author describing how two patients withdrew due to side effects of timolol, namely headache and vomiting. No sample size calculations are described and given that there were only 17 patients in the trial, it is very likely that the study was underpowered. There was a high risk of attrition bias in this study given that 2 patients withdrew for drug-specific reasons (ie. due to timolol side effects). There was unclear risk of bias related to selection bias given an inadequate description of randomization and allocation concealment. Therefore, this trial was considered to have a high risk of bias.

Based on the available evidence, there is not enough information to comment on the efficacy of timolol for pediatric migraine prophylaxis. Only one small, underpowered trial is available; future studies are therefore required prior to drawing conclusions about timolol's use for this indication.

3.3.5 Clonidine

Clonidine is an alpha-2 adrenergic agonist with several postulated mechanisms of action in pain modulation. Alpha-2 adrenergic agonists like clonidine may have a role in alleviating pain through their anti-inflammatory properties and through their ability to modulate descending pain pathways in the central nervous system: they can inhibit nitric oxide and glutamate release in central pain pathways and can increase descending inhibition in the rostral ventromedial medulla, which plays an important role in descending pain inhibition[138]. Animal experiments have lead to some interesting insights about the potential role that clonidine plays in modulating pain associated with migraine. It appears that clonidine might inhibit trigeminal referred pain in migraine by inhibiting C1 spinal neurons that receive inputs from structures believed to be involved in referred pain[139]. Also, clonidine has been shown to inhibit NMDA-evoked responses in nociceptive neurons located in the trigeminal nucleus caudalis[140], which is a brain area of central importance in migraine pathogenesis. In another animal experiment, clonidine inhibited the migration of cortical spreading

depression[141], a phenomenon that is believed to underlie migraine aura[131]. Therefore, clonidine has several plausible mechanisms of action that could lead to its efficacy in migraine prevention. Although it is not currently approved for use in migraine by the FDA nor Health Canada, it is used off-label for this indication.

Sillanpää reported the results of a double-blind, placebo-controlled, 2-arm parallel-group study involving the comparison of clonidine to placebo for migraine prophylaxis in children with migraine up to 15 years of age[142]. Although it seems implied that the trial was randomized, it is not explicitly stated in the text. Because the paper was published in 1977 with a single author for whom no current contact information was traceable, the study was included in the systematic review despite the unclear randomization status. In this study, 28 children received clonidine at a dose of 25 micrograms (mcg) daily for those weighing less than 40kg and 25 mcg bid for those weighing over 40kg, and 29 children received placebo for the 2-month treatment period. In the clonidine group, the dose was increased by 25 mcg for each participant after the first month of treatment. The reporting of outcomes is suboptimal as it is unclear which outcome(s) were primary. Also, in some instances hypothesis tests are reported and in others they are not. For the frequency of migraines outcome, which is normally the primary outcome in such trials, there did not appear to be significant differences between the groups. The groups also did not differ with respect to migraine intensity nor duration. In the subgroups of patients having a family history of migraine or migraine with aura, those treated with clonidine had significantly lower migraine frequencies during the treatment period. Those in the clonidine group reported more adverse events: 11 participants on clonidine vs. 6 participants on placebo reported adverse events. In the clonidine group, the most common adverse event was fatigue, followed by nausea. In this study, no sample size calculations are reported and given the small sample size, the trial was likely underpowered to detect small but meaningful clinical differences when comparing clonidine to placebo. There was a high risk of reporting bias given that hypothesis tests were only reported for some outcomes. There was also a

high risk of attrition bias given that 3 patients withdrew from the study and all were in the clonidine group. The risk of selection bias was unclear given the lack of clarity surrounding randomization and allocation concealment. Therefore, overall, the trial had a high risk of bias.

Based on this one study with high risk of bias, it is difficult to draw conclusions on the efficacy of clonidine for pediatric migraine prevention.

3.3.6 Trazodone

Trazodone is an anti-depressant medication that inhibits the reuptake of serotonin at the neuronal synapse. Its mechanism of action in migraine is unclear, though it has been postulated that the increased availability of serotonin could be related to its anti-migraine potential[143]. It is currently only approved for use in major depressive disorder in both Canada and the US and its use in migraine is therefore off label, even in the adult population.

Trazodone has only been assessed in one randomized study for this indication in the pediatric population. The efficacy of trazodone for the prevention of migraine in children and adolescents has been assessed in one small randomized, double-blind, placebo-controlled crossover trial involving 40 participants aged 7 to 18 years[144]. Battistella et al randomized participants to receive trazodone 1mg/kg/day divided tid or color-matched placebo daily for 12 weeks. A washout period was then initiated and maintained for 4 weeks, and participants were then crossed over to the other intervention. After the first treatment period, there was no difference comparing trazodone to placebo in terms of migraine frequency, and migraine duration was in fact longer in the trazodone group (16.1$\pm$1.4 hrs vs. 10.2$\pm$1.0, $p<0.01$). In the second treatment phase, the trazodone group had a greater reduction in migraine frequency (trazodone reduced from 2.1$\pm$0.2 attacks/month to 1.8$\pm$0.2 vs. placebo increased from 1.8$\pm$0.1 to 2.1$\pm$0.2, $p<0.005$) and duration (from 10.7$\pm$1.3 to 4.9$\pm$0.7 vs. from 11.9$\pm$1.3 to 13.1$\pm$1.3, $p<0.001$) as compared to the placebo group. No adverse events are reported in the manuscript and the authors state that no serious adverse events occurred. Two patients withdrew from the group initially randomized to trazodone and three

patients withdrew from the group initially randomized to placebo, due to errors in medication administration and onset of new illnesses. No sample size calculations are given and therefore it is unclear how the study was powered and for which outcome. The method of randomization was not described and allocation concealment is not mentioned in the text, therefore introducing an unclear risk of selection bias. The study was thus given a rating of unclear risk of bias.

Given that this is the only study on trazodone for pediatric migraine prophylaxis and given its somewhat unusual results (ie. superiority of trazodone over placebo only seen during second treatment phase), it would be imprudent to draw conclusions on the efficacy of trazodone for this indication.

3.3.7 Nimodipine

Nimodipine is a calcium-channel blocker, in the same category as flunarizine and cinnarizine. As with other migraine interventions, its exact mechanism of action is unclear. A recent animal study found that nimodipine administration resulted in downregulation of calcitonin gene-related peptide (CGRP) expression in the trigeminal nucleus caudalis[145]. CGRP is thought to play an important role in migraine pathophysiology: its levels rise during migraine, CGRP administration can trigger migraines, and a new class of medications called the CGRP receptor antagonists hold promise for migraine prophylaxis[146]. Therefore, the potential efficacy of nimodipine in migraine prophylaxis could be explained by downregulation of CGRP in the trigeminal nucleus caudalis, a brain area that is critical in migraine pathogenesis. In addition, research has shown that inhibition of L-type voltage-gated calcium channels, which occurs with nimodipine, decreases the rate of cortical spreading depression[147], which is believed to underlie migraine aura[131]. Therefore, there are a couple of potential mechanisms by which nimodipine may effectively prevent migraines. Neither Health Canada nor the FDA approved the use of nimodipine for migraine prevention in adults or children.

Only one randomized study has investigated the potential role for nimodipine in pediatric migraine prophylaxis. The Battistella et al group randomized 37 participants aged 7 to 18 years to nimodipine 10-20mg daily tid or to color-matched placebo in a double-blind, 2-arm, placebo-controlled, crossover trial[148]. Similarly to the other Battistella et al trial, a 4-week washout period occurred between the two treatment periods and each treatment period was 12 weeks in duration. After the first treatment phase, the groups did not differ in terms of migraine frequency nor migraine duration. However, migraine frequency was reduced to a greater extent in participants taking nimodipine during the second treatment phase (from 2.7$\pm$0.8 attacks/month to 1.9$\pm$1.7 vs. from 2.6$\pm$0.8 to 2.8$\pm$0.6, $p<0.01$), though no difference was seen for migraine duration in that phase. Three patients experienced mild transient gastrointestinal symptoms during the initial days of nimodipine treatment, though no other adverse events were reported. The methods of randomization and allocation concealment were not described, introducing the potential for selection bias. There may have also been attrition bias as 18.9% of the participants withdrew from the study and it was not made clear for what reason(s) and which group(s) these participants belonged to. Therefore, the risk of bias was rated as unclear for this trial.

Based on this one study, the efficacy and tolerability of nimodipine for pediatric migraine prophylaxis cannot be established.

3.3.8 Cinnarizine

Cinnarizine has two primary mechanisms of action: it acts as a calcium-channel blocker and also has antihistaminergic properties[149]. Its potential mechanism of action is migraine is not known. One small study found that cinnarizine induced serotonin release from platelets and inhibited platelet aggregation in both healthy volunteers as well as migraineurs[150]. However, given the complex pathophysiology of migraine, which is still not fully understood, it is unclear as to whether these effects seen in this small study could underlie cinnarizine's potential mechanism of action in

migraine. At the present time, cinnarizine does not have Health Canada nor FDA approval for use in any condition including migraine.

One randomized trial on cinnarizine was included in this review. Ashrafi et al randomized 62 children aged 5 to 17 years to receive either cinnarizine 1.5mg/kg daily or 50mg for those weighing above 30kg, or placebo for a 12-week treatment period[151]. There was a higher response rate in the cinnarizine group with 60% of the cinnarizine participants achieving a 50% or greater reduction in attack frequency as compared to only 31.3% of the placebo participants (p=0.023). Both groups had statistically significant reductions in headache frequency over time but no group differences were seen. It appears that cinnarizine was more effective than placebo in several of the secondary outcomes, including in reducing migraine intensity and duration. Three participants in the cinnarizine group had drowsiness as compared to one in the placebo group and one cinnarizine participant gained 2.5kg on the medication. Given the lack of description of allocation concealment in the manuscript, the study was given an unclear risk of selection bias, and thus an unclear risk of bias overall. Therefore, overall, this small study found evidence for the efficacy and tolerability of cinnarizine in this patient population, though findings need to be replicated prior to drawing conclusions on its efficacy.

3.3.9 Dimethothiazine

Dimethothiazine is a phenothiazine medication in the category of neuroleptic antipsychotic medications. It is not approved by Health Canada nor the FDA and is not available in North America, though it is available in some countries worldwide. Its potential mechanism of action in migraine is unknown.

As described above, Machín Altueña et al compared the efficacy of flunarizine, dimethothiazine and placebo in a group of 45 children aged 5 to 13 years[134]. The study was a randomized, double-blind, parallel-group trial carried out in Spain. All of the groups had similar rates of improvement: 93.3% of the dimethothiazine group had clinical improvement vs. 86.7% of the flunarizine group vs.

80% of the placebo group ($p>0.05$) and there were no significant differences in the secondary outcomes. The most common side effect was weight gain, occurring in 23.1% of the flunarizine group. The study was rated as having a high risk of bias given how small the groups were and the lack of sample size calculations, introducing the potential for a significant lack of power to detect clinically meaningful group differences. No mention is made of allocation concealment in the manuscript, and thus there was an unclear risk of selection bias. Given methodological issues with the trial, one cannot draw conclusions on the use of dimethothiazine for this indication from this one study.

3.3.10 Papaverine

Papaverine is a vasoactive compound that has been studied as potential intervention for preventing migraines. In rats, papaverine appears to revert cortical spreading ischemia to the less severe phenomenon of cortical spreading depression[152]. As has been mentioned previously, migraine aura is believed to be caused by cortical spreading depression[131], and if papaverine lessens this process, it could perhaps play a role in mitigating migraine. Papaverine does not have Health Canada nor FDA approval for use in migraine.

Sillanpää et al carried out the only randomized controlled trial assessing the efficacy of papaverine in children and adolescents with migraine[153]. Thirty-seven participants aged between 6 and 15 years with migraine or vascular headaches were randomized to receive either papaverine, starting at a dose of 5mg/kg daily divided bid or tid and doubling to 10mg/kg day in one month if tolerated, or placebo, for a 2 month treatment period. Significantly more participants taking papaverine had pain freedom during the treatment period as compared to placebo (6 participants out of 19 randomized to papaverine vs. 0 participants out of 18 randomized to placebo, $p<0.001$). Although specific numerical results are not given in the manuscript, a figure and a sentence in the text allude to significantly better improvement in migraine frequency, duration and intensity in the papaverine group as compared to placebo ($p<0.001$). The adverse event profiles are not reported in

the manuscript. This study had an overall unknown risk of bias given the probability of selection bias: no mention was made of allocation concealment. In addition, there was a potential for attrition bias, given that five participants were excluded: two for adverse events that were not described and three due to inadequate compliance with the intervention. There is no mention of which group(s) they belonged to, and therefore the risk of attrition bias is unknown. Based on this one small trial, it is not possible to make a conclusion on the efficacy, and especially the safety, of papaverine as a pediatric migraine preventative intervention.

3.4. Unpublished Trials

After searching the clinical trial registries, three unpublished randomized controlled trials with potential for eligibility were identified (clinical trial registry numbers: IRCT2013092914809N1, EUCTR2010-019947-21-ES and IRCT2013020412361N1). The authors were contacted about their trials, to inquire about eligibility and publication status: Dr. Afshin Fayyazi, Dr. Lala Jarin and Drs. Ahmad Talebian and Babak Soltani, for clinical trials IRCT2013092914809N1, EUCTR2010-019947-21-ES and IRCT2013020412361N1, respectively. Attempts at contacting the authors were made electronically via e-mail on the following dates: July 2nd 2015, July 14th 2015 and October 22nd 2015. Unfortunately, none of the authors replied to the e-mails, and contact was therefore not made. Because of the impossibility of knowing whether these trials were indeed eligible or not based on the limited information on the clinical trial registries, and because the results of these studies were unavailable, these trials could not be included in this systematic review. Their existence introduces the possibility of publication bias into this body of literature.

3.5. Meta-Analyses

3.5.1 Riboflavin vs. Placebo

Two studies assessed the efficacy of riboflavin for the prevention of migraines in children and adolescents[114,115]. However, the studies were too clinically heterogeneous to allow for pooling in a

meta-analysis. The main points of dissent were related to: 1) the dosing: riboflavin was dosed at 200mg/day in the MacLennan et al trial[114] and at 50mg/day in the Bruijn et al trial[115], 2) the outcomes: there was inadequate overlap in the measured outcomes for pooling of the data. Therefore, the results of these studies are described qualitatively above, but no statistical pooling was carried out on the riboflavin data.

3.5.2 Topiramate vs. Placebo

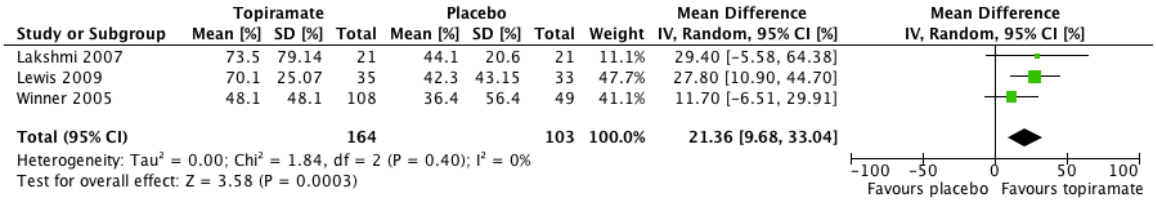
Although six studies on topiramate for pediatric migraine prophylaxis were included, only five of these studies[120–122,124,125] included efficacy data and only three of these studies[120–122] had substantial enough overlap in their reported outcomes to allow for pooling in a meta-analysis. In an attempt to include the other two topiramate studies[124,125] with efficacy data in the meta-analysis, the authors (Lisa M. Ford[125] and Paul Winner[124]) were contacted with inquiries about access to potentially unpublished data that would permit inclusion of their trials in the meta-analysis. Dr. Ford indicated to me that the manuscript associated with the published abstract[125] does contain the requested data, but that it could not be shared at this time given that the manuscript is in preparation for publication (Lisa Ford, personal communication over email, July 15th 2015). Three attempts to contact Dr. Winner (July 2nd 2015, August 11th 2015 and October 22nd 2015) were unsuccessful and the data required to add that study[124] to the meta-analysis were not obtained. In this way, the meta-analysis does not fully reflect the extent of the data on topiramate for pediatric migraine prophylaxis. Each of the studies with missing data consisted of a pooled analysis of data from previously published trials: the Ford et al[125] pooled analysis comprised 260 children aged 6 to 17 years from 5 separate trials and the Winner et al[124] pooled analysis comprised 49 adolescents aged 12 to 17 years from 3 separate trials. Thus, the number of participants from these two studies was large and failure to include this data in the meta-analysis certainly compromised the precision of the estimate of the effect size. However, both of these studies excluded from the meta-analysis also showed favorable efficacy results for topiramate, and it is not expected that their inclusion in

the meta-analysis would have resulted in a change in direction in the estimate of the effect size nor would we expect a dramatically different point estimate of the effect size.

The three studies[120–122] included in the meta-analysis were amenable to pooling given that each of the studies reported on the percentage change in the frequency of migraines comparing baseline to the treatment period. Because of significant clinical heterogeneity in the data from the three included studies, a random effects inverse variance method was used to estimate the estimate of the effect size. A pooled point estimate of the mean difference with 95% confidence intervals was generated using RevMan. The mean difference was chosen to estimate the effect given that all studies used the same scale to measure the outcome of change in migraine frequency, that is, the percentage on a 100-point scale.

The results of the meta-analysis comparing the efficacy of topiramate to placebo in terms of the percentage reduction in migraine frequency are displayed in Figure 4. The estimate of the mean difference is 21.4% (95% CI: 9.7-33.0%), which can be interpreted as such: based on the results of these three trials, topiramate is expected to reduce migraine frequency 21.4% more than placebo over the course of treatment, and this result is statistically significant.

Figure 4. Topiramate vs. placebo: pooled analysis of the percentage (%) reduction in migraine frequency comparing baseline to the treatment period



3.5.3 Flunarizine vs. Placebo

Although three trials compared flunarizine to placebo for pediatric migraine prophylaxis[132–134], there were no shared outcomes between the trials. Therefore, it was not possible to pool results from these three studies into a meta-analysis.

3.5.4 Other Interventions

All of the other interventions included in this systematic review were only assessed in isolated studies, thereby precluding the use of meta-analysis to pool data.

4. DISCUSSION

In this systematic review and meta-analysis, 19 eligible articles were identified, comprising 12 interventions for pediatric migraine prophylaxis: butterbur, riboflavin, topiramate, valproic acid, flunarizine, timolol, clonidine, trazadone, nimodipine, cinnarizine, dimethothiazine and papaverine. Only three interventions were assessed in more than one eligible study: riboflavin, topiramate and flunarizine. The remaining interventions were only studied in single trials, often of poor quality with either unclear or high risk of bias. Given this and given excessive clinical heterogeneity for the interventions that were studied in multiple trials, only one meta-analysis was possible: topiramate vs. placebo. This meta-analysis is limited by the fact that only half of the eligible studies were amenable to pooling, given a lack of overlapping outcomes and high clinical heterogeneity. Therefore, the results of this meta-analysis must be interpreted in light of the fact that the pooled results do not reflect the entire body of literature.

Given the limitations in volume and quality of evidence, few conclusions can be drawn from this systematic review. As described above, topiramate appears to be safe and effective for the prevention of migraine in the pediatric population, based on six eligible studies and one meta-analysis comprised of three of these trials. Both butterbur and valproic acid appear to have limited

tolerability in this population based on limited evidence. The remaining interventions included in this systematic review (ie. riboflavin, flunarizine, timolol, clonidine, trazadone, nimodipine, cinnarizine, dimethothiazine and papaverine) lacked the volume and quality of evidence required for making conclusions about efficacy and safety.

The most significant conclusion that can be drawn from this systematic review pertains to the paucity of evidence for interventions aimed at preventing migraine in children and adolescents. Two related projects, one systematic review[154] and one meta-analysis[155], with comparable objectives and scope other than the fact that only pharmaceutical interventions were eligible, have drawn similar conclusions about the evidence for pediatric migraine prophylaxis. There is a dire need for high quality, adequately powered and well-justified clinical trials in this body of literature.

One of the challenges in carrying out trials of interventions in the pediatric population pertains to the ethics of treating children with placebo. Although it is generally accepted that interventions must be compared to placebo in order to establish efficacy, some groups have called this philosophy into question. It has been argued that, in the pediatric population, it may be more ethical to use off-label interventions that are commonly prescribed in clinical practice as active comparators, rather than using placebo comparators[156]. In this context, non-inferiority hypotheses may be more appropriate than superiority hypotheses. Unfortunately, there are no established non-inferiority margins for common outcomes used in migraine research. Only a few published migraine trials with adult participants have used non-inferiority hypotheses[157–159], and neither employed a well-justified non-inferiority margin. In order to address this gap in the literature, the Non-Inferiority Margins in Migraine (NIMM) Research survey was conceived. The NIMM survey's rationale, methods and results are described below in Part II.

Given the need for high quality evidence in this body of literature, a clinical trial with low risk of bias and adequate power was designed. The results of the NIMM survey were used to determine the sample size for this trial, given that it is comprised of both a superiority hypothesis and a non-

inferiority hypothesis. The trial protocol is described below in Part III. With the NIMM survey and the proposed clinical trial, we aim to strengthen the body of evidence on the efficacy of interventions for the prevention of migraine in children and adolescents.

THESIS PART II: SURVEY ON NON-INFERIORITY MARGINS FOR MIGRAINE TRIALS: Determining a Non-Inferiority Margin for Migraine Trials: The Non-Inferiority Margins in Migraine Research (NIMM) Survey

1. Background

Traditionally, clinical trials have been designed around what is referred to as superiority hypotheses[160]. When setting a superiority hypothesis, the investigators are attempting to disprove the null hypothesis that two interventions do not significantly differ, that is, the goal is to show that one intervention is superior to the other. Superiority hypotheses are established based on setting a minimal clinically important difference (MCID). The MCID is the difference between the interventions that is felt to be sufficient to call the new intervention clinically superior to the comparative intervention.

Although superiority hypotheses are the most widely used in designing clinical trials and are thus the most familiar to the scientific community, they are not always the most appropriate type of hypothesis to employ for the clinical question. As the medical literature grows and the range of evidence-based treatment options expands, powering a study based on the hypothesis that one intervention is superior to the next is not always the most clinically relevant or appropriate option. For example, in many areas of medicine, there are interventions that are known to be safe and effective based on prior evidence, and investigators may wish to compare these interventions to new interventions that are less expensive, easier to use or access, or perhaps more tolerable to patients[161]. In these types of scenarios, the medical community would likely adopt the new intervention if it was shown to be no less effective than the established intervention, as opposed to requiring it to have evidence for superiority to the established intervention. The need to show

superiority is obviated by the relative advantages that the new intervention has over the established intervention (e.g. cost, ease of use, side effect profile, etc). Therefore, designing the trial with the goal of establishing superiority of the new intervention over the established intervention would be inappropriate, because if superiority is not shown statistically, the new intervention may be rejected by the medical and scientific communities, even though it may fact be as effective as the established intervention whilst offering relative advantages beyond efficacy. In this type of situation, a non-inferiority hypothesis is more appropriate than a superiority hypothesis to the goals of the trial and is more clinically relevant.

Non-inferiority hypotheses are used when the objective of the trial is to show that a new intervention is no worse than the established intervention relative to its efficacy or tolerability[162]. In order to establish a non-inferiority hypothesis and generate an estimate of an appropriate sample size to test this hypothesis, investigators must designate a non-inferiority margin (delta). Essentially, non-inferiority is based on showing that the difference found between the established intervention and the new intervention is smaller than a pre-defined margin, the non-inferiority margin (see figure 5). Therefore, the null hypothesis in a non-inferiority trial is that the new intervention is inferior to the established intervention given a difference between the interventions that is equal to the non-inferiority margin or larger than the non-inferiority margin.

Figure 5. Illustration of the difference between a superiority and non-inferiority hypothesis

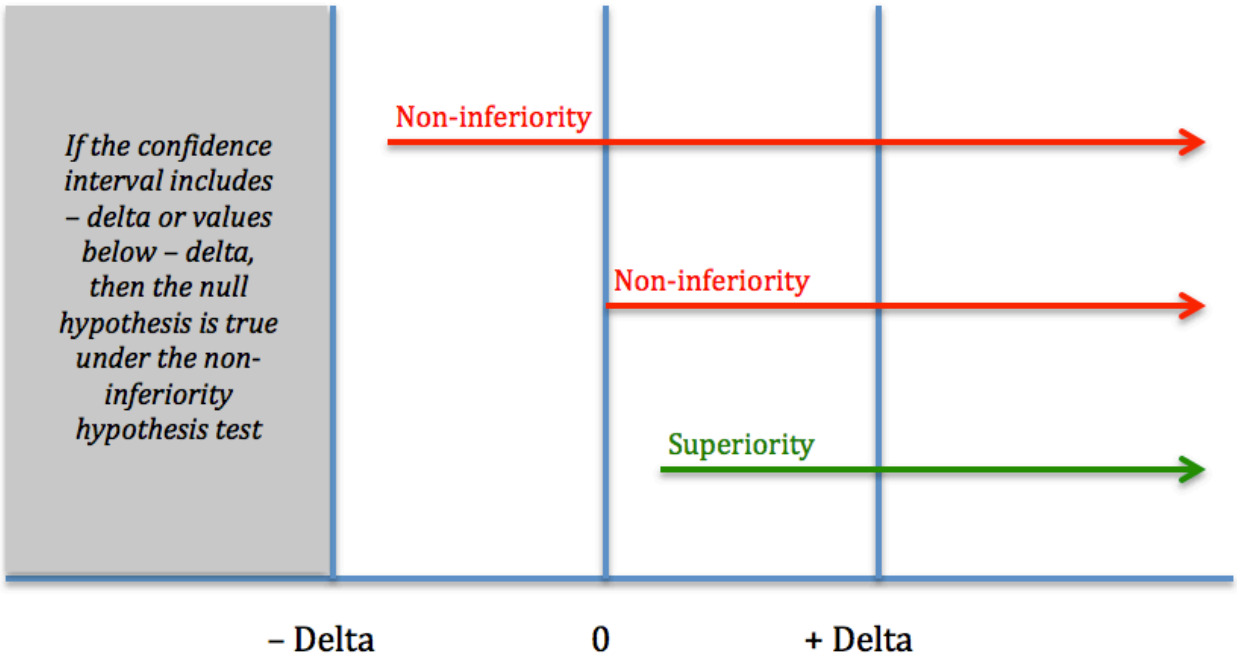


Figure 5. Illustration of the concept of a non-inferiority hypothesis. An intervention is considered non-inferior when the confidence interval for the estimate of its effect does not include values below the non-inferiority margin (– delta). As the figure illustrates, a conclusion of superiority can still be drawn with a non-inferiority hypothesis when the confidence interval for the estimate of the effect of an intervention is restricted to values above zero.

The process of establishing a non-inferiority margin requires careful consideration. Choosing an excessive margin will result in clinically inferior interventions being deemed non-inferior to establishing interventions, whereas choosing too small a margin will result in rejection of an intervention that may be clinically non-inferior, and will unnecessarily inflate the sample size of the trial[160]. In addition, non-inferiority margins should not exceed the MCID, for obvious ethical and intuitive reasons. Guidelines recommend choosing the margin based on both statistical and clinical considerations[163]. Several techniques for setting a non-inferiority margin have been described. For example, a variety of techniques have been proposed based on the use of historical data[162]. One such technique involves retrieving data from trials that have compared the established intervention

to placebo. The difference between the established intervention and placebo can thus be obtained, and one can determine a percentage of that difference that will be called the non-inferiority margin[160]. Although this historical approach theoretically allows one to conclude that a non-inferior intervention is also superior to placebo, a major assumption is made in the process: that the established intervention will have a similar effect in the current trials to its effect in prior trials[162]. This assumption can never be completely true, given that study populations, trial set-up and design issues will always create heterogeneity between trials. Another approach is based on the opinions of experts and/or stakeholders. In this way, individuals with expertise in the field and/or stakeholders are consulted about their opinions on an appropriate non-inferiority margin[163]. This approach, while subjective, is arguably preferable in that the hypothesis of the trial will be driven by expert or stakeholder consensus, and the results of the trial are therefore more likely to be pertinent to the knowledge users and consequently more likely to be applied in the clinical context.

Unfortunately, it appears that the majority of non-inferiority trials are published without an adequate description or justification for the choice of the non-inferiority margin. A recent systematic review found that only 23% of non-inferiority trials justified their choice of a non-inferiority margin[164]. This flaw in the literature, coupled with the increasing prevalence of non-inferiority trials[161,164], is alarming. Several reasons could explain this deficiency: inadequate training of investigators regarding the conduct and reporting of non-inferiority trials[164], journals not enforcing adherence to trial reporting guidelines[164], or perhaps, investigators choosing to set the non-inferiority margin themselves rather than consulting historical data or expert colleagues given the time and resource requirements associated with these approaches.

Non-inferiority trials appear to be underused in the area of migraine research. Only a few published trials in this area have tested non-inferiority hypotheses[157–159]. To our knowledge, none of these trials provided a justification for the choice of the margin. Therefore, it appears that headache experts have not yet been surveyed for their opinions on clinically acceptable non-

inferiority margins for outcomes used in migraine trials. Results of such a survey would be very useful in the design of future non-inferiority trials, given that they would provide a reference for investigators to use in choosing their non-inferiority margins. Furthermore, because the International Headache Society has published Guidelines for Controlled Trials of Drugs in Migraine[165], there are established and accepted standard primary outcomes that should be used in migraine drug trials, thus facilitating the use of not only universal primary outcomes but also associated non-inferiority margins.

The aim of this study is to survey North American headache experts regarding their opinions on acceptable non-inferiority margins for primary outcomes in migraine trials.

2. Objectives

2.1. Primary objectives

a. To establish a clinically acceptable non-inferiority margin for the recommended primary outcome in trials of migraine prophylaxis[165], that is, the change in the number of migraine attacks comparing baseline to the treatment period, through a survey of headache experts in North America.

b. To establish a clinically acceptable non-inferiority margin for the recommended primary outcome in trials of acute migraine treatment[165], that is, the percentage of patients who are headache free 2 hours after treatment, through a survey of headache experts in North America.

2.2. Secondary objectives

c. To establish clinically acceptable non-inferiority margins for important secondary outcomes in trials of migraine prophylaxis[165] through a survey of headache experts in North America. Secondary outcomes of interest will be:

- The change in the number of migraine days comparing baseline to the treatment period
- The intensity of the headache as measured by the 4-point severity scale (0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)

d. To establish clinically acceptable non-inferiority margins for important secondary outcomes in trials of acute migraine treatment[165] through a survey of headache experts in North America. Secondary outcomes of interest will be:
    - The percentage of patients who have a migraine relapse within 48 hours of treatment
    - The percentage of patients with sustained pain freedom (ie. pain freedom 2 hours after treatment and maintained 48 hours after treatment)

3. Methods

3.1. Study Design & Protocol

The Non-Inferiority Margins in Migraine Research (NIMM) survey was designed to establish clinically relevant non-inferiority margins through expert opinion for outcomes commonly used in migraine clinical trials and endorsed by the International Headache Society's Guidelines for Controlled Trials of Drugs in Migraine[165]. The NIMM survey comprised 11 questions. The first five questions pertained to determining participants' eligibility to complete the survey and to characterizing participants (eg. adult vs. child neurologist, percentage of practice devoted to research, etc – see Appendix G). The remaining six questions aimed to determine participants' opinions about non-inferiority margins for outcomes used in migraine trials. The outcomes of interest for prophylactic treatment trials were: the change in the number of monthly migraine

attacks comparing baseline to the treatment period, the change in the number of monthly migraine days comparing baseline to the treatment period and the change in the average migraine intensity comparing baseline to the treatment period. The outcomes of interest for acute treatment trials were: the absolute percentage of participants who are pain-free 2 hours after the intervention, the absolute percentage of patients who have a migraine recurrence within 48 hours of treatment and the absolute percentage of patients with sustained pain freedom. Within the initial five questions, branching logic was used to notify participants of their non-eligibility where applicable. For example, in question 1, participants were asked what kind of practitioner they identify as: an adult neurologist, a child neurologist or 'other'. For participants selecting 'other', branching logic was used to display a notification of non-eligibility (see Appendix G).

The American Headache Society (AHS) and the Canadian Headache Society (CHS) were contacted and asked to distribute the survey to their members via email. The survey was approved for distribution by both societies. The initial emails inviting AHS and CHS members to complete the survey were distributed in November 2015. Follow-up emails reminding potential participants about the survey were sent one month (December 2015) and two months (January 2016) following the initial invitation email.

The surveys were administered anonymously to participants using Research Electronic Data Capture (REDCap™). REDCap™ is a secure web application with a survey module that allows for both survey design and distribution in the context of a secure platform. Potential participants were presented with an email (see Appendix E) that briefly explains the survey and were provided with a link to the REDCap™ survey (see Appendix G). An introduction and consent script was presented to interested parties at the beginning of the survey, and provided details pertinent to the consent process. Essentially, the introduction script explained concepts pertinent to the study and the consent script explained that completion of the survey is not expected to engender any specific

harms or benefits, that identifying information will not be collected in the context of this study, and that participation in the survey is providing implied consent for participation in the study.

The Ottawa Health Science Network Research Ethics Board approved the study protocol (OHSN-REB Protocol #20150651-01H).

3.2. Inclusion & Exclusion Criteria

3.2.1 Inclusion Criteria

a. Practicing adult or child neurologist

b. Expertise in headache medicine

3.2.2 Exclusion Criteria

c. Cannot read and understand English

3.3. Statistics

Data were exported from REDCap™ into SAS® 4.0. Descriptive statistics were generated for each item (frequencies and percentages). Chi square (χ^2) tests of goodness of fit were employed to assess if there was a significant difference between the proportions of response items for each question.

4. Human Protection

4.1. Time Commitment

The time commitment involved in participating in the survey was the only ethical consideration that pertains to this project. Participants completed a ten-item survey, requiring a time commitment of 5-10 minutes for completion.

4.2. Risks Involved in Participating in the Study

It was not anticipated that any risks would be associated with study participation. The only action associated with participation was survey completion. There was no experimental manipulation, treatment nor physical testing of study participants.

4.3. Benefits Associated with Participating in the Study

There were no anticipated benefits associated with study participation. Study participants were not offered any incentives for participation and were not expected to directly benefit from publication of its results. The remote benefit of improving future non-inferiority trial designs may be construed as a benefit to some participants.

5. Results

In total, 120 individuals completed the NIMM survey. Twenty one respondents were ineligible to participate in the survey based on their responses to the initial screening questions: 20 individuals did not identify as a neurologist, and one individual indicated that they had no experience practicing Headache Medicine. After excluding these ineligible participants, the final sample size for the survey comprised 99 respondents.

Respondent characteristics are displayed in Table 3. The majority of the sample (84.9%) was comprised of adult neurologists and 74% of respondents reported practicing in the USA. The most common type of practice was academic, with 47.5% of respondents claiming to practice in this setting, while 34.3% of the respondents reported practicing in the community and the remainder reported practicing in a mixed model. Respondents had varying degrees of experience practicing Headache Medicine (see Table 1); interestingly, a large number of respondents (44.9%) reported over 20 years of practice experience. The majority of respondents reported spending less than 10% of their time on research activities (59.6%), while 23.2% reported spending 10-25% of their time

on research, and the remainder of the sample reported that over 25% of their time was spent on research (see Table 3).

Table 3. Characteristics of NIMM respondents

Characteristic	Total number of respondents (missing)	N (percentage)
Type of Neurologist		
Adult Neurologist	99 (0)	84 (84.9)
Child Neurologist		15 (15.1)
Location of Practice		
USA	96 (3)	71 (74)
Canada		25 (26)
Type of Practice		
Academic	99 (0)	47 (47.5)
Community		34 (34.3)
Mixed academic/community model		18 (18.2)
Years Practicing Headache Medicine		
0-5 years	98 (1)	16 (16.3)
5-10 years		17 (17.4)
10-15 years		7 (7.1)
15-20 years		14 (14.3)
Over 20 years		44 (44.9)
Percentage of Time Devoted to Research		
< 10%	99 (0)	59 (59.6)
10-25%		23 (23.2)
25-50%		9 (9.1)
50-75%		4 (4.0)
> 75%		4 (4.0)

The most commonly selected non-inferiority margin for the change in the number of monthly migraine attacks comparing baseline to the treatment period was 1 attack per month, with 39.4% of the respondents choosing this margin (see Table 4). The responses for the outcome of monthly attacks were not evenly distributed ($p<0.0001$). For the change in the number of monthly migraine days, 44.4% of the respondents selected 1 day as their preferred non-inferiority margin and this was the most commonly selected margin, with the responses for this outcome being unevenly distributed ($p<0.0001$). Respondents most commonly selected 1.0 as their preferred non-inferiority margin for the change in migraine intensity on the 4-point rating scale, with 31.3%

indicating this margin as their choice. Once again, the responses to this question were unevenly distributed ($p<0.0001$).

Table 4. Non-inferiority margin responses for prophylactic migraine trials

Outcome	Total number of respondents (missing)	Margin	Frequency of respondents selecting margin (percentage)
Change in the number of monthly migraine attacks comparing baseline to the treatment period	99 (0)	0.25	8 (8.1)
		0.5	28 (28.3)
		0.75	6 (6.0)
		1.0	39 (39.4)
		1.25	8 (8.1)
		Other*	10 (10.1)
Change in the number of monthly migraine days comparing baseline to the treatment period	99 (0)	0.5	20 (20.2)
		0.75	7 (7.1)
		1.0	44 (44.4)
		1.25	4 (4.0)
		1.5	16 (16.2)
		Other*	8 (8.1)
Change in the average migraine intensity comparing baseline to the treatment period (where the intensity of the headache is measured on the following 4-point severity scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)	99 (0)	0.2	9 (9.1)
		0.4	28 (28.3)
		0.6	18 (18.2)
		0.8	8 (8.1)
		1.0	31 (31.3)
		Other*	5 (5.0)

**See Appendix H*

For the first acute outcome, the absolute percentage of participants who are pain-free 2 hours after the intervention, 41.4% of respondents felt that 5% was the most appropriate non-inferiority margin (see Table 5). The latter margin was the most popular selection, and the responses to this question were unevenly distributed ($p<0.0001$). The most commonly chosen non-inferiority margin for the percentage of patients with a migraine relapse within 48 hours of treatment was 5%, with 42.4% of respondents indicating that this option was their preference. Again, the responses to this item were not evenly distributed ($p<0.0001$). Finally, for the

percentage of patients with sustained pain freedom at 48 hours, 5% was once again the most popular response item, with 42.4% of the respondents selecting this margin. The responses to this question were not evenly distributed ($p<0.0001$).

Table 5. Non-inferiority margin responses for acute migraine trials

Outcome	**Total number of respondents (missing)**	**Margin**	**Frequency of respondents selecting margin (percentage)**
Absolute percentage of participants who are pain-free 2 hours after the intervention	99 (0)	2.5	17 (17.2)
		5	41 (41.4)
		7.5	5 (5.0)
		10	25 (25.3)
		12.5	7 (7.1)
		Other*	4 (4.0)
Absolute percentage of patients who have a migraine recurrence within 48 hours of treatment	99 (0)	2.5	20 (20.2)
		5	42 (42.4)
		7.5	9 (9.1)
		10	21 (21.2)
		12.5	4 (4.1)
		Other*	3 (3.0)
Absolute percentage of patients with sustained pain freedom (ie. the percentage of patients who are pain free 2 hours after the intervention and remain pain-free 48 hours after the intervention)	99 (0)	2.5	18 (18.2)
		5	42 (42.4)
		7.5	8 (8.1)
		10	22 (22.2)
		12.5	5 (5.1)
		Other*	4 (4.0)

**See Appendix H*

Based on the most common responses selected for each item, expert opinion on appropriate non-inferiority margins for the outcomes studied is summarized in Table 6.

Table 6. Expert opinion on appropriate non-inferiority margins for commonly used migraine outcomes

Prophylactic Trial Outcomes		
Outcome	**Margin**	**Percentage of experts selecting margin**
Change in the number of monthly migraine attacks comparing baseline to the treatment period	1 day	39.4%
Change in the number of monthly migraine days comparing baseline to the treatment period	1 day	44.4%
Change in the average migraine intensity comparing baseline to the treatment period (where the intensity of the headache is measured on the following 4-point severity scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)	1.0 point	31.3%
Acute Trial Outcomes		
Outcome	**Margin**	**Percentage of experts selecting margin**
Absolute percentage of participants who are pain-free 2 hours after the intervention	5%	41.4%
Absolute percentage of patients who have a migraine recurrence within 48 hours of treatment	5%	42.4%
Absolute percentage of patients with sustained pain freedom (ie. the percentage of patients who are pain free 2 hours after the intervention and remain pain-free 48 hours after the intervention)	5%	42.4%

6. Discussion

The NIMM survey summarizes the opinions of neurologists with expertise in Headache Medicine on appropriate non-inferiority margins for outcomes commonly used in clinical trials of interventions for migraine. This survey is unique in providing the migraine research community with expert opinion from a large number of Headache Medicine specialists on optimal non-inferiority margins for migraine trial outcomes.

It is interesting to note that the majority of the respondents (59.6%) reported spending less than 10% of their time on research activities. Thus, our sample was comprised of participants who are primarily engaged in clinical Headache Medicine. We believe that this is a strength of the study, given that clinical Headache Medicine specialists are the primary knowledge users vis-à-vis clinical trials on migraine treatments. Another interesting feature of our sample pertains to the experience level of participants: 59.2% of participants reported 15 or more years of experience in practicing Headache Medicine. In addition, the various types of practice models (ie. academic vs. community vs. mixed model) were each well represented in the sample. Therefore, we believe that our sample of participants was optimal in that it was diverse and the collective degree of clinical experience was significant, thereby making the conclusions drawn more credible to a wide range of end knowledge users.

We used several evidence-based strategies in order to maximize participation[166]. We used social exchange theory in designing the email invitation by highlighting the minimal costs to participants (ie. brevity of the survey) and the potential benefits to future research studies. We did not collect any personal or sensitive information. We also attempted to optimize recruitment by sending two follow-up communications to potential participants. Finally, it is known that sending surveys through respected organizations can contribute to optimizing participation[166], and we were able to have the NIMM survey sent out through the AHS and CHS.

Respondents selected multiple-choice options in order to indicate their opinions on the non-inferiority margins. One could argue that the pre-specification of multiple choice options leads to biased results, by limiting respondents to available options. However, each survey item had an "Other" response option, whereby participants could select a margin outside of those listed in the multiple choice options. Given the low number of respondents selecting "Other" as an option (range from 3.0-10.1%), and given the heterogeneity of the written responses associated with the "Other" option (see Appendix H), it may be reasonable to conclude that designing the survey differently, for example, with free text entry as opposed to multiple choice options, would not have yielded drastically different results. The decision was made to use multiple choice options so as to simplify the survey for respondents and ensure that the survey would yield a set margin for each outcome. Designing the survey with free-text entry of margins may have avoided the potential problem of biasing respondents into selecting particular margins, but interpretation of the results would have been complicated in that it likely would not have been possible to select one preferred margin for each outcome in a valid manner. A survey with similar aims sampled expert opinion on non-inferiority margins for anticoagulants to prevent venous thromboembolism post-orthopedic surgery using free-text entry as a means of selecting the preferred margins, and the results showed a very wide range of responses that would be difficult to apply to practice[167].

Several additional limitations of this survey should be noted. There was a high likelihood of coverage bias given that AHS and CHS membership lists were used as the sampling frame. It is likely that Headache Medicine specialists who are members of these organizations differ systematically from Headache Medicine specialists who are not members of these organizations. Members are likely more involved in academic activities given that these organizations promote and support academic endeavors such as scientific meetings and research collaborations. Language minorities are likely systematically underrepresented in the AHS and CHS as all communications and meetings are held in English. The survey also had a significant potential for non-response bias for several

reasons. Firstly, although it was not possible to determine the total number of eligible Headache Medicine specialists within the AHS and CHS, we suspect that our response rate was low based on the total number of members who were sent the survey (eg. 1,211 AHS members were sent the survey). Because the survey was only sent in English, language minorities were likely systematically underrepresented amongst survey respondents. There was also a significant potential for measurement error in this survey. The survey topic was complex and although an attempt was made at formulating the clearest possible questions, the survey was not piloted and it is therefore possible that some respondents found the questions challenging to answer. Although outcomes were selected judiciously, through consultation of international guidelines, patients were not consulted on the choice of outcomes. The patient perspective is therefore lacking in this survey and this is an important limitation of the study. The recommended non-inferiority margins were selected using the mode of the responses. Although using the mode allowed us to simply translate the results of our survey, it arguably may not provide the ideal representation of the range of responses.

As the literature on migraine treatment expands and more interventions are consistently shown to have superior efficacy to placebo, non-inferiority trials will play an increasingly important role in expanding our knowledge of safe and effective treatments for migraine. This study provides a unique perspective from a large and experienced group of Headache Medicine specialists on their opinions regarding non-inferiority margins for outcomes used in migraine clinical trials. It is hoped that these results may be used in the design of future clinical trials, so that appropriate sample sizes may be calculated based in part on the recommended non-inferiority margins derived from this survey.

THESIS PART III: DESIGN OF A RANDOMIZED CONTROLLED TRIAL

1. BACKGROUND

As was summarized above, migraine is exceedingly common in children, affecting approximately 8% of all children and adolescents worldwide[1]. Migraine is also a significant cause of disability in adults[2] and children[6–8]. The literature review presented in the background section above (see thesis part I) combined with the data obtained through the systematic review (see thesis part I) provide a comprehensive overview of the evidence base for migraine management in pediatrics.

Several conclusions can be reached after reviewing the evidence for pediatric migraine prophylaxis. Firstly, amongst all categories of interventions, the pharmaceuticals have been the best studied. This is unsurprising given that funding for pharmaceutical research is more readily available than funding for non-pharmaceutical research, which tends to have less commercial value[168]. Amongst the pharmaceuticals, the most extensive body of literature pertains to the efficacy and safety of topiramate for the prevention of migraines in children and adolescents. Six studies have explored this question[120–125], and topiramate appears to be more efficacious than placebo for this indication based on both a qualitative and quantitative review of the evidence. However, topiramate also appears to be less tolerable to patients than placebo, with a host of relatively common side effects including cognitive side effects, weight loss and anorexia, paresthesias and upper respiratory tract infections. In addition to the six topiramate studies, the systematic review identified eleven other nutraceutical or pharmaceutical interventions that have been studied in randomized trials for this indication: butterbur[104], riboflavin[114,115], valproic acid[127], flunarizine[132–134], timolol[137], clonidine[142], trazadone[144], nimodipine[148], cinnarizine[169], dimethothiazine[134] and papaverine[170]. In addition to these interventions with evidence from randomized studies, a host of

pharmaceutical and nutraceutical interventions have only been assessed in non-randomized studies or low quality randomized studies that did not qualify for the systematic review: magnesium[53], coenzyme Q10[54], fish oils[55], combination nutraceutical interventions[57–59], levetiracetam[70,71], amitriptyline[75–77], L-5-hydroxytryptophan[56], cyproheptadine[76], pizotifen[171] and Botox[78,79].

Of the interventions with an evidence base other than topiramate, few hold promise as potential first-line interventions for the prevention of migraine in children and adolescents. A variety of limitations exist for some of these interventions. Several of the interventions are not available in Canada: nimodipine, cinnarizine and dimethothiazine. Nutraceuticals are considered to be natural health products and are regulated differently by Health Canada than pharmaceuticals[172] with less stringent regulations and surveillance as compared to pharmaceuticals. Therefore, the routine clinical use of nutraceuticals for the prevention of pediatric migraine is limited by the lack of stringency in regulations and quality control, with the following interventions falling into this category: butterbur, riboflavin, magnesium coenzyme Q10, fish oils, L-5-hydroxytryptophan and combination nutraceutical agents. A few of the interventions that have been studied for this indication are associated with significant side effect profiles that make their use as first-line agents less appealing to both physicians and patients, namely valproic acid, pizotifen and flunarizine. Most often, pediatricians or pediatric neurologists are prescribing prophylaxis for pediatric migraine. Several of the interventions that have been studied are of limited familiarity to these practitioners, and are therefore less likely to have successful uptake as first-line interventions: timolol, papaverine and pizotifen. Although preliminary evidence for Botox suggests that it might be efficacious in chronic migraine[78,79], it has not been studied for prophylaxis of episodic headaches.

Many practitioners use amitriptyline as a first-line intervention for migraine prevention in the pediatric age group[76]. It is therefore quite surprising that the evidence for its use is derived exclusively from non-randomized studies[75–77], with the exception of one randomized study

comparing its efficacy alone to its efficacy in combination with cognitive behavior therapy[35]. This lack of evidence and the commonality of its use render it an excellent candidate intervention for the next randomized controlled trial in the area. In fact, the Childhood and Adolescent Migraine Prevention study (CHAMP), currently underway, is comparing the efficacy of amitriptyline, topiramate and placebo in a randomized, double-blind, parallel-group design[173]. Given that amitriptyline is already being studied in a large, well-designed clinical trial, it would be difficult to justify the design of a second randomized trial aiming to answer the same question when there are so many other important and unanswered questions in this area of research.

Of the remaining interventions without limitations to successful uptake as described above and which lack consistent evidence for efficacy thus justifying study in a randomized trial, that is, clonidine, trazadone, papaverine, levetiracetam, and cyproheptadine, levetiracetam is the most likely to be deemed clinically acceptable to the medical community and to patients. As previously mentioned, clonidine has fallen out of favour as a migraine preventive agent, with recent data from one North American center suggesting that it is very infrequently prescribed for this indication[174]. Additionally, the data from the one randomized study on its efficacy is unconvincing[142] and it would therefore not be the ideal intervention to invest resources into further studying. Trazodone also lacks promise as a first-line migraine preventive agent, given that it appears to be used very infrequently in current clinical practice[174], and given that the only study on its efficacy for this indication failed to demonstrate that it has potential beyond placebo[144]. The FDA has not approved use of papaverine and Health Canada is regulating papaverine as a new drug[175], a category that applies to interventions with limited data on efficacy and safety in Canada due to a short period of sale or minimal sales. Given this and the minimal data found during this systematic review, papaverine is not an auspicious agent to be studied as a migraine preventive. Cyproheptadine, although relatively commonly used in many centers, tends to be used primarily in younger children, and much less commonly in adolescents[76,174]. The reason for its minimal use in the adolescent age

group likely pertains in part to conventional practice patterns, and in part to data from a small randomized study that found it to be less effective beyond 9 years of age as compared to its efficacy in younger children[176]. Therefore, cyproheptadine is less likely to be used in the adolescent age group, and given that migraine is the most prevalent in this pediatric subset of patients[1], it would be wiser to study another intervention that is more likely to be effective in adolescents with migraine. In contrast, levetiracetam has demonstrated promise for migraine prophylaxis in non-randomized studies[70,71], and has a relatively strong tolerability profile. Aside from the approximately 10% rate of behavioral and psychiatric side effects, it is relatively safe to use, does not require regular blood work surveillance and has the lowest toxicity ranking of all of the new anticonvulsant medications on the market[177]. In addition, pediatricians and pediatric neurologists are familiar with levetiracetam because it is commonly used for the treatment of epilepsy[178].

As is described above, only two non-randomized studies have assessed the efficacy of levetiracetam for the prevention of migraines in the pediatric population[70,71]. Because of its relative promise based on this preliminary data and because of a lack of significant barriers to uptake as compared to the other interventions identified in this review, it is of interest to investigate its efficacy and tolerability for this indication. In order to avoid duplication and to ensure that no current studies are underway to answer this question, clinical trial registries were searched for relevant protocols on July 15th 2015 (the National Institutes of Health (NIH) clinical trial registry: clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trial Registry Program: http://www.who.int/ictrp/en/). No pediatric studies were found. Only one study was identified through clinical trial registry searches (registration number: NCT00203216) and the clinical question was limited to the adult population aged 18 years and over. Therefore, levetiracetam shows promise for migraine prevention based on non-randomized data, is likely to have significant uptake clinically if found to be effective for this indication, and no competing

randomized studies are currently underway to assess its efficacy and tolerability in the prevention of pediatric migraine.

The goal of the proposed study will be to compare the efficacy and safety of levetiracetam to that of topiramate and placebo for the prevention of migraines in children and adolescents, using a randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial design.

2. METHODS

2.1. Study Objectives

The primary and secondary objectives have been chosen in order to comply with the recommendations detailed in the International Headache Society Guidelines for Controlled Trials of Drugs in Migraine[84].

2.1.1. Primary Objective

- To compare the efficacy of levetiracetam, topiramate and placebo for reducing the number of migraine attacks from baseline as compared to the final 4-week treatment interval in children and adolescents with migraine.

2.1.2 Secondary Objectives

- To compare the efficacy of levetiracetam, topiramate and placebo for reducing the number of migraine days from baseline as compared to the final 4-week treatment interval in children and adolescents with migraine.
- To compare the efficacy of levetiracetam, topiramate and placebo for reducing the average intensity of migraine attacks in children and adolescents with migraine.

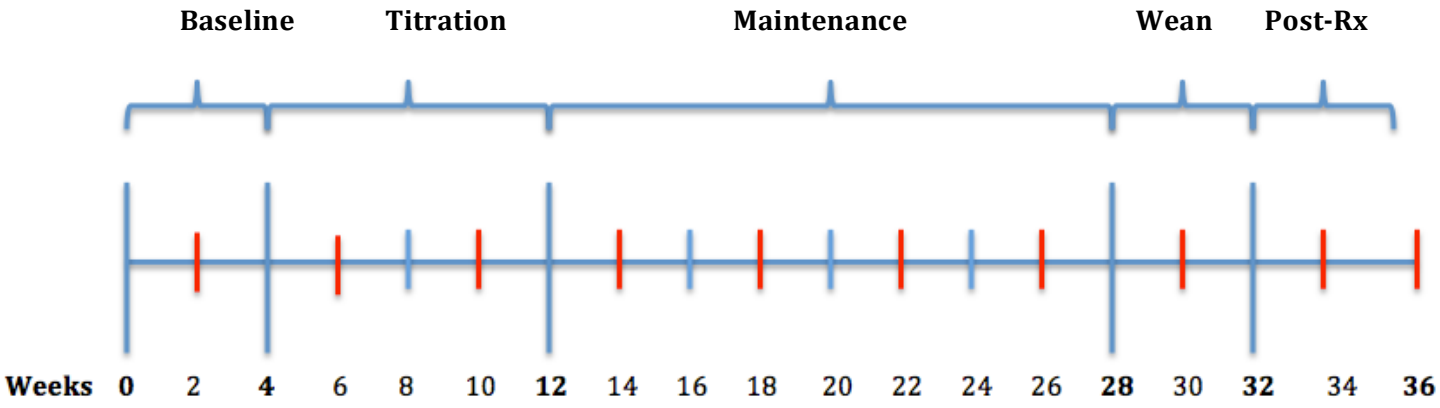
- To compare the responder rates, defined as the proportion of patients with at least a 50% reduction in migraine frequency during the treatment period, of levetiracetam, topiramate and placebo in children and adolescents with migraine.
- To compare the efficacy of levetiracetam, topiramate and placebo for reducing the disability associated with migraines in children and adolescents.
- To compare the safety of levetiracetam, topiramate and placebo in children and adolescents with migraine.

2.2. Study Design

This study will constitute a randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial. The study will be a multicenter trial given that it will not be feasible to recruit adequate numbers of patients from one center. Anticipating that each center will recruit an average of 15 patients per year, with a total sample size of 328 (see below), the plan will be to have 11 centers recruiting patients for two years. Each center will have a research coordinator assigned to the project, who will be responsible for patient recruitment, enrollment, scheduling patient follow-ups, carrying out telephone follow-ups, data entry and communication with the site investigator, the steering committee and the data and safety monitoring board. Participants will be recruited over a period of two years. After a 1-month baseline period, participants will be randomized to receive either levetiracetam, topiramate or placebo in a 1:1:1 allocation. The treatment period will begin with an 8-week titration period, followed by a 16-week maintenance period, followed by a 4-week weaning period. The trial will terminate after a 4-week post-treatment observation period following the weaning period. Telephone visits will occur with the site study coordinator and clinic visits will occur with the site investigator. Both the clinic visits and the telephone visits will occur monthly and they will be separated by 2-week intervals, such that patients have a point of contact

with the study every 2 weeks. The only exception to this alternating schedule will be for the last visit, which will be a telephone visit rather than a clinic visit. The study schedule template is displayed in figure 6.

Figure 6. Study timelines



**NB. Blue time points are clinic visits and red time points are telephone visits*

2.3. Eligibility Criteria

The eligibility criteria have been chosen based on the recommendations made by the International Headache Society in their Guidelines for Controlled Trials of Drugs in Migraine[84]. The rationale for the eligibility criteria are listed in Appendix I.

2.3.1 Inclusion Criteria

1. Migraine without aura or migraine with aura as per International Classification of Headache Disorders Third Edition, Beta Version (ICHD) criteria[86] (see Tables 7 and 8)
2. Age 8.0-18.0 years

3. Migraine frequency of 2-8 attacks per month in three month retrospective period and 1 month baseline period, with definition of attack as follows:
    i. Attacks are separated by at least a 48 hour headache-free interval
4. Migraines have been present for at least one year
5. Able to communicate sufficiently with parents in order to accurately complete a headache diary and study questionnaires

2.3.2 Exclusion Criteria

1. Other headache types are present and the participant cannot differentiate migraine from the other headache(s)
2. Fifteen or more headache days per month (ie. chronic migraine)
3. Overusing acute migraine medications:
    i. Taking a triptan on ten or more days per month
    ii. Taking acetaminophen or a non-steroidal anti-inflammatory medication on fifteen or more days per month
4. Taking a migraine prophylactic medication within three months of enrollment
5. Taking an antipsychotic or antidepressant medication within three months of enrollment
6. Received Botox injections for migraine within the past three months
7. Previous trial of topiramate or levetiracetam for migraine prophylaxis with:
    i. Adequate dosing
    ii. At least three months of prophylaxis
8. History of anaphylaxis or allergy to topiramate or levetiracetam
9. Pregnant, lactating or positive pregnancy test
10. Sexually active and not using a reliable birth control method
11. History of renal calculi

12. Significant hepatic or renal impairment
13. On the ketogenic diet
14. History of epilepsy
15. Has a psychiatric disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM V)
16. Has alcohol or drug dependence
17. History of significant behavioral problems
18. History of another chronic pain disorder

Table 7. ICHD criteria for pediatric migraine without aura

Criterion	Description
A	At least 5 attacks that fulfill criteria B-D
B	Attacks lasting 2-72 hours*
C	Two of the following four characteristics are present: • Unilateral or bilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravated by or causing avoidance of physical activity
D	During attacks, at least one of the following criteria are met: • Nausea and/or vomiting • Photophobia and phonophobia
E	Not better explained by another ICHD diagnosis

**Untreated or unsuccessfully treated*

Table 8. ICHD criteria for pediatric migraine with aura

Criterion	Description
A	At least 2 attacks meeting criteria B and C
B	One or more of the following fully reversible symptoms of aura: • Visual • Sensory • Speech and/or language • Motor • Brainstem • Retinal
C	Two of the following four characteristics are present: • At least one symptom of aura spreads gradually over five minutes or more, and/or two or more symptoms occur in succession • Each individual symptom of aura lasts between five and sixty minutes • At least one symptom of aura is unilateral • The aura is accompanied by a headache or followed by a headache within sixty minutes
D	Not better explained by another ICHD diagnosis and transient ischemic attack has been excluded

2.4. Interventions

Participants meeting all eligibility criteria after the one month baseline period will be randomized in a 1:1:1 fashion to either levetiracetam, topiramate or placebo. All interventions will be administered in an oral solution form, which will be prepared by the site pharmacy. The solutions will be matched in taste and color, so as to ensure that blinding is maintained based on the appearance of the intervention. The interventions will be titrated in a standard way during the course of the 8-week titration period following randomization.

Levetiracetam will be administered in an oral solution form, with a concentration of 100mg/mL. Participants in the levetiracetam group will be treated with a target dose of 20-40mg/kg/day, to a maximum of 3000mg/day. This target dosage was chosen based on prescription recommendations[179] and based on a previous prospective open-label study on the efficacy of levetiracetam for pediatric migraine prophylaxis[71]. The titration schedule will be as follows: initiate levetiracetam at 5mg/kg/day qHS for one week, then double to 10mg/kg/day divided bid for one

week, the increase to 15mg/kg/day divided bid for one week (ie. 5mg/kg qAM and 10mg/kg qHS), then increase to target of 20mg/kg/day and if required, can then increase in 5mg/kg/day increments weekly up to a maximum dose of 40mg/kg/day divided bid. If the patient is responding well to the intervention, then the dose of levetiracetam will be held at 20mg/kg/day; increases beyond 20mg/kg/day will only be carried out if necessary. Although levetiracetam is usually initiated at 10mg/kg/day and increased biweekly by 10mg/kg/day, the decision was made to initiate the dose at 5mg/kg/day and increase by 5mg/kg/day weekly in order to reflect the weekly titration schedule of topiramate. The similar weekly titration schedules will help to maintain participant and physician blinding.

Topiramate will be administered in oral solution form, with a concentration of 6mg/mL. Participants assigned to topiramate will have their dosage titrated up to 2-3mg/kg/day, to a maximum of 200mg daily, in accordance with dosing recommendations[179] and previous pediatric topiramate trials[120,173]. The titration will correspond to the following: 1) for children 8-12 years: initiate at 15mg qHS for one week, then double to 15mg bid for one week, then increase to 25mg bid for one week, then continue with 25mg/week increases in the dose, up to 2-3mg/kg/day or 200mg maximum, 2) for children aged over 12 years: initiate at 25mg qHS for one week, then double to 25mg bid for one week, then increase to 25mg qAM and 50mg qHS for one week, and continue titration by 25mg weekly increases up to 2-3mg/kg/day or the 200mg daily maximum (ie. 100mg bid)[179].

The placebo group will be given a matched placebo oral solution. The placebo group will follow a similar titration schedule to the intervention groups. They will be initially given 3mL of the placebo solution qHS, which will be doubled to 3mL bid after one week, and they will subsequently have 3mL/week increases up to 6mL bid, or, if required, they will continue to have 3mL/week increases throughout the titration period to a maximum of 12mL bid.

If tolerability issues arise for any of the interventions, then the investigator on site will have the liberty to deviate from the titration schedule as required clinically. The investigator will be able to hold off a dose increase, decrease a current dose or recommend discontinuation should intolerable adverse events occur. The investigator will remain blinded throughout, and will make decisions based on the clinical scenario while remaining blinded. However, if a serious adverse event occurs or if a clinical scenario arises that requires unblinding, the site investigator will contact the pharmacy department to break their blinding.

Each intervention will be weaned over the course of 4 weeks, in decrements of 25% per week. Blinding will be maintained during the weaning phase and beyond. The study investigator will have the authority to deviate from the weaning schedule at their discretion, should they believe that it is in the best interest of the patient to do so. Upon completion of the wean, at week 32, there will be a study visit with the site investigator. At this visit, the site investigator will discuss the need for ongoing prophylaxis with the patient and family, and will have the ability to start a prophylactic intervention at this point in time, if clinically indicated. Follow-up for the migraines will be arranged either with a child neurologist at that center, or with the patient's family doctor, as appropriate and depending on the patient and family's preference.

2.5. Outcomes

A paper-based headache diary will be maintained by participants from the beginning of the baseline period until the end of the follow-up period. The International Headache Society Guidelines for Controlled Trials of Drugs in Migraine recommend that headache diaries be used to track all outcomes in migraine prophylaxis trials, and recommend simple formats either in electronic or paper form that only track primary and secondary outcomes and avoid extraneous information so as to not overwhelm participants[84]. The headache diary template that will be employed for the purposes of this trial can be found in Appendix J. As recommended by the International Headache Society, it only measures the primary and secondary outcomes, with the

exception of also asking participants to report on the use of acute abortive medications. Although the International Headache Society recommends against acute medication usage as an outcome in parallel-group trials, they do state that this outcome should be included in headache diaries[84], and this is why this element was included in the template headache diary.

The choice of primary and secondary outcomes was based on the recommendations made by the International Headache Society[84]. The primary outcome will be the change in monthly migraine attacks comparing the baseline period to the final 4 weeks of treatment. Migraine attack frequency was chosen as the primary outcome given that it is likely more accurate than measuring migraine days. The problem with using migraine days for the frequency outcome lies in the fact that the number of days depends on attack duration, which is multifactorial (eg. acute treatment administered, time of day of attack onset). Thus, given that migraine days are influenced by migraine duration, this is a composite outcome, making migraine attacks better suited as the primary outcome. However, the change in migraine days comparing baseline to the final 4-weeks of treatment will be measured as a secondary outcome, given that the International Headache Society suggests that both migraine attack frequency and migraine days should be measured[84].

Other secondary outcomes of interest were also chosen based on the recommendations made by the International Headache Society[84]. Migraine intensity will be measured using a 4-point scale, as recommended in the guidelines:

- 0 – no headache
- 1 – mild headache
- 2 – moderate headache
- 3 – severe headache

The intensity of the migraines in both the baseline periods and the final 4 weeks of treatment will be averaged and compared, such that a change in average migraine intensity will constitute the outcome measured in this case.

In addition to measuring the change in migraine attack frequency and migraine day frequency, the responder rate for each group will be calculated. The responder rate is a recommended outcome by the International Headache Society, and comprises the percentage of patients achieving a 50% or greater reduction in migraine attack frequency when comparing the baseline period to the final 4 weeks of treatment[84]. It is believed to be a patient-centered outcome, given that patients often value the ability of a migraine prophylactic agent to reduce their migraine frequency by at least half[84]. However, there is no data to support which migraine outcomes are the most patient-centered, and in the absence of this data, reliance on the International Headache Society Guidelines is most appropriate.

The International Headache Society Guidelines also highlight that migraine-related disability or quality of life can be used as secondary outcomes in order to capture the global burden of migraine on the patient's life. There is a well-validated and widely used migraine-specific instrument available to measure migraine-related disability in the pediatric population: the Pediatric Migraine Disability Assessment Scale (PedMIDAS)[180]. The PedMIDAS was modeled after its adult counterpart: the MIDAS. It was developed to be simple to use, rapid to complete and sensitive to the unique lifestyle of children and adolescents. The PedMIDAS is comprised of 6 questions that evaluate the patient's ability to function in the past 90 days. Scores on the PedMIDAS range from 0 to a theoretical maximum of 540. Disability is assessed across three core domains: school functioning, home functioning and functioning in the social and play domains. PedMIDAS has good internal consistency and reliability, with a Cronbach's α score of 0.78 and a Pearson correlation score of 0.8 on test-retest[180]. In addition to its validation in the original clinical sample, the PedMIDAS has also been validated in a population-based sample[8]. The PedMIDAS also has a patient-based grading system developed by the original group who created the questionnaires: 1) Grade I: scores of 0-10 indicate little to no disability, 2) Grade II: scores of 11-30 indicate mild disability, 3) Grade III: scores of 31-50 indicate moderate disability and 4) Grade IV: scores above 51 indicate severe

disability[7]. PedMIDAS scores will be measured at baseline and at the end of treatment, and the change in the score will be compared between the groups. The PedMIDAS will be administered at the baseline visit, at the completion of the maintenance period (at week 28) and at the end of the follow-up period (at week 36), over the telephone. The PedMIDAS at baseline will be compared to both the PedMIDAS at week 28 and at week 36. The PedMIDAS questionnaire can be found in Appendix K.

Adverse events will be recorded in the headache diary. They will subsequently be coded using the Medical Dictionary for Regulatory Activity (MeDRA®), which is an international medical terminology system developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Adverse events will be classified based on the following categories: serious or non-serious, expected or unexpected, resolved, study-related, possibly study-related or unrelated to the study. Records will be kept on participants withdrawing from the trial due to an adverse event and on participants having their medication dose reduced or their titration held due to adverse events.

2.6. Randomization

Patients who are eligible for participation and who consent to participation will be randomly assigned to receive either levetiracetam, topiramate or placebo in a 1:1:1 fashion. The site research pharmacist will contact a central randomization service in order to carry out randomization. The central randomization service will be utilized in order to ensure that all sites are randomizing in the same way, and in order to facilitate allocation concealment. The central randomization service will employ a computer random number generator to assign participants to an intervention group. Randomization will be stratified by center and by age (8-13 years, $\geq$13 years to 18 years). Within each stratum, randomization will take place in blocks of 4, 6 or 8, with the size of the block being randomly selected.

The allocation will only be known to the central randomization service and to the site research pharmacist, who will have no contact with the investigators, research personnel nor with the participants. The site research pharmacist will maintain a password-protected, encrypted electronic list of patient allocations. This list will be maintained in order to have the information accessible on site for the purposes of rapid access in the event where a serious adverse event occurs and unblinding is required.

2.7. Study Visits

The study visit schedule is illustrated in figure 6. Each hospital visit will involve interaction of the participant with the study site investigator. The initial study visit at week 0 will comprise a complete history and physical exam by the study investigator. Eligibility criteria will be reviewed at the initial visit. If a patient is eligible for the study, the site investigator will contact the site research coordinator to further discuss the project with the patient and family. The research coordinator will explain study procedures to the patient and family and will seek informed consent from eligible participants aged 16 years and over and the parent or guardian (see Appendix L). Assent will be sought from eligible participants under 16 years (see Appendix M). Consenting participants will be sent home with a brochure explaining the study (see Appendix N). The research coordinator will explain the migraine diary in detail and will go over examples of how to complete it. Participants will be instructed to complete the migraine diary on a daily basis, and will be given tips on how to remember to complete the diary (eg. set alarm on phone, leave diary at the bedside and complete prior to going to sleep, etc).

Subsequent study visits will involve weight measurements, physical exams as necessary (eg. if patient is experiencing concerning side effects) and interval histories. An emphasis will be placed on reviewing the headache diary, intervention compliance and addressing any concerns from the patient or family.

During the monthly telephone visits, the site study coordinator will review the interval history, review compliance with the headache diary and intervention and discuss side effects with the patient and family. Where significant concerns arise with side effects or the patient's health, the study coordinator will liaise with the site investigator to schedule a more expedient follow-up.

3. Protecting Against Sources of Bias

3.1. Selection Bias

In order to decrease the potential for selection bias, patients will be randomized using a central randomization service that bases randomization on random number generation. This method of randomization is considered to have low risk of selection bias[83]. In addition, there is a low risk of selection bias related to allocation concealment when a central randomization service is used for the purposes of randomization[83]. To ensure that the most important covariates are balanced between the groups, stratification based on center and age (8-13 years, $\geq$13 years to 18 years) will occur during the randomization process. Other covariates (ie. gender, baseline migraine frequency) will be accounted for in linear regression models.

3.2. Performance Bias

This trial will be double-blind; only the pharmacists will know the group assignment, while the patients, families, study personnel and outcome assessors will remain blinded. The three interventions will all be administered in solution form, and the solutions will be matched for taste and color. In addition, solution volumes will be kept relatively homogeneous as will the titration schedules for each intervention. Clinical care will be identical for all three groups. In this way, several attempts have been made to ensure that blinding is both established and maintained, in order to limit the potential for performance bias.

3.3. Attrition Bias

Participants will have regular contact with study personnel, with follow-ups every 2 weeks. This will ensure that any patient and parental concerns are promptly addressed. In addition, the frequency of in-hospital follow-up visits will be minimized by providing telephone follow-up for 50% of the visits, thus minimizing the necessity for participants to displace themselves and hopefully optimizing retention. Missing data will be imputed using multiple imputation, which should also contribute to the minimization of attrition bias[83].

3.4. Detection Bias

The outcomes will primarily be derived from the participants' headache diaries. Given that the participants will be blinded and that efforts have been made to ensure that they remain blinded, detection bias should be minimized. The site study coordinators will assist in collecting some of the outcomes (eg. administration of PedMIDAS over the telephone at the last follow-up). Study coordinators will also remain blinded throughout the trial. Therefore, the risk of detection bias in this study should be low, based on how the outcomes are being ascertained.

4. STATISTICS

4.1. Sample Size Calculations

Three primary hypotheses of differing natures are being explored in the proposed study: two superiority hypotheses, whereby topiramate and levetiracetam are hypothesized to be superior to placebo, and a non-inferiority hypothesis, whereby levetiracetam is hypothesized to be non-inferior to topiramate with respect to the primary outcome. Given the three primary hypotheses, two separate sample size calculations were carried out and the final sample size was chosen based on the larger of the two results.

The primary outcome in this trial consists of the difference between the average number of monthly migraine attacks at baseline and the average number of monthly migraine attacks in the

final 4 weeks of treatment. This is a continuous outcome, characterized by standard deviation as the measure of variation. All sample size calculations were carried out using a power (1 – β) of 0.8 and an alpha (α) value of 0.05. Analyses were carried out taking into account the planned group sequential design with k=4 intervals (see below). The following data were used for the sample size calculations:

- *Topiramate vs. placebo hypothesis*: The only pediatric migraine trial comparing topiramate and placebo with similar eligibility criteria and the same primary outcome is the Winner et al trial[120]. In this trial, topiramate yielded a mean reduction in migraine attacks of 2.6 days, with a standard deviation (SD) of 2.6 days, and placebo yielded a mean reduction of 2.0 days, with a SD of 3.1 days. No sample size calculations were provided in this pediatric trial. Adult randomized controlled trials with similar eligibility criteria and assessing the efficacy of topiramate vs. placebo for migraine prophylaxis using the same primary outcome have set a minimal clinically important difference of 1.19 days per month, with a standard deviation of 2.5 days for their sample size calculations, based on pilot data[181–183]. In the absence of data on stakeholder opinion regarding the optimal MCID for this outcome, the decision was made to use the following values for the sample size calculation, based on the data from the Winner et al trial and the adult trials: 1) topiramate mean: 2.6, 2) placebo mean: 1.41, 3) SD: 2.5. Using these values, with a two-tailed hypothesis, an α of 0.05 and a power of 0.8, a sample size of N=71 per group was calculated using the PASS 14 software[184] (see Appendix O for PASS report). Planning for a drop-out rate of 25%, the final sample size to power the trial for the superiority hypothesis is 284.
- *Levetiracetam vs. placebo hypothesis*: As described above, two non-randomized studies evaluated the efficacy of levetiracetam for pediatric migraine prophylaxis[70,71]. Neither of these studies used a comparator, and both were observational. Neither used reasonably

similar inclusion criteria to the proposed study. In line with the third hypothesis, levetiracetam is expected to have similar efficacy to topiramate for this outcome. Therefore, a separate sample size calculation was not carried out for this second hypothesis as it was assumed that the required sample size would be similar to that required for the first superiority hypothesis.

- *Topiramate vs. levetiracetam hypothesis:* In order to calculate a valid sample size for this third hypothesis, the Non-Inferiority Margins in Migraine Research (NIMM) survey was carried out (see above). The NIMM survey asked experts to express their opinions on optimal non-inferiority margins for a variety of commonly used migraine outcomes. The most commonly chosen response item for the question regarding the non-inferiority margin for the primary outcome in this trial (ie. the change in the number of migraine attacks), was 1 attack, that is, experts felt that if an intervention yielded 1 additional attack per month or less as compared to the standard intervention, then it would be reasonable to consider it non-inferior. Therefore, in order to calculate a sample size for this non-inferiority hypothesis, the following values were used: 1) non-inferiority margin (delta): 1, 2) SD: 2.5 (as above). Using these values, with a non-inferiority hypothesis, which is by definition a one-tailed hypothesis, an α of 0.05 and a power of 0.8, a sample size of N=82 per group was calculated using the PASS 14 software[184] (see Appendix P). Planning for a drop-out rate of 25%, the final sample size to power the trial for the non-inferiority hypothesis is 328. Given that this calculation yielded a larger sample size than the superiority hypothesis calculation, the final sample size will be 328, so as to maintain adequate power for both hypotheses.

4.2. Planned Statistical Analyses

4.2.1 Primary Hypotheses

There will be three primary hypotheses in the proposed trial:

1. Topiramate will yield a greater decrease in the frequency of migraine attacks comparing baseline to the final 4 weeks of treatment as compared to placebo.
2. Levetiracetam will yield a greater decrease in the frequency of migraine attacks comparing baseline to the final 4 weeks of treatment as compared to placebo.
3. Levetiracetam will be non-inferior to topiramate with regards to the change in migraine attack frequency comparing baseline to the final 4 weeks of treatment as compared to placebo.

4.2.2 Primary Outcome Analysis Plan

All analyses will be performed using SAS® 4.0. Demographic characteristics for each group will be presented descriptively in tabular form.

The primary outcome in this study is a continuous outcome: the change in monthly migraine attacks comparing the baseline period to the final 4 weeks of treatment. The group means for this outcome will be compared using using a one-way ANCOVA. The response variable for the ANCOVA will be the number of monthly migraine attacks in the final 4 weeks of treatment, and analysis will adjust for the number of monthly migraine attacks at baseline as the covariate of interest. A Bonferroni correction will be applied in order to account for the multiple comparisons carried out post-hoc in the event where the initial ANCOVA is significant (ie. topiramate vs. levetiracetam, topiramate vs. placebo and levetiracetam vs. placebo).

In order to further explore the impact of covariates on the primary outcome, a linear regression model will be used to model the impact of group, age, gender and baseline migraine frequency on the change in migraine frequency.

4.2.3 Secondary Outcome Analysis Plan

The following continuous secondary outcomes will be analyzed in the same way as the primary outcome, with one-way ANCOVAs combined with Bonferroni corrections (where applicable post-hoc) in order to compare topiramate vs. placebo, levetiracetam vs. placebo and topiramate vs. levetiracetam:

1. The change in frequency in migraine days comparing baseline to the final 4 weeks of treatment
2. The change in the average migraine intensity comparing baseline to the final 4 weeks of treatment
3. The change in PedMIDAS score comparing baseline to week 28.
4. The change in PedMIDAS score comparing baseline to week 36.

The following discrete outcomes will be analyzed using chi square tests with Bonferroni corrections applied in order to compare topiramate vs. placebo, levetiracetam vs. placebo and topiramate vs. levetiracetam:

1. The proportion of participants achieving a 50% or greater reduction in migraine frequency when comparing baseline to the final 4 weeks of treatment
2. The proportion of participants with any adverse event during the trial
3. The proportion of participants who withdrew from the trial due to adverse events
4. The proportion of participants who had their dose reduced or titration held due to adverse events

4.2.4 Dealing with Missing Data and Approach to Data Analysis

Missing data will be imputed using multiple imputation techniques. Because one of the primary hypotheses of the trial is a non-inferiority hypothesis, both per-protocol and intention-to-treat analyses will be carried out.

4.2.5 Interim Data Analyses

Three interim data analyses will be planned using a group-sequential design: 1) the first analysis will occur when 25% of participants have been recruited; 2) the second analysis will occur when 50% of the participants have been recruited; 3) the third analysis will occur when 75% of the participants have been recruited; 4) the final analysis will occur when 100% of the participants have been recruited. In the interim analyses, only the primary outcome and the three outcomes related to adverse events will be analyzed (ie. the proportion of participants with adverse events, the proportion of participants who withdrew from the trial due to adverse events and the proportion of participants who had their dose reduced or titration held due to adverse events).

The O'Brien and Fleming method[185] will be used to control the level of type I error (α) in the proposed trial. The alpha will be spent in the following way, with p value cut-offs for each analysis as follows, given 4 planned analyses (k=4) at intervals i_k (see Appendix P for source of p values):

- First interim analysis (i_1): p=0.00116
- Second interim analysis (i_2): p=0.00529
- Third interim analysis (i_3): p=0.02532
- Final analysis (i_4): p=0.04643

Details regarding the boundaries used for the trial stopping rules are included in Appendix P.

5. TRIAL MANAGEMENT ISSUES

5.1. Recruitment Process

5.1.1 Recruitment Targets

Each of the eleven sites will be expected to recruit an average of 15 patients per year and recruitment will proceed over two years, so that each site recruits an average of 30 patients.

Site research coordinators will maintain a recruitment log detailing the number of patients assessed for study eligibility, the number excluded with standardized reasons for exclusion, the

number who consented to participation and the number who were randomized to an intervention. Site research coordinators will send recruitment logs to the trial's steering committee on a monthly basis. In this way, there will be an ongoing assessment as to whether recruitment targets are being met. If particular sites are struggling with recruitment, the trial steering committee will reach out to the affected site(s) and work on solutions aimed at improving the recruitment rate.

5.1.2 Strategies to Maximize Recruitment and Follow-Up

Site coordinators will host a presentation for all clinical personnel in participating clinics a few weeks prior to initiating site recruitment. Clinical personnel will be informed about the study, its purpose, its overall design as well as its recruitment methods. Posters with concise information about the study and the site coordinator's contact information will be placed in every clinic room and in multiple locations in each participating clinic. The site coordinator will send an email to clinical personnel every 3 months, which will briefly describe how recruitment at the site is proceeding relative to the site's recruitment target. Where problems with recruitment arise, the site coordinator will liaise with the trial steering committee to discuss solutions towards improving site recruitment.

Participants will be given brochures (Appendix N) that detail study procedures and what to expect as the study unfolds. Having this information at the time of recruitment should improve participants' understanding of their role in the study and hopefully improve retention and adherence long term. Biweekly follow-ups will be in place, thus giving participants the chance to have their concerns addressed expediently. At each follow-up, participants will be reminded about study procedures and the importance of adhering to their intervention as prescribed. Thus, every attempt will be made to keep the participants informed about the study and the importance of adherence. Maximizing participants' information in this way is thought to improve adherence in clinical trials[185]. Also, only 50% of the visits will be in clinic, while the other 50% will be conducted

over the phone. This should place a lesser burden of transportation and time on participants, and also hopefully contribute to optimal retention.

At the 4-week clinic visit, when patients will receive their intervention, the site study investigator will discuss means of ensuring medication adherence with participants (eg. setting an alarm on their phone, placing the medication bottle in an opportune location that will provide a visual reminder to take the medication, etc). At each follow-up, medication compliance will be addressed with participants. If issues arise, the study coordinator or investigator will re-explore means of maximizing adherence with the participant.

6. PERSONNEL AND ROLES

6.1. Study Personnel

6.1.1 Site Research Coordinators

Each site will have a site research coordinator. The time commitment of the research coordinator will vary as a function of the site recruitment target: the research coordinator will have anywhere from 0.1-0.4 full-time equivalents (FTE) devoted to this particular study and the number of FTEs will depend on the recruitment target. The site research coordinator will have a variety of roles in the study: 1) participant recruitment, 2) enrollment of eligible and consenting participants, 3) maintenance of recruitment logs, 4) hosting a presentation for clinic personnel prior to initiating the study in order to inform staff about the project, 5) setting up and maintaining posters in the clinic area with information about the study, 6) sending emails to clinic staff every 3 months with study and recruitment updates, 7) scheduling patient follow-ups and clinic visits, 8) carrying out telephone follow-ups, 9) data entry, 10) documenting and classifying adverse events, 11) notifying the trial sponsor of any serious and unexpected adverse events that require expedited reporting to Health Canada, 12) communication with the site investigator, 13) communication with the steering

committee, 14) communication with the data and safety monitoring board, and 15) communication with the lead site biostatistician. Site research coordinators will meet with site investigators on a monthly basis. Monthly reports detailing site recruitment statistics, drop-out statistics, adverse events and issues arising will be prepared by the site coordinators and sent to the trial steering committee. This information will also be compiled and sent to the data and safety monitoring board every 3 months and to the lead site biostatistician on a monthly basis. When the lead site biostatistician has determined that an interim data analysis is required (ie. when recruitment numbers have reached the threshold for interim analysis), site research coordinators will be required to complete data entry for recruited participants. All site research coordinators will enter data into REDCaP™, which is a secure, encrypted web application that allows researchers to collect data, store data and has a multitude of other functions. The use of REDCaP™ by all sites will allow for all data to be stored in one location, which will facilitate analyses for the lead site biostatistician.

6.1.2 Site Investigators

Site investigators will be responsible for filing research ethics board applications at their respective sites. Site investigators will also carry out all clinic visits with participants, which will involve weighing the patients, carrying out physical exams as required, taking interim histories, discussing intervention compliance, addressing patient concerns, inquiring about adverse events, and addressing any clinical concerns or issues arising. The documentation of adverse events, and notification of the trial sponsor of serious and unexpected adverse events that require expedited reporting to Health Canada, will not only be the responsibility of the research coordinator, but also of the site investigator, given that they may be informed of adverse events during clinic visits. Site investigators will be in regular communication with site research coordinators about issues arising from the study. Monthly meetings between the site research coordinator and site investigator will be arranged in order to ensure that issues are addressed and that the core site team is working together to maximize recruitment and follow-up.

6.1.3 Site Research Pharmacists

The site research pharmacists will be responsible for coordinating randomization. At the time of randomization, the research pharmacist will contact a central randomization service. Once randomized by this service, the site research pharmacist will record the participant's allocation into a password-protected, encrypted electronic document. The pharmacist will prepare and package the study interventions for participants. Participants will visit the site pharmacy on a monthly basis and the site research pharmacist will dispense the intervention to the participants at this time.

6.1.4 Lead Site Research Coordinator

The lead site research coordinator will be assigned all of the same roles as the site research coordinators, in addition to several other tasks: 1) serving as the primary contact person for the site research coordinators should questions about the protocol or troubleshooting arise, 2) assisting the principal investigator with the lead site research ethics board application, the Health Canada Clinical Trial Application, preparation of the trial protocol and other required documentation and 3) sitting on the trial steering committee. Given the significant time commitment required to fulfill all of these tasks, the lead site research coordinator will have 1.0 FTEs devoted to this project.

6.1.5 Lead Site Principal Investigator

The lead site principal investigator will have the same responsibilities as the site investigators, in addition to their role as principal investigator and trial sponsor. In addition to these roles, the lead site principal investigator will: 1) write the trial protocol and create protocol binders for all sites with the assistance of the lead site research coordinator, 2) act as the trial sponsor and obtain funding for the trial, given that this will be an investigator-initiated trial 3) prepare and submit a Clinical Trial Application to Health Canada along with the lead site research coordinator, 4) serve as

the primary contact point for site investigators should questions arise about research ethics board applications, the trial protocol or troubleshooting arise and 5) sit on the trial steering committee.

6.1.6 Lead Site Research Pharmacists

The lead site research pharmacists will have the same roles as the site research pharmacists.

6.1.7 Lead Site Biostatistician

The REDCaP™ database will be designed by the lead site biostatistician, in consultation with the lead site principal investigator. The lead site biostatistician will be in charge of carrying out all of the data analyses, for both the interim analyses and the final analysis. Monthly reports will be sent to the lead site biostatistician from the site research coordinators about recruitment statistics, drop-out statistics, adverse events and issues arising at individual sites. The lead site biostatistician will merge the data from the various sites in order to prepare a compiled report for the monthly steering committee meetings. In addition, interim analyses will be the responsibility of the lead site biostatistician. When recruitment targets for interim analyses have been reached, the lead site biostatistician will contact the site research coordinators to ask for all data entry to be completed on enrolled participants. This data will then be used to carry out the interim analyses, and the biostatistician will prepare a report on interim results to be submitted to the data safety monitoring board.

6.2. Data and Safety Monitoring Board

The data and safety monitoring board (DSMB) will comprise three individuals: 1) a biostatistician (not the same individual as the lead biostatistician), 2) a neurologist (not the same individual as the lead site principal investigator), 3) an epidemiologist with expertise in clinical trial design and implementation. The DSMB will meet every 3 months, during which time the reports from the site research coordinators will be reviewed. This will give the DSMB the opportunity to review adverse events and issues arising at the various sites. In addition to the scheduled meetings,

meetings will occur once interim data analyses have been completed. The lead site biostatistician will provide the interim data analysis reports to the DSMB, and an interim meeting will be scheduled. At these times, the DSMB will review the interim efficacy and safety data.

If concerning trends in adverse events arise, or if serious adverse events occur, the DSMB will contact the research pharmacists at the involved site(s) to break blinding on involved participants when necessary. The DSMB will have the authority to recommend early trial termination, should major concerns arise with regards to adverse events or at interim analyses. In the event where the DSMB does recommend early trial termination, a report will be prepared by the DSMB biostatistician, who will communicate the recommendation verbally and in writing to the trial steering committee.

6.3. Trial Steering Committee

The trial steering committee will comprise the lead site principal investigator, the lead site research coordinator and the lead site biostatistician. The steering committee will meet monthly in order to review trial progress. The monthly report from the biostatistician, consisting of a compilation of the site research coordinator reports, will be reviewed. Recruitment numbers, drop-outs, adverse events and issues arising at the sites will be discussed and reviewed. Where necessary, action points will be developed in order to improve trial implementation. As above, recommendations from the DSBM will be communicated to the steering committee through the DSBM's biostatistician.

7. ETHICAL CONSIDERATIONS

7.1. Clinical Equipoise Regarding Levetiracetam for Pediatric Migraine Prophylaxis

As is described above, there is clear uncertainty in the literature regarding the efficacy of levetiracetam for the prophylaxis of pediatric migraine. Only two non-randomized studies[70,71] have

assessed the safety and efficacy of levetiracetam for this indication. Levetiracetam has never been compared to placebo nor to topiramate in the literature. In order to establish assay sensitivity for levetiracetam as compared to placebo, which has not yet been determined in the literature, it is necessary to compare it to placebo in a double-blind, randomized fashion. In addition, the comparison of levetiracetam to topiramate will help to establish its non-inferiority with regards to efficacy and safety relative to the intervention with the highest level of evidence in the literature. The two interventions have never been compared in the past, and there is thus uncertainty as to whether levetiracetam is non-inferior to topiramate for the prevention of pediatric migraine. Therefore, there is definite clinical equipoise in the literature regarding the two primary hypotheses of this trial, that is: 1) levetiracetam will yield a greater decrease in the frequency of migraine attacks comparing baseline to the final 4 weeks of treatment as compared to placebo, 2) levetiracetam will be non-inferior to topiramate with regards to the change in migraine attack frequency comparing baseline to the final 4 weeks of treatment as compared to placebo.

7.2. Informed Consent

Informed consent will be obtained in written (see Appendix L) and verbal form from both participants aged 16 years and over and the parent(s) or guardian(s) of the participant. For participants younger than 16 years of age, verbal and written (see Appendix M) assent will be obtained. If a participant over the age of 16 years is deemed cognitively unable to provide informed consent, then assent will be sought in lieu of consent, and the parent(s) or guardian(s) will provide informed consent. The consent and assent forms have been written in accordance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*[186]. The research coordinator will explain important elements of the consent process to the participant and their parent(s) or guardian(s) and will be present to answer questions about the consent form. Participants and their parent(s) or guardian(s) will also be given the opportunity to take the consent form home to further discuss the study and their possible involvement. Contact

information for the principal investigator is available on the consent form (see Appendix L) and the principal investigator will be available to participants and their parent(s) or guardian(s) for questions related to consent should they arise.

7.3. Special Considerations in the Pediatric Population

In order to improve migraine care in children and adolescents, it is necessary to carry out well-designed clinical trials of interventions for pediatric migraine. This study will add significantly to the body of evidence in the pediatric migraine prophylaxis literature. Because this is a study involving children and adolescents, special considerations will be taken to address concerns related to carrying out research on this vulnerable population. The risk/benefit ratio in this study has been carefully considered. There is a significant anticipated benefit to participants through participation in this trial: participants from all three intervention groups are expected to benefit from reduced migraine frequency over time. Although there are risks of adverse events for both topiramate and levetiracetam, the participants and their parent(s) or guardian(s) will be notified about these potential risks during the consent process. Also, the risk of serious adverse events for each of these interventions is very low.

Because of the young age of the participants, both a consent and an assent process will be available. Participants under the age of 16 years or those who are not cognitively able to provide informed consent will be guided through an assent process. The assent form will be tailored for younger children, with a more concise presentation and the use of simplified language.

7.4. Privacy and Confidentiality

The privacy and confidentiality of participants will be protected in a variety of ways. Contact information for participants will be stored in a separate file to the data collection files. Storage of contact information is required in order for the research coordinator to have the ability to contact participants for telephone follow-ups. This information will be stored in an encrypted, password-protected electronic file that will be divorced from any of the other study data. In addition, the

research pharmacists will maintain an encrypted, password-protected electronic file of participant group assignments, which will include participant names and contact information. This is necessary in order to ensure that unblinding can occur should a serious adverse event be reported. The remaining study data will be entered by the site research coordinators into REDCaP™, which, as described above, is a web-based, secure and encrypted data storage software that is widely used for research purposes. The REDCaP™ database will contain only de-identified data: study identification numbers, generated at random, will be used for data storage. No identifiers will be included in the database.

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Thesis Appendix

8. Appendix A. Electronic search strategies for identification of studies

MEDLINE Search Strategy:

1. exp Migraine Disorders/
2. status migra*.mp.
3. migraine*.tw.
4. or/1-3
5. pc.fs.
6. prophyl*.mp. or prevent*.ti,ab.
7. Amitriptyline/
8. exp Botulinum Toxins/
9. Clonidine/
10. exp Cyproheptadine/
11. Domperidone/
12. flunarizine/ or trazodone/
13. Piracetam/
14. Metoclopramide/
15. Nimodipine/
16. Papaverine/
17. Pizotyline/
18. Propranolol/
19. Timolol/
20. Topiramate.mp.
21. Valproic Acid/
22. 5-Hydroxytryptophan/
23. exp Fatty Acids, Omega-3/
24. Q10.ti,ab.
25. Coenzyme.mp.
26. Riboflavin/
27. Magnesium/
28. Petasites/ or butterbur*.tw.
29. exp Ginkgolides/
30. or/5-29
31. 4 and 30
32. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
33. (child* or adolescent* or infan*).mp.
34. 31 and 32 and 33
35. remove duplicates from 34

Embase Search Strategy:

1. exp migraine/
2. status migrainosus.mp.
3. migrain*.tw,kw.
4. Alice in Wonderland Syndrome.tw.
5. or/1-4
6. prophyl*.mp. or prevent*.ti,ab.
7. prophylaxis/
8. amitriptyline/
9. botulinum toxin/
10. clonidine/
11. cyproheptadine/
12. domperidone/
13. flunarizine/
14. trazodone/
15. piracetam/
16. metoclopramide/
17. nimodipine/
18. papaverine/
19. pizotifen/
20. propranolol/
21. timolol/
22. topiramate/
23. valproic acid/
24. 5 hydroxytryptophan/
25. omega 3 fatty acid/
26. ubidecarenone/
27. riboflavin/
28. magnesium/
29. butterbur/
30. ginkgolide/
31. or/6-30
32. 5 and 31
33. (random$ or factorial$ or crossover$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
34. limit 32 to (child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
35. (pediatric or paediatric or child$ or newborn$ or adolescen$ or infan$ or neonat$ or youth$ or teen$ or baby$ or babies$ or preschool$ or pre-school$ or elementary school$ or elementary student$ or kindergarten or nursery school$ or grade school$ or public school$ or highschool$ or high school$ or schoolchild$).mp.
36. 32 and 33 and (34 or 35)
37. limit 36 to embase
38. remove duplicates from 37

CENTRAL Search Strategy:

1. migrain*.tw,kw.
2. prophyl*.mp. or prevent*.ti,ab.

3. (Amitriptyline or Botox or Clonidine or Cyproheptadine or Domperidone or Flunarizine or Trazadone or Levetiracetam or Metoclopramide or Nimodipine or Papaverine or Pizotifen or Propranolol or Timolol or Topiramate or Valproic Acid or L-5-hydroxytryptophan or Omega-3 or Coenzyme Q10 start here or Riboflavin or Magnesium or Butterbur or Ginkgolide).tw.

4. 1 and (2 or 3)

5. (pediatric or paediatric or child$ or newborn$ or adolescen$ or infan$ or neonat$ or youth$ or teen$ or baby$ or babies$ or preschool$ or pre-school$ or elementary school$ or elementary student$ or kindergarten or nursery school$ or grade school$ or public school$ or highschool$ or high school$ or schoolchild$).mp.

6. 4 and 5

7. remove duplicates from 6

9. Appendix B. Systematic Review Included Studies Eligibility Forms

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Oelkers-Ax 2008
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: MacLennan 2008
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Bruijn 2010
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?		x	

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Winner 2005
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Lakshmi 2007
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	X		
Was the study randomized?	X		
Was the study either single or double blind?	X		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	X		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	X		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Lewis 2009
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	X		
Was the study randomized?	X		
Was the study either single or double blind?	X		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	X		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	X		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Pandina 2010
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	X		
Was the study randomized?	X		
Was the study either single or double blind?	X		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	X		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	X		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Winner 2006 Pooled Analysis
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Apostol 2008
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	X		
Was the study randomized?	X		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	X		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	X		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	X		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Sorge 1988
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Sorge 1985
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?		x	

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Noronha 1985
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?		x	

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Sillanpää 1977
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Battistella 1993
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?		x	

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Battistella 1990
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?		x	

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Ford 2014
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Ashrafi 2014
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? ☐ Include ☐ Exclude ☐ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Machín Altueña 1987
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

Prophylactic Interventions for Pediatric Migraine: *Study Eligibility Checklist*

Study ID#: Sillanpää 1978
Screened by: SLO

Table 1: Inclusion Criteria

Characteristic	Yes (Include)	No (Exclude)	Unsure (Discuss)
Study Design			
Is the study a clinical trial?	x		
Was the study randomized?	x		
Was the study either single or double blind?	x		
Participants			
Was the study limited children and/or adolescents, aged 18 and under?	x		
Was the study limited to participants with one or more of the following: episodic migraine, chronic migraine, migraine with aura or migraine without aura?	x		
Was the diagnosis of migraine made using ICHD criteria (1988 and later) or other validated diagnostic criteria (before 1988)?	x		
Interventions			
Was the treatment a pharmacologic or nutraceutical intervention (or interventions) taken daily to prevent migraines?	x		
Comparison			
Was there a placebo as comparison?	x		

Table 2: Exclusion Criteria

Characteristic	Yes (Exclude)	No (Include)	Unsure (Discuss)
Study Design			
Was the study randomized in clusters (ie. a cluster RCT*)?		x	
For cross-over trials only: Was the washout period less than 4 weeks?			

*Cluster RCT: A cluster RCT is a trial in which individuals are randomized in groups (i.e. the group is randomized, not the individual).

Should this study be included in the review? □ Include □ Exclude □ Unsure

10. Appendix C. Systematic Review Included Studies 'Characteristics of Studies' Tables

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Oelkers-Ax 2008
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, partly double-blind, 3-arm parallel-group trial • 8 week baseline period followed by 12 week treatment phase followed by 8 week post-treatment/follow-up phase • Patients were recruited using advertisements from the catchment area of the Heidelberg University hospital
Participants	• Children aged 8-12 with migraine meeting ICHD criteria • All had at least 1yr history of migraine • Had to report 2 or more migraines/month in 3 months preceding enrollment and during the baseline period • Higher baseline migraine frequency in the butterbur group (9.8 ± 7.6 vs. 5.5 ± 4.4 vs. 5.0 ± 2.5, p=0.409)
Interventions	• Petadolex®: 20 patients randomized to receive 50mg/day if 8-9yo or 50mg bid if 10-12yo with a dose increase to 75mg/day for 8-9yo or if 10-12yo 75mg bid at 8 weeks if suboptimal response in the first 8 weeks of treatment • Placebo: 19 patients randomized to placebo, with a "dose increase" at 8 weeks if suboptimal response • Music therapy: 24 patients randomized to 12 weekly sessions of music therapy involving music-aided relaxation training, body awareness techniques and conflict training
Outcomes	• Primary outcome: All three groups had a statistically significant reduction in headache frequency comparing baseline to post-treatment and follow-up in both as-treated and intention-to-treat analyses (ITT) (see Table 3). In post-treatment, music therapy was superior to placebo (p=0.042 in ITT) but there was no difference between placebo and butterbur. At 6 months post-treatment, both music therapy (p=0.018) and butterbur (p=0.042) were superior to placebo. • Secondary outcome: Responder rates, that is those achieving a 50% or greater reduction in migraine frequency, were highest in the music group at post-treatment (p=0.01), but did not differ between the groups at the 6 month follow-up. • Adverse events: No difference in adverse events between groups nor study periods; butterbur group mostly reported

	gastrointestinal symptoms, dermal or allergic symptoms
Notes	• Higher drop-out rate in intervention groups: 5% in the placebo group vs. 25% in butterbur group vs. 29% in the music therapy group

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: MacLennan 2008
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, 2-arm, parallel group clinical trial • Patients were followed for a 4-week baseline period and treated for 12 weeks • Recruitment through local schools, the ED or the outpatient department of the Children's Hospital of Westmead, Australia
Participants	• Children aged 5-15 years with migraine meeting ICHD criteria • Participants had to have migraine for at least 3 months with monthly migraine frequency between 2 and 8 attacks/month • Participants also had to have at least one migraine in 4 week baseline period • No significant differences found between the groups at baseline
Interventions	• Riboflavin: 27 participants were randomized to riboflavin 200mg daily • Placebo: 21 participants were randomized to placebo
Outcomes	• The trial was stopped after a 12 month interim data analysis due to lack of evidence for a difference between the groups • Primary outcome: There were no group difference in the proportion of participants achieving a 50% or greater reduction in migraine frequency (66.6% of placebo vs. 44.4% of riboflavin, p=0.125) • Secondary outcomes: No change in migraine intensity in either group, mean number of days with associated symptoms decreased for placebo but not for riboflavin, both groups had a decrease in number of treated migraine attacks • Adverse events: One child taking riboflavin had an increase in the number of tension headaches, and 4 children in the riboflavin group noted a change in their urine color
Notes	• There is no note about what type of stopping rule they used in the interim data analysis and it is questionable as to whether early termination was warranted.

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Bruijn 2010
Study Status: □ Included □ Excluded □ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, cross-over study • 4 week baseline period followed by 16 week treatment period followed by 4 week washout period followed by another 16 week treatment period • Recruitment from 2 hospitals in the Netherlands
Participants	• Children aged 6-13 years with migraine meeting ICHD criteria • Participants had to have at least 2 migraines per month at baseline • There were no significant baseline differences between the groups
Interventions	• Riboflavin: 20 patients randomized to receive riboflavin 50mg daily for first treatment period • Placebo: 22 patients randomized to receive matched placebo (containing carotene) capsules for first treatment period
Outcomes	• Primary outcome: The groups did not differ with regards to change in migraine frequency (p=0.44) • Secondary outcomes: No other measured outcomes significantly differed between the groups • No adverse events were reported in either group • Analysis for period of carry-over effect was inconclusive
Notes	• The study was powered to detect a difference of 0.6 SD between the groups in terms of the primary outcome

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Winner 2005
Study Status: □ Included □ Excluded □ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, placebo-controlled, 2-arm parallel group trial with 2:1 assignment to the intervention group • Comprised of 4 week baseline period followed by 8 week medication titration period followed by 12 week maintenance period • Recruitment from 17 medical center in the US
Participants	• Children aged 6-15 years with migraine meeting ICHD criteria • Required 3-10 migraine days/month in 4 week baseline period and 3 months preceding study entry • Chronic migraine excluded • There were no significant differences between the groups at baseline
Interventions	• Topiramate: 112 patients randomized to topiramate, at a starting dose of 15mg daily, which was titrated up as needed to 200mg daily or 2-3mg/kg/day, whichever was achieved first • Placebo: 50 patients randomized to placebo with identical "titration" schedule to topiramate
Outcomes	• Primary outcome: In the intention-to-treat analysis, the topiramate group showed a trend towards a greater mean reduction in migraine frequency during the treatment period as compared to the placebo group (2.6±2.6 days vs. 2.0±3.1 days, p=0.061); the difference between the groups was statistically significant in the per-protocol analysis (2.8±2.4 vs. 2.2±2.1, p=0.033) • Secondary outcomes: the topiramate group had a greater reduction than placebo in migraine days during the last treatment month as compared to the baseline period; no difference in proportion of participants having 50% or greater reduction in migraine frequency, but higher proportion of topiramate group with 75% or greater reduction in migraine frequency; • Adverse events: no significant difference in incidence of adverse events in placebo vs. topiramate group; 4 serious adverse events in topiramate group
Notes	• 16% of patients in the placebo group vs. 20.5% of patients in the topiramate group dropped out of the study

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Lakshmi 2007
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, placebo-controlled, 2-arm parallel-group study • Comprised of a 4-week titration period followed by a 12-week maintenance period • Carried out in outpatient department of the Postgraduate Institute of Medical Education and Research in India
Participants	• Children aged 8-14 years with migraine meeting ICHD criteria • Participants had to have 2 or more migraines per month in the 3 months preceding enrollment
Interventions	• Topiramate: 22 randomized to topiramate at a starting dose of 25mg daily with weekly 25mg increases to a maximum of 50mg bid • Placebo: 22 randomized to placebo
Outcomes	• Primary outcome: The topiramate group had a greater decrease in migraine frequency comparing baseline to the end of the study (from 16.14±9.35 to 4.27±1.95 vs. from 13.38±7.48 to 7.48±5.94, p=0.025) • Secondary outcomes: There was a higher proportion of patients in the topiramate group showing a 50% or greater reduction in migraine frequency following treatment as compared to placebo; no difference in the mean change in migraine duration or mean migraine severity; no difference in rescue medication use between the groups; greater decrease in PedMIDAS disability score in the topiramate group; greater improvement in school absenteeism in the topiramate group • Adverse events: There were more adverse events in the topiramate group, with weight loss, loss of appetite, paresthesias and lack of concentration in school being the most common
Notes	• Only one patient lost to follow-up in each group

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Lewis 2009
Study Status: □ Included □ Excluded □ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, placebo-controlled, double-blind, 3-arm, parallel-group study • Comprised 9 week baseline (1 week screening, 4 week washout of prophylactic medications and 4 week baseline period) followed by 16 week treatment period followed by 2 week taper and then 4 week exit phase • Recruitment from 31 US and non-US sites
Participants	• Adolescents aged 12-17 years with migraine meeting ICHD criteria • Participants had to have migraines for a minimum of 6 months • Participants had to have 3-12 migraine days/month in the 3 months preceding enrollment
Interventions	• Low dose topiramate: 35 patients randomized to topiramate initiated at 25mg/day up to a maximum of 25mg bid as needed over 4 weeks and then maintained for 12 weeks • High dose topiramate: 35 patients randomized to topiramate initiated at 25mg/day up to a maximum of 50mg bid as needed over 4 weeks and then maintained for 12 weeks • Placebo: 33 patients randomized to placebo for the treatment period • NB. All patients received 4 tablets/day throughout, with the tablets consisting of either placebo, 25mg topiramate or a combination thereof
Outcomes	• Primary outcome: The high dose topiramate group had a significant larger decrease in migraine frequency when comparing the last 12 weeks of treatment to baseline as compared to placebo (72.2% vs. 444%, p=0.016), but there was no significant difference comparing low dose topiramate and placebo (p=0.798) • Secondary outcomes: More than 50% of participants treated with high dose topiramate were migraine-free during the last 4 weeks of treatment; high dose topiramate but not low dose topiramate was superior to placebo in reducing migraine frequency during the last 4 weeks of treatment as compared to baseline; most secondary analyses also found that high dose topiramate was superior to placebo but not low dose topiramate • Adverse events: There were more adverse events in the topiramate groups as compared to the placebo group (74%

	vs. 48%), with the most common adverse events in the topiramate groups being upper respiratory tract infections, paresthesias and decreased appetite; there were 2 serious adverse events in the high dose topiramate group that were deemed unlikely to be related to treatment by the investigators
Notes	• None

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Pandina 2010 (analysis of subset of the data from Lewis 2009)
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, placebo-controlled, double-blind, 3-arm, parallel-group study • Comprised 9 week baseline (1 week screening, 4 week washout of prophylactic medications and 4 week baseline period) followed by 16 week treatment period followed by 2 week taper and then 4 week exit phase • Recruitment from 31 US and non-US sites
Participants	• Adolescents aged 12-17 years with migraine meeting ICHD criteria • Participants had to have migraines for a minimum of 6 months • Participants had to have 3-12 migraine days/month in the 3 months preceding enrollment
Interventions	• Low dose topiramate: 35 patients randomized to topiramate initiated at 25mg/day up to a maximum of 25mg bid as needed over 4 weeks and then maintained for 12 weeks • High dose topiramate: 35 patients randomized to topiramate initiated at 25mg/day up to a maximum of 50mg bid as needed over 4 weeks and then maintained for 12 weeks • Placebo: 33 patients randomized to placebo for the treatment period • NB. All patients received 4 tablets/day throughout, with the tablets consisting of either placebo, 25mg topiramate or a combination thereof
Outcomes	• Primary outcome: This was reported in the Lewis et al 2009 publication. In this paper, the focus was on cognitive and mood side effects. • Outcomes for this publication: As compared to placebo, the high dose topiramate group had small increases in their psychomotor reaction times; the high dose topiramate group also had a decrease in the number of unique words they could generate; no other changes were seen in cognitive scores on the CANTAB assessment (ie. memory, learning, visual processing); none of the groups differed significantly in the changes seen in their Profile of Mood States scores
Notes	• None

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Winner 2006 Pooled Analysis
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Analysis from 3 adults studies where data on adolescent participants aged 12-18 years was pooled • All three adult trials were double-blind, randomized, parallel-group, placebo-controlled studies • Recruitment from 150 different sites in North America, Europe and Asia • Comprised a 2-week washout period, followed by a 4-week baseline period, followed by an 8-week titration phase and then an 18-week maintenance phase
Participants	• Analysis is restricted to adolescent participants aged 12-18 years with migraine meeting ICHD criteria • Participants had to have 3-12 migraines/month in the 3 months prior to enrollment and in the baseline period • There were no major baseline differences between the groups
Interventions	• Low dose topiramate: Two of the studies randomized a total of 11 participants to topiramate 50mg daily • Medium dose topiramate: All three studies had a group randomized to topiramate 100mg daily, comprising 13 participants • High dose topiramate: All three studies had a group randomized to topiramate 200mg daily, comprising 13 participants • Placebo: All three studies had a placebo arm, comprising 12 participants • Propranolol: One study used propranolol as an active comparator instead of the low dose topiramate • NB. All groups on topiramate started at a dose of 25mg daily, with 25mg/week increases until the maximum dose for their assigned group was reached
Outcomes	• Primary outcome: The topiramate 100mg daily and 200mg daily groups had significantly greater reductions in migraine frequency comparing the treatment period to baseline as compared with placebo (63% and 65% compared to 13% reductions, $p<0.04$) • Secondary outcomes: No significant differences were seen for the secondary outcomes • Adverse events: There were no meaningful differences in the frequency of adverse events between the groups; there were no serious adverse events in any of the topiramate groups; weight loss appeared to be more common for topiramate; the

	most common adverse events were upper respiratory tract infections, paresthesias and weight loss; 7 patients on topiramate vs. 2 patients on placebo had cognitive side effects
Notes	• None

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Apostol 2008
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, placebo-controlled, 4-arm parallel group trial • Comprised of 2 week washout period, followed by a 4 week baseline period followed by 2 week titration period followed by 10 weeks of maintenance treatment • Recruitment from 38 different US centers
Participants	• Adolescents aged 12-17 with migraine meeting ICHD criteria • Participants had to have 3-12 migraines/month in 3 month period prior to study entry • No statistically or clinically significant baseline differences between the groups
Interventions	• Low dose divalproex: 83 participants randomized to divalproex 250mg daily, which was maintained throughout titration and maintenance • Medium dose divalproex: 74 participants randomized to divalproex 500mg daily, which started at a dose of 250mg daily during the 2-week titration and double subsequently for the 10-week maintenance • High dose divalproex: 75 participants randomized to divalproex 1000mg daily, which started at a dose of 500mg daily during the 2-week titration and doubled subsequently for the 10-week maintenance • Placebo: 73 participants randomized to placebo
Outcomes	• Primary outcome: There was no difference between any of the divalproex doses and placebo in terms of the change in migraine frequency comparing baseline to the 12 week treatment period • Secondary outcomes: None of the secondary outcomes showed any difference when comparing any of the divalproex doses to placebo • Adverse events: There were no groups differences in the frequency of adverse events; the most common side effects for the divalproex groups were upper respiratory tract infections, somnolence and fatigue
Notes	• Used an effect size derived from an adult study, which is perhaps not appropriate given that children are known to have a more dramatic placebo response than adults.

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Sorge 1988
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Double-blind, placebo-controlled crossover trial • Recruitment from Headache Center at 11nd Medical School of Naples • Comprised 4-week baseline, followed by 12-week treatment period, followed by 4-week washout period, followed by cross-over to another 12-week treatment period
Participants	• Children aged 5-11 years of age with migraine meeting Vahlquist's criteria • Participants had to have minimum of 6 months of migraines • There were no significant differences between the groups at baseline
Interventions	• Flunarizine: 35 patients were randomized to first receive flunarizine 5mg daily for the initial treatment period, and then they received matched placebo • Placebo: 35 patients were randomized to first received matched placebo for the initial treatment period, and then they received flunarizine 5mg daily
Outcomes	• Primary outcome: Both groups had a statistically significant reduction in migraine frequency during their treatment with flunarizine ($p<0.001$ in both groups) as compared to the placebo phases • Secondary outcomes: The duration of migraine attacks was reduced by 3 months of flunarizine in group A and by 2 months of flunarizine in group B and this was significantly different from the placebo phases ($p<0.001$ in both groups) • Adverse events: There is no detail about which adverse events occurred in which groups; the most common side effects were drowsiness and weight gain, which occurred in 9.5% and 22.2%, respectively
Notes	• 7 patients withdrew from the study; 2 during the flunarizine phase and 5 during the placebo phase

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Sorge 1985
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Double-blind, placebo controlled, 2-arm, parallel-group study • Recruitment from the Headache Center of the Naples IIed Medical School • Baseline period followed by randomization to an intervention for 3 months
Participants	• Children under the age of 18 years with migraine meeting the Vahlquist criteria • Baseline characteristics were similar between the groups, except that the flunarizine group had shorter migraines at baseline (2.76±1.13 hours/migraine vs. 2.95±2.47 hours/migraine)
Interventions	• Flunarizine: 24 participants were randomized to 3 months of flunarizine 5mg qHS • Placebo: 24 participants were randomized to 3 months of placebo
Outcomes	• Primary outcome not explicitly defined • At trial completion, the flunarizine group had significantly less frequent headaches than the placebo group ($p<0.001$) during the treatment period • The flunarizine group had significantly shorter migraines during the treatment period as compared to placebo ($p<0.05$), but they also had shorter migraines at baseline • Adverse events: There is no detailed description of adverse events, only a mention that 3 patients withdrew from the flunarizine group due to side effects, namely gastrointestinal symptoms, drowsiness and fatigue) and a mention that the most common side effects were weight gain and sleepiness (but no details about frequency per group)
Notes	• 3 participants withdrew from flunarizine group because of side effects and 3 participants withdrew from placebo group due to lack of efficacy

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Noronha 1985
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• This was a double-blind, randomized cross-over study • The site of recruitment is not listed, but presumably recruitment was from a site in England given the author's location • Comprised 4-week baseline period, followed by 8 weeks of treatment, followed by 4-week washout period, followed by 8 weeks of treatment with alternate agent
Participants	• Children aged 5 to 16 years with migraine meeting the Vahlquist criteria • Participants had to have a history of at least 2 attacks/month, though it is unclear how long of a history was required • Participants had similar baseline migraine frequencies
Interventions	• Timolol: 9 patients were randomized to first receive timolol 5mg daily and then were crossed over to placebo • Placebo: 8 patients were randomized to first receive placebo then timolol 5mg daily
Outcomes	• It is unclear which outcome(s) were primary • There was no difference between timolol and placebo relative to reducing migraine frequency, migraine severity nor duration • There was a similar progressive decrease in the frequency of migraines in both groups • Adverse events are not detailed beyond the statement made about 2 patients dropping out during the timolol phase due to side effects, namely headache and vomiting
Notes	• 2 patients excluded given that they dropped out from timolol side effects

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Sillanpää 1977
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Double-blind, placebo-controlled, 2-arm, parallel-group trial • Although it seems implied that the trial was randomized, it is not clear • Patients were treated for 2 months, and then had a mean follow-up of 7.9 months • Patients were recruited from the Pediatric Outpatient Departments in Turku or Tempere, Finland
Participants	• Children up to age 15 years with migraine or other paroxysmal vascular headaches (categorized as such if one migraine criterion was missing; ie. analogous to probable migraine in ICHD criteria) according to Vahlquist's criteria • The groups had similar baseline headache types and headache frequencies
Interventions	• Clonidine: 28 participants randomized to clonidine 25 micrograms daily for children <40kg and 25 micrograms bid for children >40kg; after 1 month, the dose was increased by 25 micrograms for all patients in this group • Placebo: 29 participants randomized to placebo
Outcomes	• It is unclear which outcome(s) were primary • Hypothesis testing results are not reported for most of the outcomes • In both groups, 1/3 of the participants were headache-free during treatment • 57% of clonidine participants and 42% of placebo participants had only 1 or 2 headaches during the entire study (no p given) • There were no statistically significant differences between the groups in terms of headache intensity or duration (no p given) • Participants with migraine with aura who received clonidine had less frequent and less intense headaches during treatment as compared to placebo ($p<0.05$) • 14 participants on clonidine vs. 10 participants on placebo had less need for rescue medication (no p given) • 11 participants on clonidine vs. 6 participants on placebo reported adverse events; the most common side effects for clonidine were fatigue and nausea
Notes	• No sample size calculations are reported; 3 drop-outs are reported, all from the clonidine group

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Battistella 1993
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized*, double-blind, placebo-controlled, 2-arm, crossover trial • 4 week run-in period, followed by 12 week treatment period, followed by 4 week washout period, followed by second 12 week treatment period (with other intervention)
Participants	• 40 children aged 7-18 years with migraine without aura as per ICHD criteria • All had migraine for at least 6 months • Had to report at least 3 migraines per month
Interventions	• Trazodone: 20 patients randomized to receive trazadone 1mg/kg/day divided tid for first phase of treatment • Placebo: 20 patients randomized to receive placebo for the first phase of treatment
Outcomes	• Primary outcome: There was no difference between the groups in reduction of migraine frequency in the first treatment phase; in the second treatment phase, the trazadone group had a greater reduction in frequency than the placebo group (trazodone reduced from 2.1±0.2 attacks/month to 1.8±0.2 vs. placebo increased from 1.8±0.1 to 2.1±0.2, $p<0.005$) • Secondary outcome: At the end of the first treatment phase, the trazodone group had a higher duration of migraine than placebo (16.1±1.4 hrs vs. 10.2±1.0, $p<0.01$); at the end of the second treatment phase, the trazodone group had a greater reduction in migraine duration than placebo (from 10.7±1.3 to 4.9±0.7 vs. from 11.9±1.3 to 13.1±1.3, $p<0.001$) • Adverse events: No serious adverse events reported; no details given about potential non-serious side effects
Notes	• 5 patients withdrew (2 from one group and 3 from the other)

**NB. Author contacted to ensure that the trial was randomized as manuscript was vague*

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Battistella 1990
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized*, double-blind, placebo-controlled, 2-arm, crossover trial • 4 week run-in period, followed by 12 week treatment period, followed by 4 week washout period, followed by second 12 week treatment period (with other intervention)
Participants	• 37 patients aged 7 to 18 years with migraine with or without aura according to the Ad Hoc criteria • Patients were required to have at least 1 migraine/month in the 6 months preceding the trial
Interventions	• Nimodipine: 18 patients randomized to nimodipine 10mg to 20mg tid for the first treatment period • Placebo: 19 patients randomized to colour-matched placebo for the first treatment period
Outcomes	• Primary outcome: There was no difference between the groups in reduction of migraine frequency in the first treatment phase; in the second treatment phase, the nimodipine group had a greater reduction in frequency than the placebo group (from 2.7±0.8 attacks/month to 1.9±1.7 vs. from 2.6±0.8 to 2.8±0.6, $p<0.01$) • Secondary outcome: There was no difference between the groups in reduction of migraine frequency in either treatment phase • Adverse events: 3 patients had mild abdominal discomfort with nimodipine in initial days of treatment
Notes	• 7 patients withdrew for reasons not related to the interventions; the authors do not specify which group(s) they belonged to

**NB. Author contacted to ensure that the trial was randomized as manuscript was vague*

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Ford 2014
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Analysis from 5 studies where data on participating children aged 6-17 years were analyzed (ie. only pediatric patients analyzed) • All three trials that involved a randomized, double-blind, placebo-controlled, parallel-group design • All trials were multicenter • The trials ranged from 16-26 week treatment periods, including 4-8 week titration periods • NB. Many details are lacking as this analysis was only available in conference abstract form
Participants	• Analysis was restricted to pediatric patients aged 6-17 years meeting ICHD criteria for migraine
Interventions	• A total of 309 patients were analyzed, but the abstract does not report how many belonged to each group • Topiramate: Various topiramate dosing groups were included: topiramate 2-3 mg/kg/day, 50mg daily, 100mg daily or 200mg daily • Placebo: All studies had a placebo arm • Propranolol: One of the studies had an active comparator arm involving propranolol 160mg daily
Outcomes	• No primary outcomes specified • Percent reduction in migraine attack rate: in TOPMAT-MIG-3006 trial the topiramate 100mg daily was superior to placebo (p=0.0164); in CAPS-122 the topiramate and placebo groups did not differ; in TOPMAT-MIGR-001/002/003 there was a trend towards topiramate 100mg daily being superior to placebo • 50% responder rate: in TOPMAT-MIG-3006 the topiramate 100mg daily had a significantly higher responder rate (p=0.0048), but no differences in responder rates comparing topiramate with placebo in the other studies • Adverse events: Most common side effects were influenza-like symptoms, language problems and paresthesias
Notes	•

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Ashrafi 2014
Study Status: ☐ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Double-blind, placebo-controlled, 2-arm, parallel-group RCT • 4 week pre-randomization phase and 12 weeks for the treatment phase • Participants were recruited from the Children's Medical Center in Tehran, Iran
Participants	• Children 5-17 years with migraine as per the ICHD criteria • All had at least 6 months of migraine • All had at least 4 attacks per month in the 6 months preceding enrollment • No clinically significant differences between the groups in baseline characteristics
Interventions	• Cinnarizine: 30 participants randomized to cinnarizine 1.5mg/kg/day for those weighing less than 30kg and 50mg daily for those weighing 30kg or more • Placebo: 32 participants were randomized to placebo
Outcomes	• Primary outcomes: There were more participants achieving a 50% or more reduction in headache frequency in the cinnarizine group as compared with placebo (60% vs. 31.3%, p=0.023); both cinnarizine and placebo yielded significant decreases in the monthly migraine frequency over time, but no group differences were reported (cinnarizine: baseline 8 attacks/month, at 1 month reduced to 5, 4.5 at 2 months and 4 at 3 months, p<0.001; placebo: baseline 8 attacks/month, at 1 month increased to 12, reduced to 6.5 at 2 months and 6 at 3 months, p<0.001) • Secondary outcomes: Headache severity was reduced to a greater extent after 3 months of treatment in the cinnarizine group (p<0.001); headache duration was significantly reduced in the cinnarizine group as compared to the placebo group (p=0.042) • Adverse events: No serious adverse events in either group; 3 cinnarizine participant vs 1 placebo participant had drowsiness; 1 cinnarizine participant had significant weight gain (2.5kg) resulting in the need to reduce the dose
Notes	•

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Machín Altueña 1987
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• Randomized, double-blind, three-arm, placebo-controlled clinical trial • No baseline period, randomized to 4 month treatment period
Participants	• Children aged 5 to 13 years with migraine meeting Ad Hoc criteria • None of the children had been previously treated • Baseline demographics not described
Interventions	• Flunarizine: 15 patients randomized to flunarizine 0.15mg/kg once daily • Dimethothiazine: 15 patients randomized to dimethothiazine 1mg/kg/day divided bid • Placebo: 15 patients randomized to placebo
Outcomes	• Primary outcome: Clinical improvement was seen in 93.3% of the dimethothiazine group vs. 86.7% of the flunarizine group vs. 80% of the placebo group ($p>0.05$) • Secondary outcomes: In the dimethothiazine group, 35.7% had complete improvement and 64.3% had partial improvement vs. in the flunarizine group 38.4% had complete improvement and 61.5% had partial improvement vs. in the placebo group 41.7% had complete improvement and 59.3% had partial improvement (no significant differences between the groups); 41.3% reduction in migraine frequency in the dimethothiazine group vs. 46.8% in flunarizine group vs. 45.8% in placebo group (no significant differences); no significant differences in change in migraine intensity nor duration • Adverse events: 23.1% of flunarizine patients gained weight, 1 patient (group not mentioned) had IgA deficiency but no other biochemical abnormalities were noted
Notes	• Translated from Spanish

Prophylactic Interventions for Pediatric Migraine: *Characteristics of Studies*

Study ID#: Sillanpää 1978
Study Status: ☒ Included ☐ Excluded ☐ Uncertain
Reviewed by: SLO

Characteristics of Study

Characteristic	Description of Findings
Methods	• This was a double-blind, placebo-controlled, 2-arm parallel-group, randomized trial • The treatment period was 2 months in duration; no baseline period is described in the text • Patients were recruited from the outpatient departments of two hospitals in Finland
Participants	• Patients aged 6-15 years with migraine as per Vahlquist criteria or vascular headache (meeting only one Vahlquist criteria) • Participants were required to have at least 2 headaches/month • There were no significant differences comparing baseline characteristics between the groups
Interventions	• Papaverine: 19 participants randomized to papaverine 5-10mg/kg/day divided bid or tid, starting at a dose of 5mg/kg/day and doubled to 10mg/kg/day after 1 month • Placebo: 18 participants randomized to placebo
Outcomes	• No primary outcome was specified • 6/19 papaverine participants vs. 0/18 placebo participants were pain-free during treatment ($p<0.001$) • Headache frequency, intensity and duration were significantly more reduced in the papaverine group as compared to placebo ($p<0.001$) • Adverse events: not reported
Notes	• 5 patients were excluded (two because of side effects and three due to intervention compliance issues; groups not specified)

11. Appendix D. Systematic Review Included Studies 'Risk of Bias Assessment' Tables

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Oelkers-Ax 2008
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		x		From text: "Patients were allocated to one of the three treatment groups after baseline by computerized randomization"
Allocation concealment (selection bias)		x		From text: "Randomization was accomplished by the first author (not involved in patient contacts) who assigned the subject numbers in ascending numerical sequence (block randomization a 9) to the subjects who qualified for randomization"
Blinding of participants and personnel (performance bias)	x			This study was partially double-blind, meaning that those on placebo vs. butterbur were blinded, but there was no way of maintaining blinding for the music group.
Blinding of outcome assessment – self-reported outcomes (detection bias)	x			All outcomes were self-reported in a headache diary, except adverse events that were reported at visits. Again, the music therapy group was unblinded.
Blinding of outcome assessment – objective measures (detection bias)				No objective measures were studied.
Incomplete outcome data (attrition bias)	x			There were more drop-outs in the music therapy and butterbur groups than in the placebo group. They did do an ITT analysis.
Selective reporting (reporting bias)		x		No concern for that here.
Other bias	x			There was a clinically meaningful

				difference between the groups. Butterbur had almost double the baseline migraine frequency.

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: MacLennan 2008
Reviewed by: SLO
Final quality rating: Low risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		From text: "Randomization was performed by the biased coin technique. The computer generated list of random numbers was created and administered by the hospital Pharmacy Department".
Allocation concealment (selection bias)		x		Given that the Pharmacy department were the ones using the allocation sequence software there is low risk of bias for allocation concealment.
Blinding of participants and personnel (performance bias)		x		The study was double blind and efforts were made to maintain blinding. From text: "The riboflavin and placebo capsules were produced by the same manufacturer to obtain an identical appearance. As riboflavin is bright orange, an orange food dye was used in the manufacture of the placebo"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		"Each family collected their capsules directly from the Pharmacy, and treatment allocation was concealed to the participants and investigators for the duration of the study. Only the data monitoring committee could view unblinded data, and they did not have any contact with study participants"
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes assessed
Incomplete outcome data (attrition bias)		x		"Efficacy analysis was performed on an intention-to-treat population that included all randomized patients"
Selective reporting (reporting bias)				None identified
Other bias			x	It is unclear what kind of stopping rule they used for their interim analysis.

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Bruijn 2010
Reviewed by: SLO
Final quality rating: unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	The method of randomization is not detailed beyond reference to a "randomization key".
Allocation concealment (selection bias)		x		From the text: "Treatment allocation was concealed from the participants and investigators for the duration of the study. The hospital pharmacists guarded the randomization key"
Blinding of participants and personnel (performance bias)		x		Efforts were made to blind and maintain blinding. For example, because riboflavin can discolor the urine, carotene was added to placebo. Also, from text:" To evaluate blinding, at the last visit parents were asked which treatment they believed that their child had received in which phase, and the reasons for their assumptions"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above, efforts were made to blind the patients who reported the outcomes through their headache diaries.
Blinding of outcome assessment – objective measures (detection bias)		x		No objective outcomes were assessed.
Incomplete outcome data (attrition bias)		x		4 patients dropped out of the group assigned to placebo initially and none dropped out of the group assigned to riboflavin initially. However, intention-to-treat analyses were used.
Selective reporting (reporting bias)		x		No evidence for reporting bias.

Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Winner 2005
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	From text: "medication code schedule generated before the trial". It is unclear how the code was generated.
Allocation concealment (selection bias)		x		It seems as though the allocation sequence was kept from those involved in the study: "A physician drug assignment/inventory (PDA) that listed the unique medication code number was supplied to each investigator. The investigator entered the subject's identification information in numerical order, thereby assigning the subject to 1 of 2 treatment groups"
Blinding of participants and personnel (performance bias)		x		From text: "Treatment assignments were not revealed to study patients, investigators, clinical staff, or study monitors until all patients had completed the study and the database had been finalized"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above.
Blinding of outcome assessment – objective measures (detection bias)		x		No objective outcomes
Incomplete outcome data (attrition bias)		x		16% of patients in the placebo group vs. 20.5% of patients in the topiramate group dropped out of the study. Also, ITT analyses were used.
Selective reporting		x		None identified

(reporting bias)				
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Lakshmi 2007
Reviewed by: SLO
Final quality rating: Low risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		From text: "A random number table was used to draw up randomized blocks of subjects for allocation to each arm of the study, and a randomization sequence was generated."
Allocation concealment (selection bias)		x		From text: "The original sequence and the code numbers were placed in sealed envelopes and opened only after the data analysis was completed"
Blinding of participants and personnel (performance bias)		x		From the text: "The subjects themselves, their parents, the person engaged in interviewing and administering the drugs, both at enrollment and follow-up, were all blinded to the assignment. Dispensing both the drug and the placebo in identical forms with similar appearance, pack- aging, taste, and other factors further ensured this implementation"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above
Blinding of outcome assessment – objective measures (detection bias)		x		There were no objective outcomes
Incomplete outcome data (attrition bias)		x		There was only one drop-out in each group and both were attributed to financial limitations.
Selective reporting (reporting bias)		x		No evidence of selective reporting.
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Lewis 2009
Reviewed by: SLO
Final quality rating: Low risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		From text: "Subjects were assigned randomly by using permuted blocks and a computer-generated schedule, with stratification according to age (12–14 years and 15–17 years). Central randomization was implemented in this study."
Allocation concealment (selection bias)		x		There was low risk of allocation concealment failure given that central randomization was used.
Blinding of participants and personnel (performance bias)		x		The study was double-blind and efforts were made to maintain blinding: "Treatment was taken in the form of identical-appearing capsules at the end of the prospective baseline period (day 1)"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above
Blinding of outcome assessment – objective measures (detection bias)		x		No objective outcomes in this study
Incomplete outcome data (attrition bias)		x		Intention-to-treat analyses were used and drop-out rates were similar across groups.
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Pandina 2010 (analysis of subset of the data from Lewis 2009)
Reviewed by: SLO
Final quality rating: low risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		From Lewis 2009 text: "Subjects were assigned randomly by using permuted blocks and a computer-generated schedule, with stratification according to age (12–14 years and 15–17 years). Central randomization was implemented in this study."
Allocation concealment (selection bias)		x		There was low risk of allocation concealment failure given that central randomization was used.
Blinding of participants and personnel (performance bias)		x		The study was double-blind and efforts were made to maintain blinding (from Lewis 2009 text): "Treatment was taken in the form of identical-appearing capsules at the end of the prospective baseline period (day 1)"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above
Blinding of outcome assessment – objective measures (detection bias)		x		Some of the features of the CANTAB were objective (ie. reaction time) and the test was completed by the participants, who were blinded.
Incomplete outcome data (attrition bias)		x		Intention-to-treat analyses were used and drop-out rates were similar across groups.
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Winner 2006 Pooled Analysis
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		From text: "randomized in equal proportions to 1 of 4 treatment groups according to a computer-generated randomization schedule"
Allocation concealment (selection bias)			x	No mention of allocation concealment (original studies accessed)
Blinding of participants and personnel (performance bias)		x		All trials were double-blind and the patients reported the outcomes.
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above.
Blinding of outcome assessment – objective measures (detection bias)		x		No objective outcomes.
Incomplete outcome data (attrition bias)		x		Nineteen patients out of the 51 total withdrew from the study. The text does not say which group(s) they belonged to. However, intention-to-treat analyses were used.
Selective reporting (reporting bias)		x		None identified.
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Apostol 2008
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	There is no detailed description of how the random sequence was created: "The randomization schedule was prepared by the sponsor's statistics department prior to the start of the study"
Allocation concealment (selection bias)			x	There is no description as to how allocation was concealed.
Blinding of participants and personnel (performance bias)		x		The trial was double-blind and efforts were made to maintain blinding: "Study medication consisted of unmarked DVPX ER 250 mg tablets and matching placebo tablets provided in sets of 4 bottles"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above, participants were blinded and they reported all outcomes.
Blinding of outcome assessment – objective measures (detection bias)		x		There were no objective outcomes in this study.
Incomplete outcome data (attrition bias)		x		Intention-to-treat analyses were used.
Selective reporting (reporting bias)		x		No evidence of reporting bias
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Sorge 1988
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	There are no details about how the random sequence was created.
Allocation concealment (selection bias)			x	There is no mention as to how allocation was concealed.
Blinding of participants and personnel (performance bias)		x		From text: 'Flunarizine and placebo were identical in shape and colour. Both patients and physicians were blinded with regard to medication."
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		The patients reported on the outcomes and they were blinded.
Blinding of outcome assessment – objective measures (detection bias)		x		There were no objective outcomes in this study.
Incomplete outcome data (attrition bias)	x			2 patients withdrew from the flunarizine group and 5 withdrew from the placebo group. No ITT analyses were used.
Selective reporting (reporting bias)		x		None identified.
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Sorge 1985
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	No description of random sequence generation.
Allocation concealment (selection bias)			x	No mention of allocation concealment.
Blinding of participants and personnel (performance bias)		x		The study is labeled as double-blind though no further details are given.
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		Given that the patients reported the outcomes and that they were blinded, there should be a low risk of detection bias.
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes in this study.
Incomplete outcome data (attrition bias)	x			Three patients withdrew from each group: 3 from placebo for lack of efficacy and 3 from the flunarizine group for side effects. No ITT analyses were used. Given that the reasons for withdrawal were different, there was high risk of attrition bias.
Selective reporting (reporting bias)		x		None evident.
Other bias		x		None identified.

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Noronha 1985
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	The way that randomization was carried out is not described.
Allocation concealment (selection bias)			x	Allocation concealment is not described.
Blinding of participants and personnel (performance bias)		x		The trial is described as being "double-blind" though no details are given.
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		The trial was double-blind and participants reported on the outcomes.
Blinding of outcome assessment – objective measures (detection bias)		x		There were no objective outcomes in this study.
Incomplete outcome data (attrition bias)	x			Two patients withdrew due to side effects deemed to be related to timolol. No intention-to-treat analyses were used. Although two patients is a small number, there were only 17 patients in the trial so it is not negligible.
Selective reporting (reporting bias)		x		None identified.
Other bias		x		None identified.

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Sillanpää 1977
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	It is unclear if the trial was randomized. It appears to be implied in the following sentence: "When the code was broken at the end of the study …", but is never explicitly stated.
Allocation concealment (selection bias)			x	Not described
Blinding of participants and personnel (performance bias)		x		The patients were blinded and reported on the outcomes.
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above.
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes in this study.
Incomplete outcome data (attrition bias)	x			3 drop-outs reported; all from the clonidine group
Selective reporting (reporting bias)	x			Some of the hypothesis testing is not reported (ie. no p values given for some outcomes).
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Battistella 1993
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	The study was randomized but the method of randomized is not specified
Allocation concealment (selection bias)			x	No mention of allocation concealment
Blinding of participants and personnel (performance bias)		x		The trial was double-blind and efforts were made to maintain blinding (eg. the color of placebo was identical to trazadone)
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		The trial was double-blind and patients reported on the outcomes
Blinding of outcome assessment – objective measures (detection bias)				There were no objective outcomes
Incomplete outcome data (attrition bias)		x		12.5% of patients withdrew (2/5 from group that received trazadone first and 3/5 from group that received placebo first; withdrawals due to drug administration errors or onset of new diseases)
Selective reporting (reporting bias)		x		None evident
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Battistella 1990
Reviewed by: SLO
Final class rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)			x	The trial was randomized but the method of randomization is not described
Allocation concealment (selection bias)			x	There is no mention of allocation concealment
Blinding of participants and personnel (performance bias)		x		The study was double-blind and efforts were made to maintain blinding (eg. the placebo was color-matched to nimodipine)
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		As above, the trial was double-blind and the patients reported the outcomes
Blinding of outcome assessment – objective measures (detection bias)				There were no objective outcomes
Incomplete outcome data (attrition bias)			x	18.9% of the patients withdrew and it is not made clear why they withdrew and which group(s) they belonged to
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Ford 2014
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		x		All studies were randomized.
Allocation concealment (selection bias)			x	Unclear if all studies had allocation concealment.
Blinding of participants and personnel (performance bias)		x		All studies were double-blind
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		Participants reported on all outcomes and they were blinded
Blinding of outcome assessment – objective measures (detection bias)				There were no objective outcomes in these studies
Incomplete outcome data (attrition bias)			x	No mention of pediatric-specific drop-out rates
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Ashrafi 2014
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		This was a randomized study using a random number table
Allocation concealment (selection bias)			x	There is no mention of allocation concealment
Blinding of participants and personnel (performance bias)		x		This was a double-blind study and efforts were made to maintain blinding: "Both cinnarizine and placebo formulations were dispensed to the patients in identical envelopes with similar appearance. Cinnarizine and placebo pills were identical in shape, color, and taste"
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		The patients were blinded and they reported on the outcomes.
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes in this study.
Incomplete outcome data (attrition bias)		x		6 patients lost to follow up from the study (4 in the cinnarizine group and 2 in the placebo group) due to relocation or early discontinuation of the study intervention
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Machín Altueña 1987
Reviewed by: SLO
Final quality rating: High risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		This was a randomized study, though the method of randomization is not described.
Allocation concealment (selection bias)			x	No mention of allocation concealment in the text.
Blinding of participants and personnel (performance bias)			x	It is unclear if the study was blinded or not, although it is implied to be so.
Blinding of outcome assessment – self-reported outcomes (detection bias)			x	Because the blinding status was not explicitly detailed, it is unclear if detection bias could exist for self-reported outcomes.
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes in this study.
Incomplete outcome data (attrition bias)		x		No drop-outs reported.
Selective reporting (reporting bias)		x		None identified.
Other bias	x			There are no sample size calculations given and the study was very likely underpowered to detect clinically meaningful group differences

Prophylactic Interventions for Pediatric Migraine: *Risk of Bias Assessment*

Study ID#: Sillanpää 1978
Reviewed by: SLO
Final quality rating: Unclear risk of bias

Risk of Bias Table

Bias	Author's judgment			Support for judgment
	High risk of bias	*Low risk of bias*	*Unclear risk of bias*	
Random sequence generation (selection bias)		*x*		This study was randomized but the method of randomization is not described.
Allocation concealment (selection bias)			x	There is no mention of allocation concealment.
Blinding of participants and personnel (performance bias)		x		The study was double-blind.
Blinding of outcome assessment – self-reported outcomes (detection bias)		x		The participants were blinded and reported on the outcomes.
Blinding of outcome assessment – objective measures (detection bias)				No objective outcomes.
Incomplete outcome data (attrition bias)			x	Five patients were excluded (two because of side effects and three due to intervention compliance issues). The group(s) that they belonged to were not described.
Selective reporting (reporting bias)		x		None identified
Other bias		x		None identified

12. Appendix E. Email Invitation to Potential Participants

Dear _____,

You are receiving this email because you have significant expertise in Headache Medicine.

We are carrying out a brief survey amongst Headache Medicine specialists with the goal of determining clinically relevant non-inferiority margins for outcomes commonly used in migraine clinical trials. We are hoping that the results of this survey can be applied to the design of future non-inferiority migraine trials, and that they may help to improve the quality of the data and the clinical relevance of study results.

Your participation in the survey is complete voluntary. **The survey will take no more than 5-10 minutes to complete**. You can access the survey through the following link:
_____

We understand that you are very busy, but we urge you to consider taking the time to complete this survey as it may help to improve future research in the area of migraine treatment.

Thank you for your time and considerations.

Sincerely,

The NIMM Survey Study Group
Serena Orr, MD, MSc Candidate
Dariush Dowlatshahi, MD, PhD, FRCPC
Suzanne Christie, MD, FRCPC
Timothy Ramsay, PhD
David Dodick, MD, FRCPC, FACP, FAHS
Jonathan Gladstone, MD, FRCPC

Appendix F. Email Invitation to Potential Participants

Dear _____,

This is a reminder email regarding your participation in a brief survey. You are receiving this email because you have significant expertise in Headache Medicine.

We are carrying out a brief survey amongst Headache Medicine specialists with the goal of determining clinically relevant non-inferiority margins for outcomes commonly used in migraine clinical trials. We are hoping that the results of this survey can be applied to the design of future non-inferiority migraine trials, and that they may help to improve the quality of the data and the clinical relevance of study results.

Your participation in the survey is complete voluntary. **The survey will take no more than 5-10 minutes to complete**. You can access the survey through the following link:
_____

We understand that you are very busy, but we urge you to consider taking the time to complete this survey as it may help to improve future research in the area of migraine treatment.

Thank you for your time and considerations.

Sincerely,

The NIMM Survey Study Group
Serena Orr, MD, MSc Candidate
Dariush Dowlatshahi, MD, PhD, FRCPC
Suzanne Christie, MD, FRCPC
Timothy Ramsay, PhD
David Dodick, MD, FRCPC, FACP, FAHS
Jonathan Gladstone, MD, FRCPC

13. Appendix G. Non-Inferiority Margins in Migraine Research (NIMM) Survey

Introduction Script: "Clinical trials can be designed around a variety of hypothesis types. Traditionally, superiority hypotheses have been used, whereby the aim is to show that one intervention is superior to the other. Non-inferiority hypotheses are aimed at showing that a new intervention is not worse than an established intervention. Non-inferiority hypotheses are more appropriate when a new intervention is cheaper, easier to use or has a better side effect profile than the established intervention, because a degree of inferior efficacy can be accepted in the context of other relative advantages associated with the new intervention. The use of non-inferiority hypotheses in clinical trials is increasing. To date, only two migraine trials have employed non-inferiority hypotheses.

In order to properly design and power a non-inferiority study, a **non-inferiority margin** must be determined a priori in order to calculate a sample size. A non-inferiority margin is set for the primary outcome. It constitutes a number below which we would consider the new intervention to be clinically inferior to the established intervention. In other words, it is the **margin above which the new intervention would be considered not worse than the established intervention**, and above which the intervention would be clinically acceptable to practitioners and patients. An accepted way of setting a non-inferiority margin is by sampling opinions from experts in the field or other stakeholders. In this process, experts or stakeholders are asked to express their opinion on an acceptable non-inferiority margin for a particular clinical question.

You are being asked to complete this survey because you have expertise in treating migraines. Through this survey, we are hoping to establish non-inferiority margins for commonly used and accepted outcomes in migraine intervention trials, so as to improve the design of future non-inferiority trials in migraine therapeutics".

Consent Script: "If you choose to complete this survey, you will be providing implicit consent for us to use this data for the purposes of compiling survey results. This data may also be used in future abstracts, publications and/or academic presentations. Your responses are completely anonymous and will not be traced back to individual respondents. We will not be collecting any personal identifying information nor personal health information as part of this study. Research records will be kept for 10 years, as required by the OHSN-REB. At the end of the storage time, all electronic records will be securely deleted. We do not anticipate that you will suffer any harm from participation in this study. We do not foresee any risks associated with this study. You will not receive any direct benefit from participation. The survey consists of **10 multiple choice questions and will require 5-10 minutes of your time to complete**. You can choose to not participate. Your participation in this study is voluntary. You may decide to complete the survey now and withdraw your data at a later time, without affecting your current or future employment at The Ottawa Hospital Research Institute. There are no conflicts of interest to declare related to this study. If you have any questions about this study, or if you feel that you have experienced a study-related injury or illness, please contact Dr. Serena Orr at (613) 737-7600 ext. 1605.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed this protocol. The Board considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital Research Institute. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719."

Non-Inferiority Margins in Migraine Research (NIMM) Survey

1. What kind of practitioner are you?
    - ☐ Adult neurologist
    - ☐ Child neurologist
    - ☐ Other*

    If 'other' was selected, branching logic was used to display the following:
    You selected "Other" for practitioner. You are not eligible for this survey.
    Please confirm.

    - ☐ I am NOT a Neurologist (adult or child) and I am NOT eligible for this survey.
    - ☐ I am a Neurologist (adult or child) and I am eligible for this survey (eligible)

2. Where do you practice Headache Medicine?
    - ☐ Canada
    - ☐ United States

3. In what setting do you practice Headache Medicine?
    - ☐ Academic practice
    - ☐ Community practice
    - ☐ Mixed academic/community practice

4. For how many years have you been practicing Headache Medicine?
    - ☐ 0-5 years*
    - ☐ 5-10 years
    - ☐ 10-15 years
    - ☐ 15-20 years
    - ☐ Over 20 years

    **If '0-5 years' was selected, branching logic was used to display the following*:
    "If you have not been practicing Headache Medicine (i.e. practicing 0 years), then you may not have sufficient expertise in the area to meet eligibility criteria for this survey. Please indicate which statement applies to you"

    - ☐ I have NOT been practicing Headache Medicine and I do NOT have Headache Medicine expertise through other experience (eg. research, etc) (ineligible)
    - ☐ I have NOT been practicing Headache Medicine but I have Headache Medicine expertise through other experience (eg. research, etc) (eligible)
    - ☐ I have been practicing Headache Medicine (eligible)

5. What percentage of your time is devoted to research?
    - ☐ Under 10%
    - ☐ 10-25%
    - ☐ 25-50%
    - ☐ 50-75%
    - ☐ Over 75%

6. What do you think would be an acceptable non-inferiority margin for the following outcome used in migraine prophylaxis trials: the change in the number of **monthly migraine attacks** comparing baseline to the treatment period?

   - ☐ A reduction of 0.25 attacks per month (*ie. if the new intervention yields 0.25 attacks per month more than the established intervention, or anything less than 0.25 attacks more, it is non-inferior*)
   - ☐ A reduction of 0.5 attacks per month (*ie. if the new intervention yields 0.5 attacks per month more than the established intervention, or anything less than 0.5 attacks more, it is non-inferior*)
   - ☐ A reduction of 0.75 attacks per month (*ie. if the new intervention yields 0.75 attacks per month more than the established intervention, or anything less than 0.75 attacks more, it is non-inferior*)
   - ☐ A reduction of 1 attack per month (*ie. if the new intervention yields 1 attack per month more than the established intervention, or anything less than 1 attacks more, it is non-inferior*)
   - ☐ A reduction of 1.25 attacks per month (*ie. if the new intervention yields 1.25 attacks per month more than the established intervention, or anything less than 1.25 attacks more, it is non-inferior*)
   - ☐ Other – Please specify your suggested non-inferiority margin for this outcome: _____

7. What do you think would be an acceptable non-inferiority margin for the following outcome used in migraine prophylaxis trials: the change in the number of **monthly migraine days** comparing baseline to the treatment period?

   - ☐ A reduction of 0.5 days per month (*ie. if the new intervention yields 0.5 days per month more than the established intervention, or anything less than 0.5 days more, it is non-inferior*)
   - ☐ A reduction of 0.75 days per month (*ie. if the new intervention yields 0.75 days per month more than the established intervention, or anything less than 0.75 days more, it is non-inferior*)
   - ☐ A reduction of 1 day per month (*ie. if the new intervention yields 1 day per month more than the established intervention, or anything less than 1 day more, it is non-inferior*)
   - ☐ A reduction of 1.25 days per month (*ie. if the new intervention yields 1.25 days per month more than the established intervention, or anything less than 1.25 days more, it is non-inferior*)
   - ☐ A reduction of 1.5 days per month (*ie. if the new intervention yields 1.5 days per month more than the established intervention, or anything less than 1.5 days more, it is non-inferior*)
   - ☐ Other – Please specify your suggested non-inferiority margin for this outcome: _____

8. What do you think would be an acceptable non-inferiority margin for the following outcome used in migraine prophylaxis trials: the change in the **average migraine intensity** comparing baseline to the treatment period (where the intensity of the headache is measured on the following 4-point severity scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)?

- ☐ A reduction of 0.2 points in average intensity (*ie. if the new intervention yields a reduction in intensity that is 0.2 points less than the established intervention, or anything less than 0.2 points less, it is non-inferior*)
- ☐ A reduction of 0.4 points in average intensity (*ie. if the new intervention yields a reduction in intensity that is 0.4 points less than the established intervention, or anything less than 0.4 points less, it is non-inferior*)
- ☐ A reduction of 0.6 points in average intensity (*ie. if the new intervention yields a reduction in intensity that is 0.6 points less than the established intervention, or anything less than 0.6 points less, it is non-inferior*)
- ☐ A reduction of 0.8 points in average intensity (*ie. if the new intervention yields a reduction in intensity that is 0.8 points less than the established intervention, or anything less than 0.8 points less, it is non-inferior*)
- ☐ A reduction of 1 point in average intensity (*ie. if the new intervention yields a reduction in intensity that is 0.6 points less than the established intervention, or anything less than 0.6 points less, it is non-inferior*)
- ☐ Other – Please specify your suggested non-inferiority margin for this outcome: _____

9. What do you think would be an acceptable non-inferiority margin for the following outcome used in trials of acute migraine interventions: the **absolute percentage of participants who are pain-free 2 hours after the intervention**?
   - ☐ 2.5% fewer participants (*ie. if 2.5% fewer of the participants receiving the new intervention are pain-free as compared to those receiving the established intervention, or any difference under 2.5% exists, it is non-inferior*)
   - ☐ 5% fewer participants (*ie. if 5% fewer of the participants receiving the new intervention are pain-free as compared to those receiving the established intervention, or any difference under 5% exists, it is non-inferior*)
   - ☐ 7.5% fewer participants (*ie. if 7.5% fewer of the participants receiving the new intervention are pain-free as compared to those receiving the established intervention, or any difference under 7.5% exists, it is non-inferior*)
   - ☐ 10% fewer participants (*ie. if 10% fewer of the participants receiving the new intervention are pain-free as compared to those receiving the established intervention, or any difference under 10% exists, it is non-inferior*)
   - ☐ 12.5% fewer participants (*ie. if 12.5% fewer of the participants receiving the new intervention are pain-free as compared to those receiving the established intervention, or any difference under 12.5% exists, it is non-inferior*)
   - ☐ Other – Please specify your suggested non-inferiority margin for this outcome: _____

10. What do you think would be an acceptable non-inferiority margin for the following outcome used in trials of acute migraine interventions: the **absolute percentage of patients who have a migraine recurrence within 48 hours of treatment**?
    - ☐ 2.5% more participants (*ie. if 2.5% more of the participants receiving the new intervention have a recurrence as compared to those receiving the established intervention, or any difference under 2.5% exists, it is non-inferior*)
    - ☐ 5% more participants (*ie. if 5% more of the participants receiving the new intervention have a recurrence as compared to those receiving the established intervention, or any difference under 5% exists, it is non-inferior*)

- ☐ 7.5% more participants (*ie. if 7.5% more of the participants receiving the new intervention have a recurrence as compared to those receiving the established intervention, or any difference under 7.5% exists, it is non-inferior*)
- ☐ 10% more participants (*ie. if 10% more of the participants receiving the new intervention have a recurrence as compared to those receiving the established intervention, or any difference under 10% exists, it is non-inferior*)
- ☐ 12.5% more participants (*ie. if 12.5% more of the participants receiving the new intervention have a recurrence as compared to those receiving the established intervention, or any difference under 12.5% exists, it is non-inferior*)
- ☐ Other – Please specify your suggested non-inferiority margin for this outcome: _____

11. What do you think would be an acceptable non-inferiority margin for the following outcome used in trials of acute migraine interventions: the **absolute percentage of patients with sustained pain freedom** (ie. the percentage of patients who are pain free 2 hours after the intervention and remain pain-free 48 hours after the intervention?
    - ☐ 2.5% fewer participants (*ie. if 2.5% fewer of the participants receiving the new intervention have sustained pain-freedom as compared to those receiving the established intervention, or any difference under 2.5% exists, it is non-inferior*)
    - ☐ 5% fewer participants (*ie. if 5% fewer of the participants receiving the new intervention have sustained pain-freedom as compared to those receiving the established intervention, or any difference under 5% exists, it is non-inferior*)
    - ☐ 7.5% fewer participants (*ie. if 7.5% fewer of the participants receiving the new intervention have sustained pain-freedom as compared to those receiving the established intervention, or any difference under 7.5% exists, it is non-inferior*)
    - ☐ 10% fewer participants (*ie. if 10% fewer of the participants receiving the new intervention have sustained pain-freedom as compared to those receiving the established intervention, or any difference under 10% exists, it is non-inferior*)
    - ☐ 12.5% fewer participants (*ie. if 12.5% fewer of the participants receiving the new intervention have sustained pain-freedom as compared to those receiving the established intervention, or any difference under 12.5% exists, it is non-inferior*)

Other – Please specify your suggested non-inferiority margin for this outcome:

_____

14. Appendix H. NIMM Responses in "Other" Category

Item	Outcome	"Other" Responses
6	Change in the number of monthly migraine attacks comparing baseline to the treatment period	• "A reduction of 1.5 migraine day per month (ie. if the new intervention yields 1 day per month more than the established intervention, or anything less than 1.5 day more, it is non-inferior). Should always use migraine days and not attacks or episodes. Measuring attacks is insensitive given the high variability in attack duration between and within individuals". • "1 if episodic migraine" • "I don't think we have a sufficient body of evidence in the migraine prophylaxis literature to support non-inferiority trials at all. That is, it's not really an appropriate study design when so many of the studies of medications we currently use produced such a slight decrease in number of headache attacks or days vs placebo. The PREEMPT study is a good example: the treatment group had 1.8 migraine days per month as compared to placebo. And we think that onabotulinum toxin is one of the most effective preventive treatments we have. In terms of oral treatments, it looks like valproate is the most effect we have, and that showed a reduction of 2.4 migraine days per month. Given these numbers compared to placebo, I would argue that we don't have a treatment that's 'established' to the point that we can use it as the reference in a non-inferiority trial. I think we are still at the stage of needing to do placebo-controlled trials. I will also point out that that IHS Guidelines for controlled trials of drugs in migraine recommends including a placebo group". • "A change in 1 attack per month is clinically meaningless. Look for a change in 2-4 attacks per month" • "I would go with a percentage like 20% - I think the question applied both to frequent migraine or chronic migraine" • ". 2 attacks per month" • "50% or greater reduction in headache attack frequency" • "Number of attacks alone cannot tell us if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows." • "A reduction of at least 2 attacks per month"
7	Change in the number of monthly migraine days comparing baseline to the treatment period	• "0.25" • "5" • "Please see my answer to the previous question".

		• "2-4 days" • "I would go with a percentage like 20% - I think the question applied both to frequent migraine or chronic migraine" • "greater than 4 headache days" • "50% or greater reduction in headache day frequency" • "Number of migraine days alone cannot tell us if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows".
8	Change in the average migraine intensity comparing baseline to the treatment period (where the intensity of the headache is measured on the following 4-point severity scale: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)	• "No prophylactic trial has ever shown a significant reduction in migraine intensity. Using a 4-point ordinal scale does not provide the sensitivity sufficient to detect a difference. Its a meaningless outcome measure in prophylactic trials using this Glaxo Smith Kline scale for acute therapy trials". • "Again, I don't think we have a consistent enough response in the treatments we currently use, as compared to placebo, to be able to run a non-inferiority trial". • "3 points or more" • "intensity by itself will not matter" • "The change of average migraine intensity alone cannot tell you if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows".
	Absolute percentage of participants who are pain-free 2 hours after the intervention	• "I would have results compared by severity at time the first dose is taken. This has an effect that I recall is as large as your percentages above. You cannot assume that randomization will achieve equal distribution of headache severity at the time of headache treatment - once this is controlled for - 10%" • "20%" • "25% fewer" • "The absolute percentage of pain freedom alone cannot tell you if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows".
	Absolute percentage of patients who have a migraine recurrence within 48 hours of treatment	• "20%" • "25% more" • "The absolute percentage of migraine recurrence in 48h alone cannot tell you if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows".
	Absolute percentage of patients with sustained pain freedom (ie. the percentage of patients who are pain free 2 hours after the intervention and	• "20%" • "20% fewer" • "10% above. Overall depends on whether you include placebo run-in (single blind phase before randomization to active comparators)"

	remain pain-free 48 hours after the intervention)	• "The absolute percentage of patients with sustained pain freedom alone cannot tell you if there is a difference or in our case non-inferiority. It will depend on what the statistical analysis shows".

15. Appendix I. RCT Eligibility Criteria Rationale

The eligibility criteria for the proposed randomized controlled trial were chosen for a variety of reasons, all of which fall into one of the following categories (see Table): 1) compliance with the International Headache Society Guidelines on Controlled trials of Drugs in Migraine, 2) safety, that is, ensuring that exposure to one of the active interventions does not result in an adverse event, and 3) ensuring that participants have ability to participate in the trial and respond to interventions. The upper limit of the age criterion, that is, that participants must be between 8.0 and 18.0 years, was chosen in order to limit the study to pediatric patients. The lower limit of the age criterion was chosen based on the lower limit of a similar large, well-designed pediatric trial that is underway[173] and because it can be more difficult to diagnose migraine accurately in younger children.

Table. Rationale for Specific Inclusion and Exclusion Criteria

Rationale	Inclusion Criteria	Exclusion Criteria
Compliance with the International Headache Society Guidelines on Controlled Trials of Drugs in Migraine	• Migraine without aura or migraine with aura as per International Classification of Headache Disorders Third Edition, Beta Version (ICHD) criteria • Migraine frequency of 2-8 attacks per month in three month retrospective period and 1 month baseline period • Migraines have been present for at least one year	• Other headache types are present and the participant cannot differentiate migraine from the other headache(s) • Fifteen or more headache days per month (ie. chronic migraine) • Overusing acute migraine medications • Taking a migraine prophylactic medication within three months of enrollment • Taking an antipsychotic or antidepressant medication within three months of enrollment • Pregnant, lactating or positive pregnancy test
Safety	N/A	• History of anaphylaxis or allergy to topiramate or levetiracetam • Pregnant, lactating or positive pregnancy test • Sexually active and not using a reliable birth control method • History of renal calculi • Significant hepatic or renal impairment • On the ketogenic diet

		• Has alcohol or drug dependence • History of significant behavioral problems • Has a psychiatric disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM V)
Ensuring that participants have ability to participate in trial and respond to interventions	• Able to communicate sufficiently with parents in order to accurately complete a headache diary and study questionnaires	• Overusing acute migraine medications • Taking a migraine prophylactic medication within three months of enrollment • Taking an antipsychotic or antidepressant medication within three months of enrollment • Received Botox injections for migraine within the past three months • Previous trial of topiramate or levetiracetam for migraine prophylaxis • History of epilepsy • Has a psychiatric disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM V) • Has alcohol or drug dependence • History of another chronic pain disorder
Other	• Age 8.0-18.0 years	

16. Appendix J. RCT Headache Diary Template

Participant number: _____ Month: _____ Year: _____

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	Did you have a headache today?																														
Yes																															
No																															
	Was this headache a migraine? ***If yes, please answer questions below.***																														
Yes																															
No																															
	How bad was the migraine? ***Please record the worst pain that you felt with this migraine.***																														
Mild																															
Moderate																															
Severe																															
	At what time did the migraine start?																														
Start Time																															
	At what time did the migraine end? ***If into next day(s), extend arrow into day where it ended and indicate time it ended there.***																														
End Time																															
	Did you experience any of the following symptoms today? ***Tick all that apply.***																														
Increased appetite																															
Decreased appetite																															
Fatigue																															
Problems concen-trating																															
Tingling sensations																															
Changes in behavior																															
Aggression																															
Paranoia																															
Problems thinking																															
Other (please indicate what the symptom was)																															

	Did you take any of these medications to relieve the migraine today? ***Indicate how many doses you took today in the box.***																														
Acetamino-phen																															
Ibuprofen																															
Naproxen																															
Ketorolac																															
Diclofenac																															
Indo-methacin																															
Suma-triptan																															
Almotriptan																															
Rizatriptan																															
Eletriptan																															
Naratriptan																															
Frova-triptan																															
Zolmi-triptan																															
Other (please indicate name)																															

17. Appendix K. PedMIDAS Questionnaire

PedMIDAS

The following questions try to assess how much the headaches are affecting day-to-day activity. Your answers should be based on the last three months. There are no "right" or "wrong" answers so please put down your best guess.

1. How many full school days of school were missed in the last 3 months due to headaches? _____

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)? _____

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)? _____

4. How many days were you not able to do things at home (i.e. chores, homework, etc.) due to a headache? _____

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)? _____

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)? _____

Total PedMIDAS Score: _____

18. Appendix L. Trial Informed Consent Form for Parents and Participants Aged 16 and Over

Title: Optimizing Migraine Prophylaxis in Pediatrics (OMPP Trial): A Randomized Controlled Trial Comparing the Efficacy of Levetiracetam, Topiramate and Placebo for Preventing Migraines in Children and Adolescents

Principal Investigator: Dr. Serena Orr, MD, MSc Candidate, Pediatric Neurology Resident
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, ON, Canada, K1H 8L1
Phone: (613) 737-7600 ext. 1605

1. Introduction

You are being invited to participate in a research study. In this study, we are trying to determine if the medications topiramate and levetiracetam might help to prevent migraines in children and adolescents.

In order to participate in any research study you have to: a) understand what is involved in participating, b) understand the risks and benefits of participating and c) make an informed decision to voluntarily accept or decline participation. This process is called 'informed consent'. This form is meant to help you understand the study so that you can make an informed decision to take part in the study or not.

You may come across words in this consent form that you do not understand. Please ask the study research coordinator or study investigator to explain anything that you do not clearly understand. You can take time to read through an unsigned copy of this consent form so that you can think about it. You can also discuss it with family or friends before making a decision.

You are being asked to join this study because you have migraine headaches. We are looking for information from children and adolescents who DO HAVE migraine headaches. The research coordinator has reviewed the eligibility criteria and has determined that you are suitable for participation in this study.

2. Purpose of the Study

Migraines are very common in children and adolescents, and can have a large impact on their day-to-day lives. Children and adolescents with frequent migraines can consider two types of treatment: treating the headaches when they come and taking a medication every day to prevent migraines in the first place. Although several different medications are used to prevent migraines, we don't have a lot of information about which ones are the most effective, because there aren't very many research studies that have been done in this area.

In this study, we are trying to compare two medications, levetiracetam and topiramate, to a placebo medication, in order to determine if these medications can help to prevent migraines.

3. Overview of the Study

Preventative medications are given to patients to try and decrease the number of migraines they are having. Not only should these medications work to decrease the migraines, but they must also be tolerable to the patients; that is, they must not have too many unpleasant side effects.

Several studies suggest that topiramate is safe and effective in preventing migraines in children and adolescents. Levetiracetam has not been studied as much as topiramate for migraines, but preliminary studies suggest that it might help to prevent them. Levetiracetam is commonly used to treat seizures in children and adolescents, and has been found to be safe in that context.

In this study, we would like to compare topiramate, levetiracetam and placebo to determine how well these interventions work to prevent migraines. Participants will be randomly assigned to be treated with either topiramate, levetiracetam or placebo. A placebo is a matching pill that does not contain any active ingredients. When researchers are trying to study whether a drug works or not, they must compare it to placebo. This helps to account for the fact that many patients tend to do better just by taking a pill or by participating in a research study.

In order to compare these three interventions, participants in this study will be randomly assigned to receive 24 weeks of treatment with either topiramate, levetiracetam or placebo. This means that each person participating in this study will have an equal chance of getting either of the interventions, and that the decision about who receives which intervention is random.

4. Study Inclusion & Exclusion Criteria

A. Inclusion Criteria

In order to participate, you must meet all of the following criteria:

6. Migraine without aura or migraine with aura as per International Classification of Headache Disorders Third Edition, Beta Version (ICHD) criteria
7. Age 8.0-18.0 years
8. Migraine frequency of 2-8 attacks per month in three month retrospective period and 1 month baseline period, with definition of attack as follows:
    a. Attacks are separated by at least 48 hour headache-free interval
9. Migraines have been present for at least one year
10. Able to communicate sufficiently with parents in order to accurately complete a headache diary and study questionnaires

B. Exclusion Criteria

In order to participate, you must meet NONE of the following criteria:

19. Other headache types are present and the participant cannot differentiate migraine from the other headache(s)
20. Fifteen or more headache days per month (ie. chronic migraine)
21. Overusing acute migraine medications:
    a. Taking a triptan on ten or more days per month
    b. Taking acetaminophen or a non-steroidal anti-inflammatory medication on fifteen or more days per month

22. Taking a migraine prophylactic medication within three months of enrollment
23. Taking an antipsychotic or antidepressant medication within three months of enrollment
24. Received Botox injections for migraine within the past three months
25. Previous trial of topiramate or levetiracetam for migraine prophylaxis with:
    a. Adequate dosing
    b. At least three months of prophylaxis
26. History of anaphylaxis or allergy to topiramate or levetiracetam
27. Pregnant, lactating or positive pregnancy test
28. Sexually active and not using a reliable birth control method
29. History of renal calculi
30. Significant hepatic or renal impairment
31. On the ketogenic diet
32. History of epilepsy
33. Has a psychiatric disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM V)
34. Has alcohol or drug dependence
35. History of significant behavioral problems
36. History of another chronic pain disorder

5. Study Procedures

If you decide to participate in this study, you will first enter a 4 week baseline period, during which you will complete a headache diary and have a baseline assessment with the study doctor. If you continue to meet our eligibility criteria after that 4 week period, you will be randomly assigned to either receive topiramate, levetiracetam or placebo for 24 weeks, followed by a 4 week period during which we will slowly take you off the medication. Neither you, the study coordinator nor the study doctor will know which medication you are taking. The research pharmacist will maintain a password-protected list with this information in case there is a need for you, the study coordinator or the study doctor to have access to that information at any point in time. The purpose of not knowing which medication you are taking is to make sure that any effect of the medication that we observe is due to the medication itself and not what you, the study doctor or the study coordinator expect the medication to be like.

During the first 8 weeks of the study, the study doctor will adjust the dose of the medication to reach a dose that works best to prevent your migraines and is tolerable to you in terms of side effects. You will then take the medication for 16 more weeks. After the 16 weeks are complete, the medication will be tapered off over 4 weeks. Once you are off the medication, there will be another 4 week period for follow-up. During the study, you will be asked to fill out a daily headache diary in order to keep track of your migraines. You will have monthly telephone check-ins with the study research coordinator and monthly visits with the study doctor in the clinic.

At each study visit, you will see the study doctor. Your weight will be taken and you will report on how you are feeling (ie. how your headaches are and whether you are having any new symptoms that might be side effects). If needed, you will have a physical exam. The study doctor will also review your headache diary to see how things are going with your migraines.

During each monthly telephone check-in, the study research coordinator will contact you to ask you how things are going with the medication and your headaches. The coordinator will review your use of the headache diary and will ask you about progress with your headaches as well as other symptoms that could be related to the medication.

Throughout the study, you will be able to take medications like Tylenol or Advil to treat migraines as they come. You will be asked to not take any other medication every day to prevent migraines, because it is important for us to see what the effects of these medications are alone, without the added effect of other daily medications taken to prevent migraines.

6. Possible Risks Involved in Participating in this Study

Topiramate and levetiracetam are both commonly used medications, and both have been found to be safe to use in children and adolescents. Each does have potential side effects, some of which are weight loss, decreased appetite, changes in behavior or concentration and a very small increase in the risk of getting kidney stones. The placebo medication will not contain active ingredients. However, some people still experience relief from their headaches with placebo, and it is also possible to have side effects from placebo. Throughout the study, you will be closely monitored for medication side effects, and the dosing of your medication can be adjusted if you get any side effects that you cannot tolerate.

7. Possible Benefits Involved in Participating in the Study

If you participate in this study, you might receive a medication that significantly helps to prevent your migraines. You will receive this medication for 24 weeks at no cost. The information gained from this study will help us to improve the care of children and adolescents with migraine. Your involvement will potentially benefit many children and adolescents in the future, because of the information that we will gain from this study.

8. Voluntary Participation and Withdrawal

Your decision about whether or not to participate in this study is voluntary. You can choose to participate, or you can choose to withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care.

There will be no consequences of your decision to withdraw from the study.

You can decide not to be in the study without losing any medical benefits you would otherwise receive. If you do enter the study, you can leave the study at any time without loss of any medical benefits or any other penalty. If you leave the study, your usual medical care will not be affected in any way.

9. Payment for Injury and Harm

In the event that you suffer injury as a direct result of participating in this study, normal legal rules of compensation will apply. By signing this consent form, you are in no way waiving your legal rights or releasing the investigators from their legal and professional responsibilities.

10. Compensation

If you take part in this study, you will not be paid or rewarded in any way. You will not be compensated for any discoveries made as a result of this study.

11. Confidentiality

Only you, the study doctor, the study coordinator and members of the Neurology clinic who are treating you will know that you are involved with this study. Because the study coordinator will be contacting you on a monthly basis over the phone, we will need to collect your contact information. We will store this information in a password-protected, encrypted electronic file. The remaining records kept for this study will identify you by a number, not by name, nor date of birth. All information obtained during this study, including your medical records, personal data and research data, will be kept strictly confidential except as required by law. Your name or material identifying you as a study participant will not be released without written permission, except when it is required or permitted by law. Any personal information that leaves the hospital or clinic will be coded so that you cannot be identified by name. You will not be identified in any publication or presentation of this study. The study records will be retained for a period of 7 years as per Canadian regulations. CHEO internal monitoring research staff may review charts and medical records for quality improvement purposes.

12. Contact Persons

The CHEO Research Ethics Boards is a committee of the hospital that includes individuals from different backgrounds. The Board reviews all research that takes place at the hospital. Its goal is to ensure that the rights and welfare of people participating in research are protected. The Board's work is not intended to replace a parent or child's judgment about what decisions and choices are best for them. This study has been reviewed and approved by the CHEO Research Ethics Board. You may contact the Chair of the Research Ethics Board, for information regarding patients' rights in research studies at: (613) 737-7600 ext. 3272, although this person cannot provide any health-related information about the study. If you have any questions about participation in this study, or if you feel that you have experienced a study-related injury, please call Dr. Orr at (613) 737-7600 ext. 1605.

CONSENT

I have read this consent form and its contents were explained. My questions have been answered. I give consent voluntarily to participate in this study and I will receive a signed and dated copy of this consent form for my records.

By signing this informed consent form I am authorizing such access to my personal data as described in this content.

I am aware that I can request a copy of the results of this study upon its completion, if I wish to do so.

Name of Subject (Printed) Date: mm/dd/yyyy

_____Signature of Subject Date: mm/dd/yyyy
(or Parent/Legal Guardian)

_____Signature of Parent/Legal Guardian Date: mm/dd/yyyy

_____
Signature of Investigator Date: mm/dd/yyyy

_____
Signature of Person Conducting Consent Discussion Date: mm/dd/yyyy

19. Appendix M. Trial Assent Form for Participants Aged Less 16 Years

Title: Optimizing Migraine Prophylaxis in Pediatrics (OMPP Trial): A Randomized Controlled Trial Comparing the Efficacy of Levetiracetam, Topiramate and Placebo for Preventing Migraines in Children and Adolescents

Principal Investigator: Dr. Serena Orr, MD, MSc Candidate, Pediatric Neurology Resident
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, ON, Canada, K1H 8L1
Phone: (613) 737-7600 ext. 1605

This form may contain words you do not understand. Please ask the study doctor to explain anything you do not understand. If you wish to talk to the study doctor please ask.

1. What is this study about?

This is a research study. Research studies are done when we are trying to find out more about something. We are trying to find out more about how to treat headaches called migraines. You are being asked to participate in this study because you have migraines. We are hoping to figure out if the medications topiramate and levetiracetam work to prevent migraines in kids.

2. Do I have to be in this study?

No. You do not have to be in this study if you don't want to.

Even if you say that you want to be in this study, you can change your mind later. If you change your mind, please tell your doctor or the research coordinator. They can answer questions you have about the study before you make up your mind. You can talk to your mom, or dad, or the person who looks after you about it. They can read you the information the research coordinator gave them to help you make up your mind.

If you want to be in this study, you will have to sign this form.

3. What will happen during the study?

In this study, we are trying to compare two medications, levetiracetam and topiramate, to a placebo medication, to figure out if these medications can help to prevent migraine headaches. A placebo is a matching pill that has no active drugs in it. When we are trying to study if a drug works or not, we have to compare it to placebo.

If you join this study, you will fill out a headache diary every day. After one month, if you still have enough headaches and still want to be in the study, you will start treatment. You will have an equal chance of getting treated with either levetiracetam, topiramate or placebo. The pharmacist will use a computer to figure out which treatment you will get. You will not know which treatment you are getting. The study doctor and coordinator will also not know which treatment you are on. You will take the treatment every day for 24 weeks. After that, we will slowly take you off the treatment over 4 weeks, and then follow you for another 4 weeks to see how you are doing.

You will have monthly calls from the study research coordinator and monthly visits with the study doctor in the clinic. At each visit, you will see the study doctor. Your weight will be taken and you will tell the doctor how you are feeling with your headaches and any problems you are having. If needed, you will have a physical exam. The study doctor will also look at your headache diary to see how things are going. At each monthly telephone call, the study coordinator will contact you to ask you how things are going with the medication and your headaches.

4. The good and the bad things about doing this study

If you decide to be in this study, good things might happen. The medication that you get might help to prevent your migraines and make you better able to function in school, at home and in activities. You will get this medication for 24 weeks at no cost. The information that we get from this study might help kids with migraines in the future.

If you decide to be in this study, some bad things could happen. The medication could give you side effects. Some of the possible side effects with levetiracetam and topiramate are weight loss, decreased appetite, changes in behavior or concentration and a very small increase in the chance of getting kidney stones. The placebo medication will not have active drugs in it. Some people feel better with placebo, and some people also have side effects from placebo.

5. Will anyone know that I did this study?

We will not share any information about you with anyone outside of the study. We will not tell anyone outside of this study that you participated.

6. Do I have to do this?

You do not have to be in this study. It is okay to say no. You can tell your parents or the study doctor that you do not want to be in this study at any time. That will be okay. It will not affect any care that you receive or will receive at CHEO.

If you decide to be in the study, you can change your mind at any time later. You can still say no and that will be okay.

7. Who can I talk to about the study?

The research coordinator can answer your questions about the study at any time. You can also talk to your mom, your dad or whoever looks after you.

8. Confidentiality

CHEO internal monitoring research staff may review the research files for quality improvement purposes. Your contact information will be stored in a safe, encrypted software so that the study coordinator can contact you. The rest of the study documents will not contain any information that can be linked to you specifically, like your name or date of birth. The rest of the documents will only contain your study identification number.

ASSENT FORM

Do you want to be in this study?

Please check one box: □ Yes, I want to be in the study.

□ No, I do not want to be in the study.

_____
Name of Child (Print)

_____ _____
Signature of Child Date: mm/dd/yyyy

_____
Name of Parent or Legal Guardian (Print)

I attest that the participant had enough time to consider this information, had an opportunity to ask questions and voluntarily agreed to be in the study

_____
Name of Person Explaining Assent (Print)

_____ _____
Signature Person Explaining Assent Date: mm/dd/yyyy

20. Appendix N. Brochure to Explain Study Procedures to Participants

OPTIMIZING MIGRAINE PROPHYLAXIS IN PEDIATRICS (OMPP Trial)

1. What is this study about?

This study is trying to determine if levetiracetam and topiramate are effective in preventing migraines in kids.

2. What will happen in this study?

If you agree to participate in this study, you will be randomly assigned to receive either topiramate, levetiracetam or placebo for 24 weeks.

Throughout the study, you will be asked to complete a headache diary every day. The first 4 weeks will be a baseline period, where you fill out the diary so that we can see how many migraines you are having. If, after the 4 weeks, you are still having enough migraines and still want to participate, then you will be assigned to one of the study medications. After this, the 24 weeks of treatment will start. You will then be slowly taken off the medication for a period of 4 weeks, and followed for another 4 weeks. During the study, you will be monitored with study visits and telephone follow-ups.

3. How many study visits will I have?

Every month, you will come into the hospital to have a visit with the study doctor. During these visits, you will have your weight taken, a physical exam if needed, and the study doctor will go over how things are going with your headaches and the medication. It is very important that you fill out your headache diary every day and bring it to your visits, because this is how the study doctor will know if your migraines are getting better or not.

4. How many telephone follow-ups will I have?

Every month, the study coordinator will call you to check in. The study coordinator will go over how things are with your headaches and whether you are experiencing any side effects from the medication. It is very important that you fill our your headache diary every day, because it will help you to give the study coordinator accurate information and it will help you to keep track of how you are doing.

5. What else will I have to do for this study?

As is described above, you will have to fill out a headache diary every day. This diary will only take a couple of minutes to fill out. The diary is easy to fill out: it has a few questions that require only checkbox answers, and one question where you record how many rescue medications you took for your headache(s) that day with a number. We will also give you a questionnaire to see how your migraines are affecting your life. You will take this survey three times: once at baseline, once at the end of treatment and once at the end of follow-up. This survey only takes a few minutes to complete.

As is described above, you will be asked to attend monthly hospital visits with the study doctor and to take monthly telephone calls from the study coordinator.

6. When will my involvement in the study be over?

After the study follow-up period is over, you will no longer be involved with this study. Your study doctor will ensure that you have follow-up for your migraines with either a child neurologist at the hospital or your family doctor.

21. Appendix O. PASS Report 1 – Superiority Hypothesis Sample Size Calculation

Group Sequential - Means

Numeric Results for Two-Sided Hypothesis Test of Means

Target Power	Actual Power	N1	N2	N	Mean1	Mean2	S1	S2	Alpha
0.80	0.80197	71	71	142	2.60	1.41	2.5	2.5	0.050

References

Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.

Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.

O'Brien, P.C. and Fleming, T.R. 1979. 'A multiple testing procedure for clinical trials.' Biometrics, 35, pages 549-556.

Pocock, S.J. 1977. 'Group sequential methods in the design and analysis of clinical trials.' Biometrika, 64, pages 191-199.

Reboussin, D.M., DeMets, D.L., Kim, K, and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

Report Definitions

Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.

Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.

N1 and N2 are the number of items sampled from each population.

N is the total sample size, N1 + N2.

Mean1 is the mean of populations 1 and 2 under the null hypothesis of equality.

Mean2 is the mean of population 2 under the alternative hypothesis.

S1 and S2 are the population standard deviations of groups 1 and 2.

Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

Sample sizes of 71 and 71 achieve 80% power to detect a difference of 1.19 between the group means with standard deviations of 2.5 and 2.5 at a significance level (alpha) of 0.050 using a two-sided z-test. These results assume that 4 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries.

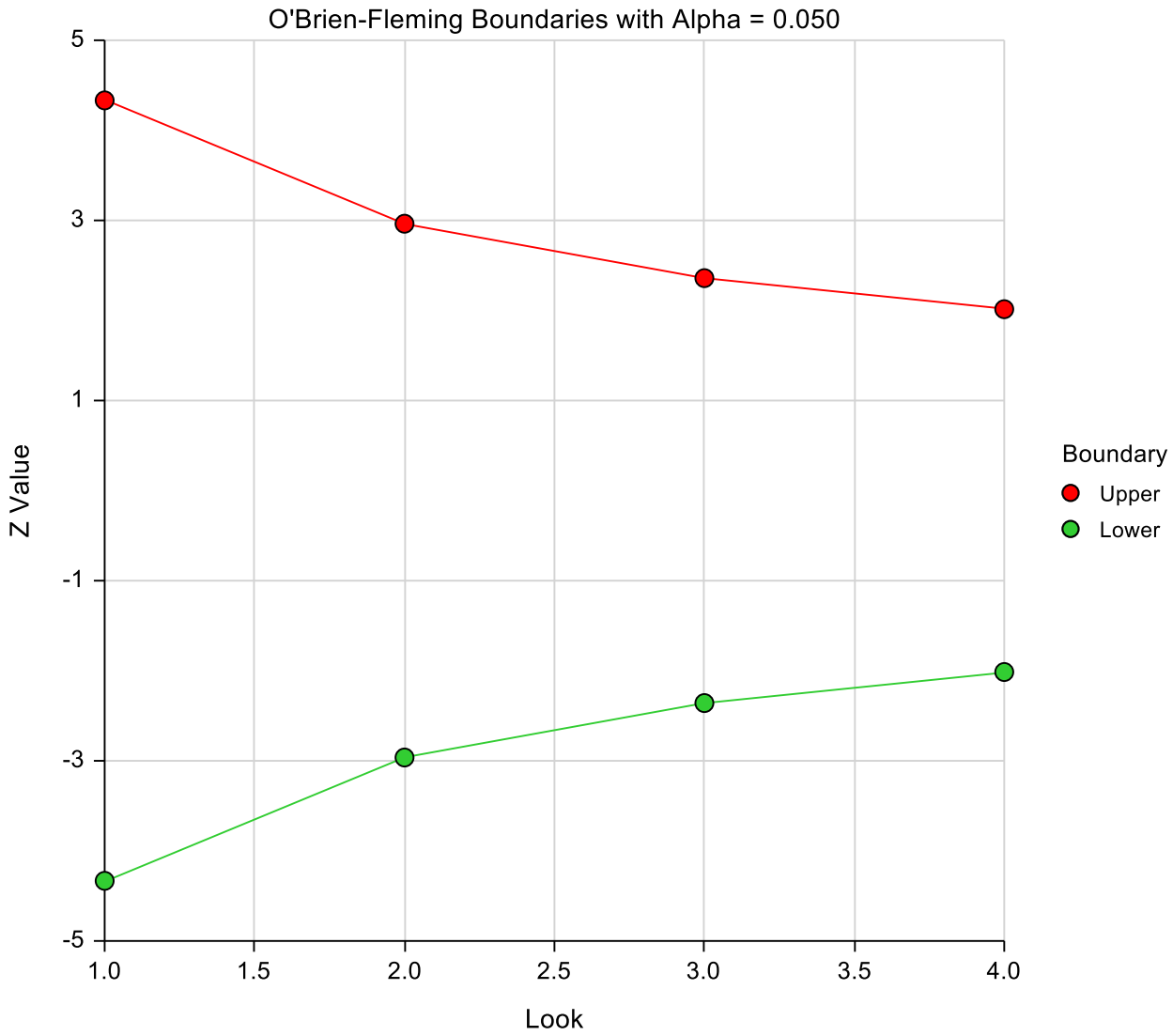
Details when Spending = O'Brien-Fleming, N1 = 71, N2 =71, S1 = 2.5, S2 = 2.5, Diff = 1.19

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.50	-4.33263	4.33263	0.000	0.000	0.000	0.00178	0.002
2	1.00	-2.96311	2.96311	0.003	0.003	0.003	0.16739	0.169
3	1.50	-2.35902	2.35902	0.018	0.016	0.019	0.37325	0.542
4	2.00	-2.01406	2.01406	0.044	0.031	0.050	0.25955	0.802

Drift 2.83610

Group Sequential - Means

Chart Section



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22. Appendix P. PASS Report 2 – Non-Inferiority Hypothesis Sample Size Calculation

Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Scenario 1 Numeric Results for Group Sequential Test of Non-Inferiority
Higher Means are Better
Hypotheses: H0: Mean1 - Mean2 = NIM; H1: Mean1 - Mean2 < NIM
Test Statistic: T-Test
Alpha-Spending Function: O'Brien-Fleming Analog
Beta-Spending Function: None
Futility Boundary Type: None
Number of Looks: 4
Simulations: 2000
Pool Size: 10000

Numeric Summary for Scenario 1

Power			Alpha				
Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
0.811	0.794	0.828	0.050	0.050	0.040	0.060	0.189

		Average Sample Size							
		Given H0		Given H1		Non-Inf.			Std
N1	N2	Grp1	Grp2	Grp1	Grp2	Margin	Mean1	Mean2	Dev
79	79	78	78	62	62	1.0000	2.6000	2.6000	2.5000

References

Jennison, C.; Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman &
Hall. Boca Raton, FL.
Devroye, Luc. 1986. Non-Uniform Random Variate Generation. Springer-Verlag. New York.
Matsumoto, M. and Nishimura,T. 1998. 'Mersenne twister: A 623-dimensionally equidistributed uniform pseudorandom number generator.' ACM Trans. On Modeling and Computer Simulations.
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Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Report Definitions

Power is the probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.

Power 95% LCL and UCL are the lower and upper confidence limits for the power estimate. The width of the interval is based on the number of simulations.

Target Alpha is the user-specified probability of rejecting a true null hypothesis. It is the total alpha spent.

Actual Alpha is the alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.

Alpha 95% LCL and UCL are the lower and upper confidence limits for the actual alpha estimate. The width of the interval is based on the number of simulations.

Beta is the probability of accepting a false null hypothesis. It is the total proportion of alternative hypothesis simulations that do not cross the significance boundaries.

N1 and N2 are the sample sizes of each group if the study reaches the final look.

Average Sample Size Given H0 Grp1 and Grp2 are the average or expected sample sizes of each group if H0 is true. These are based on the proportion of null hypothesis simulations that cross the significance or futility boundaries at each look.

Average Sample Size Given H1 Grp1 and Grp2 are the average or expected sample sizes of each group if H1 is true. These are based on the proportion of alternative hypothesis simulations that cross the significance or futility boundaries at each look.

Non-inferiority margin is the distance from the control mean that is still considered non-inferior.

Mean1, Mean2, and Std Dev are the parameters that were set by the user to define the null and alternative simulation distributions.

Summary Statements

Group sequential trials with group sample sizes of 79 and 79 at the final look achieve 81% power to detect a difference of 1.0000 at the 0.050 significance level (alpha) using a one-sided T-Test.

Accumulated Information Details for Scenario 1

	Accumulated Information	-------- Accumulated Sample Size --------		
Look	Percent	Group 1	Group 2	Total
1	25.0	20	20	40
2	50.0	40	40	80
3	75.0	60	60	120
4	100.0	79	79	158

Accumulated Information Details Definitions

Look is the number of the look.

Accumulated Information Percent is the percent of the sample size accumulated up to the corresponding look.

Accumulated Sample Size Group 1 is total number of individuals in group 1 at the corresponding look.

Accumulated Sample Size Group 2 is total number of individuals in group 2 at the corresponding look.
Accumulated Sample Size Total is total number of individuals in the study (group 1 + group 2) at the corresponding look.

Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Boundaries for Scenario 1

	-- Significance Boundary --	
	T-Value	P-Value
Look	Scale	Scale
1	-3.26419	0.00116
2	-2.61944	0.00529
3	-1.97462	0.02532
4	-1.69088	0.04643

Boundaries Definitions

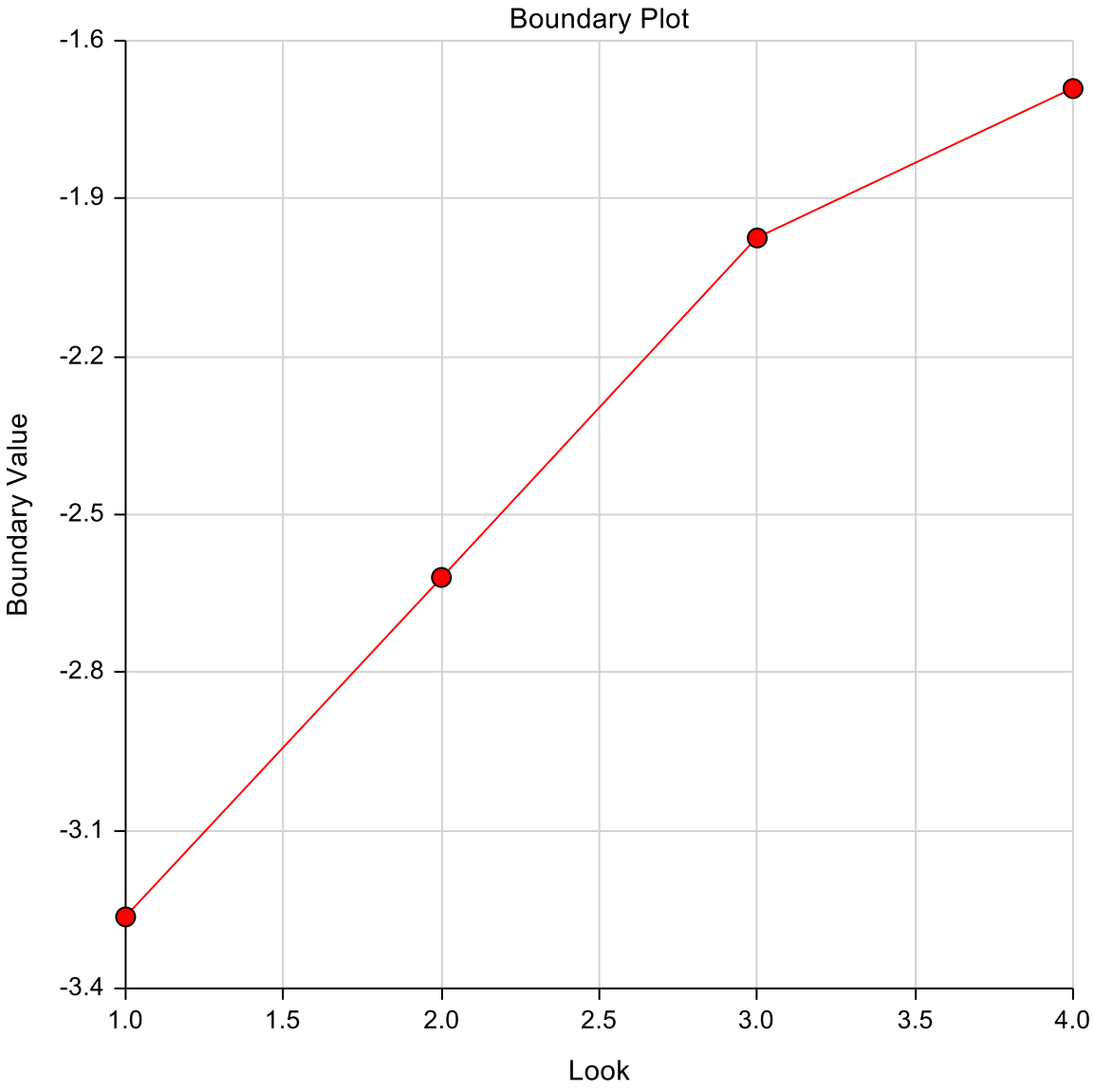
Look is the number of the look.

Significance Boundary T-Value Scale is the value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.

Significance Boundary P-Value Scale is the value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the T-Value Boundary and is sometimes called the nominal alpha.

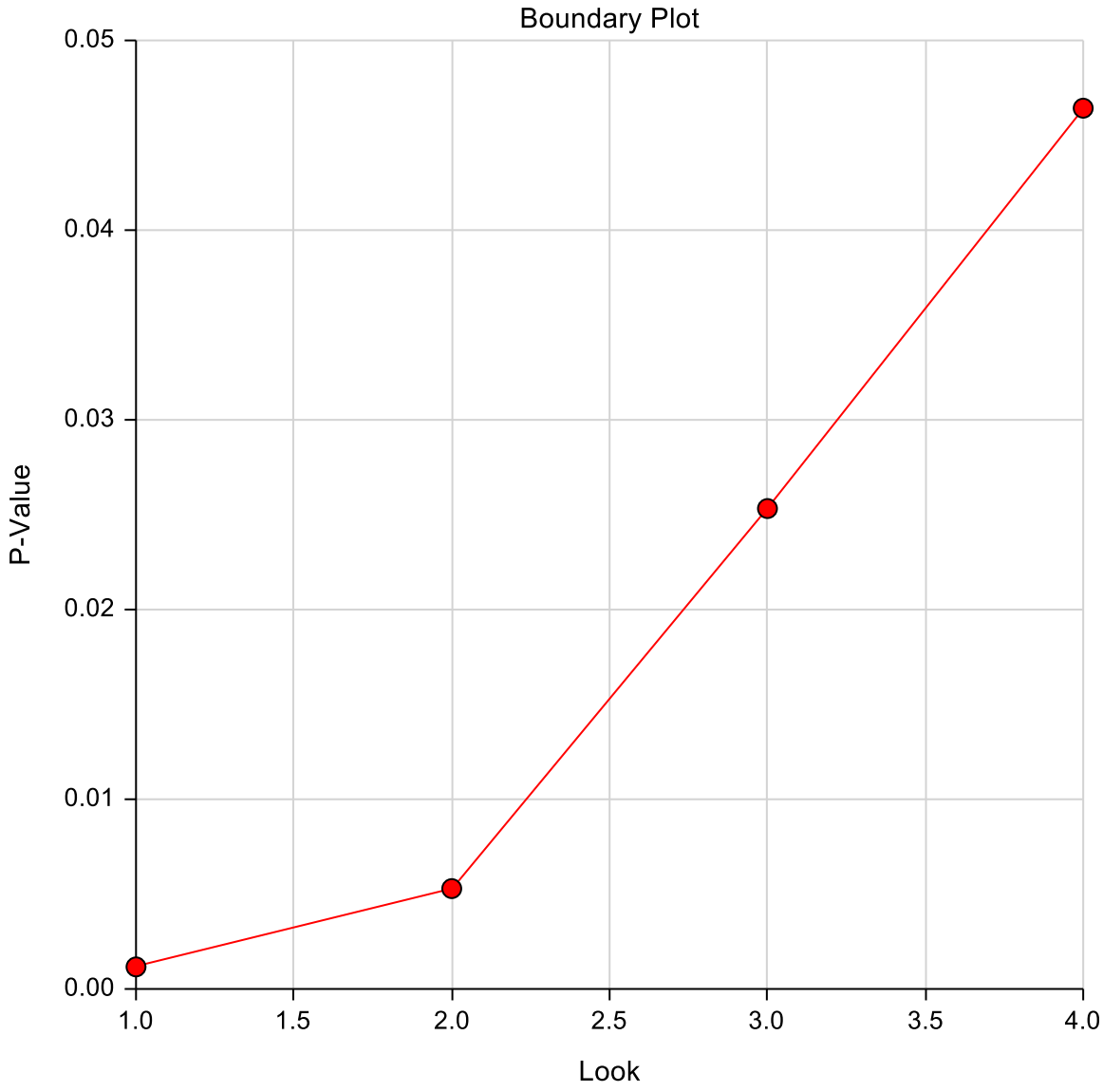
Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Boundary Plot



Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Boundary Plot - P-Value



Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Significance Boundaries with 95% Simulation Confidence Intervals for Scenario 1

	--------- T-Value Boundary ---------			--------- P-Value Boundary ---------		
Look	**Value**	**95% LCL**	**95% UCL**	**Value**	**95% LCL**	**95% UCL**
1	-3.26419			0.00116		
2	-2.61944	-2.88807	-2.42370	0.00529	0.00251	0.00884
3	-1.97462	-2.07622	-1.86435	0.02532	0.02002	0.03238
4	-1.69088	-1.82038	-1.62086	0.04643	0.03531	0.05353

Significance Boundary Confidence Limit Definitions

Look is the number of the look.

T-Value Boundary Value is the value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.

P-Value Boundary Value is the value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the T-Value Boundary and is sometimes called the nominal alpha.

95% LCL and UCL are the lower and upper confidence limits for the boundary at the given look. The width of the interval is based on the number of simulations.

Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Alpha-Spending and Null Hypothesis Simulation Details for Scenario 1

			--- Target ---		--- Actual ---		Proportion	
	--- Signif. Boundary ---			Cum.			H1 Sims	Cum. H1 Sims
	T-Value	P-Value	Spending	Spending		Cum.	Outside	Outside
Look	Scale	Scale	Function Alpha	Function Alpha	Alpha Spent	Alpha Spent	Signif. Boundary	Signif. Boundary
1	-3.26419	0.00116	0.000	0.000	0.000	0.000	0.036	0.036
2	-2.61944	0.00529	0.005	0.006	0.006	0.006	0.191	0.226
3	-1.97462	0.02532	0.018	0.024	0.018	0.024	0.382	0.608
4	-1.69088	0.04643	0.026	0.050	0.027	0.050	0.204	0.811

Alpha-Spending Details Definitions

Look is the number of the look.

Significance Boundary T-Value Scale is the value such that statistics outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. They are sometimes called efficacy boundaries.

Significance Boundary P-Value Scale is the value such that P-Values outside this boundary at the corresponding look indicate termination of the study and rejection of the null hypothesis. This P-Value corresponds to the Significance T-Value Boundary and is sometimes called the nominal alpha.

Spending Function Alpha is the intended portion of alpha allocated to the particular look based on the alpha-spending function.

Cumulative Spending Function Alpha is the intended accumulated alpha allocated to the particular look. It is the sum of the Spending Function Alpha up to the corresponding look.

Alpha Spent is the proportion of the null hypothesis simulations resulting in statistics outside the Significance Boundary at this look.

Cumulative Alpha Spent is the proportion of the null hypothesis simulations resulting in Significance Boundary termination up to and including this look. It is the sum of the Alpha Spent up to the corresponding look.

Proportion H1 Sims Outside Significance Boundary is the proportion of the alternative hypothesis simulations resulting in statistics outside the Significance Boundary at this look. It may be thought of as the incremental power.

Cumulative H1 Sims Outside Significance Boundary is the proportion of the alternative hypothesis simulations resulting in Significance Boundary termination up to and including this look. It is the sum of the Proportion H1 Sims Outside Significance Boundary up to the corresponding look.

Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Scenario 1 Numeric Results for Group Sequential Test of Non-Inferiority
Higher Means are Better
Hypotheses: H0: Mean1 - Mean2 = NIM; H1: Mean1 - Mean2 < NIM
Test Statistic: T-Test
Alpha-Spending Function: O'Brien-Fleming Analog
Beta-Spending Function: None
Futility Boundary Type: None
Number of Looks: 4
Simulations: 2000
Pool Size: 10000

Numeric Summary of Scenarios

Scenario	Power	N1	N2	Alpha	Non-Inf. Margin	Mean1	Mean2	Std Dev
1	0.811	79	79	0.050	1.0000	2.6000	2.6000	2.5000

References

Jennison, C.; Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman &
Hall. Boca Raton, FL.
Devroye, Luc. 1986. Non-Uniform Random Variate Generation. Springer-Verlag. New York.
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Report Definitions

Power is the probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.
Alpha is the alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.
N1 and N2 are the sample sizes of each group if the study reaches the final look.
Non-inferiority margin is the distance from the control mean that is still considered non-inferior.
Mean1, Mean2, and Std Dev are the parameters that were set by the user to define the null and alternative
simulation distributions.

Power and Alpha Summary

	Power			Alpha				
Scenario	Value	95% LCL	95% UCL	Target	Actual	95% LCL	95% UCL	Beta
1	0.811	0.794	0.828	0.050	0.050	0.040	0.060	0.189

Group Sequential Two Means Non-Inferiority Power Analysis using Simulation

Report Definitions

Power is the probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.

Power 95% LCL and UCL are the lower and upper confidence limits for the power estimate. The width of the interval is based on the number of simulations.

Target Alpha is the user-specified probability of rejecting a true null hypothesis. It is the total alpha spent.

Alpha or Actual Alpha is the alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.

Alpha 95% LCL and UCL are the lower and upper confidence limits for the actual alpha estimate. The width of the interval is based on the number of simulations.

Beta is the probability of accepting a false null hypothesis. It is the total proportion of alternative hypothesis simulations that do not cross the significance boundaries.

Sample Size Summary

					------- Average Sample Size -------			
					--- Given H0 ---		--- Given H1 ---	
Scenario	**Power**	**Alpha**	**N1**	**N2**	**Grp1**	**Grp2**	**Grp1**	**Grp2**
1	0.811	0.050	79	79	78	78	62	62

Report Definitions

Power is the probability of rejecting a false null hypothesis at one of the looks. It is the total proportion of alternative hypothesis simulations that are outside the significance boundaries.

Alpha is the alpha level that was actually achieved by the experiment. It is the total proportion of the null hypothesis simulations that are outside the significance boundaries.

N1 and N2 are the sample sizes of each group if the study reaches the final look.

Average Sample Size Given H0 Grp1 and Grp2 are the average or expected sample sizes of each group if H0 is true. These are based on the proportion of null hypothesis simulations that cross the significance or futility boundaries at each look.

Average Sample Size Given H1 Grp1 and Grp2 are the average or expected sample sizes of each group if H1 is true. These are based on the proportion of alternative hypothesis simulations that cross the significance or futility boundaries at each look.

Run Time: 23.15 seconds.