

# Utah Medicaid Pharmacy and Therapeutics Committee Review

## FDA-Approved Agents for Migraine Prophylaxis

### Anticonvulsants

Divalproex sodium (*Depakote DR, Depakote ER, Generics*)  
Topiramate (*Topamax, Topamax Sprinkles, Trokendi XR, Qudexy XR*)

### Monoclonal Antibodies, Calcitonin Gene-Related Peptide Antagonists

Erenumab-aooe (*Aimovig*)  
Fremanezumab-vfrm (*Ajovy*)  
Galcanezumab-gnlm (*Emgality*)

### Botulinum Toxin, Type A

OnabotulinumtoxinA (*Botox*)

### Beta Blockers

Propranolol (*Inderal LA, Generic IR Tablet and Solution*)  
Timolol maleate (*Generics*)

AHFS Classification: 28.32.92 Antimigraine Agents, Miscellaneous;  
24:24 Beta Adrenergic Blocking Agents; 28.12.92 Anticonvulsants, Miscellaneous;  
92:92 Other Miscellaneous Therapeutic Agents

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## Executive Summary

Migraine headache is a common neurological condition impacting about 18% of women and 7% of men.<sup>1,2</sup> Between 20% to 50% of patients experience moderate to severe disability<sup>3</sup> and most patients rate their migraine-associated pain as severe.<sup>4,5</sup> Migraine is classified by symptomatology (migraine with or without aura) and frequency (episodic migraine [EM] or chronic migraine [CM]). The diagnosis and classification of migraine is delineated in the International Classification of Headache Disorders-3 (ICHD-3), developed by the International Headache Society.<sup>6</sup> Patients who experience headache (migraine-like or tension-like) occurring  $\geq 15$  days per month for at least 3 months, with at least 8 days/month involving features of migraine headache, are classified as having chronic migraine. Chronic migraine accounts for about 8% of the total migraine cases.<sup>3,6</sup>

This review focuses on the Food and Drug Administration (FDA)-approved products for migraine prophylaxis: divalproex, erenumab, galcanezumab, fremanezumab, onabotulinumtoxinA (OBTA), propranolol, timolol, and topiramate. The efficacy of the newly approved, injectable, monoclonal antibodies (erenumab, galcanezumab, fremanezumab) was demonstrated for both episodic migraine and chronic migraine prophylaxis. The oral agents (divalproex, topiramate, propranolol and timolol) were FDA-approved for migraine prophylaxis prior to the diagnostic distinction between chronic and episodic migraine (a classification introduced in 2004 by the International Headache Society); approvals for oral agents were based on data from study populations primarily with episodic migraine.<sup>7</sup> OBTA has been approved for patients with chronic migraine (headaches  $\geq 15$  days/month with headache lasting  $\geq 4$  hours/day) since 2010; OBTA is not approved for the prophylaxis of episodic migraine.

The oral options (divalproex, topiramate, propranolol, and timolol) are administered daily. The monoclonal antibodies are administered less frequently, by subcutaneous injection: erenumab and galcanezumab are administered once monthly, and fremanezumab has monthly or quarterly dosing options. The neuromuscular blocking agent, onabotulinumtoxinA, is administered intramuscularly, across head and neck muscle areas, once every 12 weeks.

A systematic literature search was conducted in OvidMedline and Embase for direct head-to-head comparative evidence from systematic reviews (SRs) and randomized controlled trials (RCTs) for the FDA-approved migraine prophylactic agents. Most comparative evidence identified was conducted in the adult population.

### PEDIATRIC POPULATION

The only FDA-approved medication for migraine prophylaxis for the pediatric population is topiramate (for adolescents 12 years and older). Guidelines for the treatment of migraine in the pediatric population by the American Academy of Neurology were last published in 2004 and are currently being updated. In the 2004 guideline, the authors could not make strong recommendations for or against divalproex, topiramate, or propranolol.

Authors of a 2015 SR (Barnes et al) conclude that there is limited evidence to support the use of beta-blockers in pediatric patients.<sup>8</sup> However, provided that propranolol has a good safety profile in patients without respiratory or cardiovascular co-morbidities, authors conclude that it may be reasonable to try, with the understanding that only some patients will have an adequate response. The authors found that topiramate is potentially beneficial compared to placebo, though evidence is limited, and that the difference in the treatment effect between topiramate and propranolol is unclear.<sup>8,9</sup>

#### ADULTS

The 2012 American Academy of Neurology and the American Headache Society (AAN/AHS) guideline for the prevention of episodic migraine in adults classifies the following therapies as having established efficacy based on high-quality evidence: divalproex, sodium valproate, topiramate, metoprolol, timolol, and propranolol. Additional off-label agents with lower levels of evidence supporting their use are listed as probably or possibly effective in the AAN/AHS guideline, as outlined in the Table 2 of this report. Regarding chronic migraine, a 2015 “best-practices” guide by neurologist experts of the Mayo Clinic described that only OBTA and topiramate had been shown to be efficacious in randomized, placebo-controlled trials of patients with chronic migraine.<sup>10</sup> The AAN has concluded that there is insufficient evidence comparing OBTA to topiramate for chronic migraine.<sup>11</sup>

Our literature search identified head-to-head RCT comparative evidence for the following comparisons: divalproex versus propranolol; divalproex versus OBTA; topiramate versus OBTA; topiramate versus propranolol; and propranolol versus timolol. Divalproex was similarly effective compared to propranolol (1 small RCT for EM) and to OBTA (1 small RCT including a mixed population with CM and mostly EM patients).<sup>12,13</sup> Topiramate was similarly effective compared to OBTA (in a population with CM) and compared to propranolol.<sup>12,14</sup> Propranolol appears similarly effective compared to timolol.<sup>13</sup> With regard to safety, OBTA appears better tolerated compared to topiramate and divalproex.<sup>13,14</sup> A 2017 meta-analysis suggested that propranolol is better tolerated compared to topiramate, with a significantly lower rate of composite adverse events and rate of withdrawal due to adverse events.<sup>12</sup>

There is no head-to-head evidence directly comparing the newly approved monoclonal antibodies to each other or another active agent at this time. No serious safety issues surfaced during the clinical trials for these monoclonal antibodies. The most common adverse event was injection-site reactions. Constipation was also more common with the 140 mg/month maintenance dose regimen of erenumab compared to placebo. Overall, the monoclonal antibodies were well-tolerated with low study drop-out rates ( $\leq 2\%$ ) due to adverse events in the double-blind pivotal trials.<sup>15-17</sup>

Low rates of long-term adherence to the oral migraine prophylactic agents have been observed in patients with chronic migraine (29% at 6 months, and 20% at 12 months) and is thought to be due to a mix of factors including adverse reactions and in-adequate response to therapy.<sup>18</sup> Poor persistence and adherence to the oral therapies remains a

topic of discussion with room for improvement.<sup>18-21</sup> The anticonvulsants, divalproex and topiramate, can produce intolerable neurological and gastrointestinal effects, and can cause fetal harm (black box warning for divalproex).<sup>22,23</sup> Paresthesia is common with topiramate; though, cognitive dysfunction is described as the main adverse event-related reason that a patient discontinues this medication.<sup>24</sup> Weight gain, tremor, and alopecia can occur with long-term use of divalproex, while gastrointestinal issues can cause significant distress early on.<sup>25</sup> With beta-blockers, patients may experience fatigue, reduced exercise tolerance, hypotension, sexual dysfunction, sleep disturbance, light-headedness, disorientation, and gastrointestinal side effects.

For the purpose of the preferred drug list (PDL), we suggest maintaining at least 2 oral agents of different drug classes included as preferred, for migraine prophylaxis. At least 1 injectable agent may be preferred considering the opportunity for once monthly administration (with all CGRP antagonists) or once quarterly (with fremanezumab and OBTA), and the positive tolerability profile of these agents. Keep in mind that the CGRP antagonists reviewed are indicated for EM and CM, and OBTA is indicated for CM. Furthermore, the DUR Board plans to review the CGRP antagonists in December for the development of potential prior authorization criteria. Prior authorization criteria are currently in place for [botulinum toxins](#).

## Introduction

Migraine headache is a common neurological condition impacting about 18% of women and 7% of men and varies among patients with respect to frequency, intensity, duration, and the extent of disability experienced.<sup>1,2</sup> Migraine pharmacotherapy includes acute (ie, abortive therapy) and preventative medications. Preventative treatment is generally offered to patients when migraine attacks have “...substantial impact on their lives and have not responded to acute care, or where the frequency of migraine attacks is such that the reliance on acute care medications would increase the potential for drug-induced (rebound) headache.”<sup>1</sup> In 2000, the American Academy of Neurology (AAN) summarized that the goals of migraine-related pharmacotherapy are to reduce migraine frequency, severity, disability, and reliance on inadequate acute pharmacotherapies; improve quality of life; and avoid medication-overuse headache.<sup>1</sup>

This report will discuss the head-to-head comparative evidence available for the FDA-approved products indicated for migraine prophylaxis, listed in **Table 1**. The anticonvulsants (divalproex and topiramate) and the beta-blockers (timolol and propranolol) are oral options, administered daily. The newly approved monoclonal antibodies for migraine prophylaxis are administered less frequently, by subcutaneous injection: erenumab and galcanezumab with once monthly dosing, and fremanezumab with monthly or quarterly administration intervals. The neuromuscular blocking agent, onabotulinumtoxinA (OBTA) has been approved for chronic migraine (not for episodic migraine) since 2010, and is administered intramuscularly every 12 weeks.

The efficacy of the monoclonal antibodies was demonstrated for both episodic migraine (EM) and chronic migraine (CM) prophylaxis. The oral agents (divalproex, topiramate, propranolol and timolol) were FDA-approved for migraine prophylaxis prior to the diagnostic distinction between chronic and episodic migraine (a classification introduced in 2004 by the International Headache Society); approvals were based on data from study populations primarily with episodic migraine.<sup>7</sup> OBTA is approved for the subpopulation with chronic migraine (headaches  $\geq 15$  days/month with headache lasting  $\geq 4$  hours/day), accounting for approximately 8% of the migraine population,<sup>3</sup> and is administered intramuscularly, across head and neck muscle areas, once every 12 weeks.

The Utah Medicaid Preferred Drug List (PDL) classifies divalproex, topiramate, timolol, propranolol as preferred agents under the anticonvulsant or the beta adrenergic-blocking agent sections, respectively. OBTA (Botox) and the 3 monoclonal antibody, calcitonin-gene related peptide (CGRP)-pathway antagonists are not listed on the PDL. There are prior-authorization criteria in place for [botulinum toxins](#) and the Medicaid DUR Board plans to review the monoclonal antibodies for migraine prophylaxis in December. Off-label options (ie, products without FDA approval for migraine prophylaxis) that are represented in the 2012 AAN/AHS guideline as “probably effective” or “possibly effective”<sup>26</sup> and that are listed as preferred drugs in various sections among the Medicaid PDL include amitriptyline, atenolol, carbamazepine, cyproheptadine, lisinopril, valproic acid, metoprolol, nadolol, pindolol, and venlafaxine; alpha agonists, clonidine and guanfacine, are open access.

Table 1. FDA-Approved Agents for Migraine Prophylaxis<sup>15-17,22,23,27-36</sup>

Generic Name	Brand Name Formulations <sup>a</sup>	FDA Indication Dosage
<b>Anticonvulsants</b>		
<p style="text-align: center;"><b>Divalproex sodium</b></p>	<p><b>Depakote DR</b> Oral Tablet, Delayed Release: 125 mg, 250 mg, 500 mg; <a href="#">generics available</a></p>	<p><b>Migraine prophylaxis in adults</b></p> <ul style="list-style-type: none"> <li>• Depakote ER: Initial: 500 mg daily for 1 week, then increase to 1000 mg daily (effective dosage range 500 mg – 1000 mg daily)</li> <li>• Depakote DR: Initiate at 250 mg twice daily; may titrate dose up to a maximum of 1000 mg/day</li> </ul> <p>Other indications: manic bipolar I disorder, epilepsy (absence and complex partial seizure)</p>
	<p><b>Depakote ER</b> Oral Tablet, Extended Release: 250 mg, 500 mg; <a href="#">generics available</a></p>	
<p style="text-align: center;"><b>Topiramate</b></p>	<p><b>Topamax</b> Oral Tablet: 25 mg, 50 mg, 100 mg, 200 mg <a href="#">generics available</a></p>	<p><b>Migraine prophylaxis in adults and <u>adolescents 12 years and older</u></b></p> <ul style="list-style-type: none"> <li>• Topamax: Initiate at 25 mg in the evening and titrate up according to labeling to the recommended maintenance dose of 50 mg twice daily</li> <li>• Trokendi XR, Qudexy XR and generic topiramate ER: Initiate at 25 mg daily for 1 week and then increase the daily dose by 25 mg each week until reaching the recommended total daily dose of 100 mg per day.</li> </ul> <p>The dose titration rate should be guided by clinical outcome; long-titration intervals may be needed.</p> <p>Other indications: epilepsy (Lennox-Gastaut syndrome, adjunct; partial seizure initial monotherapy; tonic-clonic seizure, primary generalized initial or adjunct therapy)</p>
	<p><b>Topamax Sprinkles</b> Oral Capsule: 15 mg, 25 mg <a href="#">generics available</a></p>	
	<p><b>Trokendi XR</b> Oral Capsule, Extended-Release: 25 mg, 50 mg, 100 mg, 200 mg <a href="#">generics available, except for the 200mg strength</a></p>	
	<p><b>Qudexy XR</b> Oral Capsule, Extended Release (sprinkle): 25 mg, 50 mg, 100 mg 150 mg, 200 mg</p>	
<b>Beta-blockers</b>		
<p style="text-align: center;"><b>Propranolol</b></p>	<p><b>Inderal LA</b> Oral capsule, ER: 60 mg, 80 mg, 120 mg, 160 mg <a href="#">generics available</a></p>	<p><b>Migraine prophylaxis</b> (safety and effectiveness has not been established in pediatric patients)</p> <ul style="list-style-type: none"> <li>• Initiate at 80 mg (taken once daily for Inderal LA, and as divided doses for propranolol tablets and solution). The maintenance dose range is 160-240 mg daily.</li> </ul> <p>If a satisfactory response is not noted at 4-6 weeks at maximum dosage, discontinue propranolol.</p> <p>Other indications: hypertension, chronic angina pectoris, atrial fibrillation, post-myocardial infarction, essential tremor, capillary hemangioma, cardiac dysrhythmia, idiopathic hypertrophic subaortic stenosis, pheochromoxytoma adjunct</p>
	<p><i>Generic only</i> Oral tablet: 10 mg, 20 mg, 40 mg, 60 mg, 80 mg</p>	
	<p>Oral solution (strawberry-mint flavor): 20 mg/5mL, 40 mg/5mg</p>	

<b>Timolol maleate</b>	<i>Generic only</i> Oral tablet: 5 mg, 10 mg, 20 mg	<b>Migraine prophylaxis</b> (safety and effectiveness has not been established in pediatric patients) Initiate at 10 mg twice daily. Maintenance dosage range 10 mg once daily to 30 mg in divided doses. If a satisfactory response is not noted at 6-8 weeks at maximum dosage, discontinue timolol.  Other indications (oral): hypertension, post-myocardial infarction
<b>Monoclonal Antibodies</b>		
<b>Erenumab-aooe</b>	<b>Aimovig</b> Injection: 70 mg/mL in a single-dose prefilled SureClick autoinjector  Injection: 70 mg/mL in a single-dose prefilled syringe	<b>Migraine prophylaxis in adults</b> (episodic or chronic migraine) Initiate as 70 mg injected subcutaneously <u>once monthly</u> . Some patients benefit from a dose of 140 mg administered as two consecutive subcutaneous injections of 70 mg each.
<b>Fremanezumab-vfrm</b>	<b>Ajovy</b> Injection: 225 mg/1.5 mL in a single-dose prefilled syringe	<b>Migraine prophylaxis in adults</b> (episodic or chronic migraine) Two subcutaneous dosing options: 225 mg <u>monthly</u> or 675 mg <u>every 3 months</u>
<b>Galcanezumab-gnlm</b>	<b>Emgality</b> Injection: 120 mg/mL in a single-dose prefilled pen  Injection: 120 mg/mL in a single-dose prefilled syringe	<b>Migraine prophylaxis in adults</b> (episodic or chronic migraine) Initiate as 240 mg subcutaneous loading dose (administered as 2 consecutive injections of 120 mg each), followed by <u>once monthly</u> doses of 120 mg
<b>Type A Botulinum Toxin</b>		
<b>OnabotulinumtoxinA</b>	<b>Botox</b> Injection solution: 100 units, 200 units	<b>Chronic migraine prophylaxis in adults</b> (for headaches $\geq 15$ days/month with and lasting $\geq 4$ hours/day) <ul style="list-style-type: none"> <li>Recommended total dose is 155 units <u>once every 12 weeks</u>, administered intramuscularly, divided across 7 different sites of head/neck muscles. Each 155 unit dose must be divided and administered bilaterally, into 31 total sites as described in the package insert</li> </ul> Other indications: axillary hyperhidrosis, cervical dystonia, upper/lower limb spasticity, overactive bladder, urinary incontinence, strabismus and blepharospasm

Abbreviations: DR, delayed release; ER, extended release; FDA, Food and Drug Administration

<sup>a</sup> Notes pertaining to other formulations: (1) Depakote Sprinkles DR Capsule and its generics are not approved for migraine prophylaxis, (2) The delayed release valproic acid capsule (Stavzor) was approved for migraine prophylaxis but the manufacturer discontinued production in 2013, (3) Inderal XL, Innopran XL, and Hemangeol are not approved for migraine prophylaxis



## Methods

### *Systematic Literature Search*

Search strategies were developed for Ovid-Medline and Embase. The complete search strategies and terms are available in **Appendix A**. Strategies consisted of controlled vocabularies, such as Medical Subject Headings (MeSH), and keyword phrases. Results were limited to English language and de-duplicated in Covidence. In Embase, we excluded conference abstracts.

Methodological filters were used for systematic reviews (SRs): the University of McMaster's review filter for maximized specificity<sup>37</sup> in Ovid-Medline syntax, and an independently-derived filter for Embase. Databases were searched through July 2018 for SRs and through August 2018 for randomized controlled trials (RCTs) (see precise dates in Appendix A). The Cochrane filter for identifying RCTs in Ovid-Medline was used (sensitivity- and precision-maximizing version [2008 revision], Ovid format).<sup>38</sup> Upon identifying several systematic reviews for inclusion, literature searches for RCTs were developed to capture evidence for unaccounted dates among the included SRs. Date limits for RCT searches were based on the following SR search dates:

- OBTA comparisons were addressed in the Cochrane review by Herd et al 2018.<sup>13</sup> Authors searched up to December 7, 2017. RCT information for OBTA was queried from 2017 onward for our review.
- Anticonvulsant comparisons were addressed by Jackson et al 2015,<sup>39</sup> and by Barnes et al 2015.<sup>8</sup> Literature databases were searched in 2014 for these 2 SRs. RCTs regarding anticonvulsants versus active-comparators were searched from 2014 onward, for our review.
- The SRs by He et al 2017,<sup>12</sup> Jackson et al 2015,<sup>39</sup> and Mulleners et al 2015,<sup>9</sup> all considered available RCTs regarding the beta-blockers for migraine prophylaxis. RCTs were searched from 2014 onward for our review.
- All dates were searched for RCT evidence regarding the monoclonal antibodies.

We also screened the reference lists and other relevant websites for further information:

- I. For treatment guidelines addressing migraine prevention: websites of American Academy of Neurology (AAN), and the National Institute for Health and Care Excellence (<https://www.nice.org.uk/>)
- II. For prescribing information product labeling: The Food and Drug Administration website Drugs@FDA and [dailymed.nlm.nih.gov](http://dailymed.nlm.nih.gov)
- III. Drug information databases, Micromedex and Lexicomp

### *Screening*

Two reviewers independently screened publication titles and abstracts. Conflicts were resolved by consensus between reviewers. The full text for all citations receiving 2

inclusion votes were retrieved. The lead author made the final determination for inclusion upon full-text review. **Figure 1** on page 23 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

#### *Inclusion and Exclusion Criteria*

Considered for inclusion was data from SRs and RCTs that provided head-to-head efficacy or safety comparisons between the FDA-approved medications for migraine prophylaxis listed in Table 1. Direct pair-wise meta-analysis data was included, while mixed- or indirect-comparative data (ie, network meta-analyses) was excluded. During the full-text screening stage, SRs published earlier than 2013 were excluded because they represented information that was included in more recent evidence syntheses. A list containing excluded references is provided in **Appendix B**.

## Disease Overview

Migraine is a common primary headache disorder. Data from a 2012 national survey found that about 14% of US adults experienced migraine or severe headache in the 3-month recall period.<sup>4</sup> Migraine occurs more often in women (11% to 16%) compared to males (5% to 8%) and most patients rate their pain level as severe.<sup>5</sup> In the pediatric population, prevalence increases with increasing age.<sup>40</sup> Between 8% and 23% of adolescents ages 15 years or older experience migraine.<sup>40</sup> Migraine symptoms can reduce quality of life and negatively affect school, work, or social engagement and productivity.<sup>2,5</sup> Approximately 20% of patients with episodic migraine suffer from moderate to severe headache-related disability.<sup>3</sup> Of the subpopulation experiencing high-frequency migraines (ie, chronic migraine), approximately 50% have moderate to severe disability.<sup>3</sup>

Migraines can be classified according to symptoms (migraine with or without aura) and frequency (episodic or chronic migraine). The diagnosis and classification of migraine has been delineated in the International Classification of Headache Disorders-3 (ICHD-3), developed by the International Headache Society.<sup>6</sup> Migraine without aura usually presents unilaterally and is often depicted as a pulsating moderate to severe pain that can be aggravated by physical exertion. Patients may experience nausea and become sensitive to light and noise. Migraine without aura can last 4 to 72 hours (2 to 72 hours in children). Migraine with aura is characterized by reversible neurological symptoms of the brainstem that usually precede the migraine, but may also occur during the episode. Aura symptoms include any of the following: dysarthria, vertigo, tinnitus, impaired hearing, diplopia, or ataxia. Hemiplegic type aura involves motor weakness, and other reversible visual, sensory or speech dysfunction presentations. Patients who experience headache occurring  $\geq 15$  days per month for at least 3 months and with at least 8 days/month involving features of migraine headache are classified as having chronic migraine.<sup>6</sup>

### I. Prophylactic Pharmacotherapy for Migraine

Many drugs in various pharmacological classes (eg, antihypertensives, antiepileptics, antidepressants, beta-blockers, calcium channel blockers, etc.) have been studied for prophylactic treatment of migraine. A portion of them has formal FDA approval for this indication; however, some off-label medications have supportive evidence for their use. The most recent (2012) American Academy of Neurology and the American Headache Society (AAN/AHS) guideline for long-term prevention of episodic migraine in adults classifies therapies based on the level of evidence supporting their use.<sup>26</sup> Medications with established efficacy supported by the highest-quality evidence include divalproex, sodium valproate, topiramate, metoprolol, timolol, and propranolol. Agents that are probably effective include amitriptyline, venlafaxine, atenolol, and nadolol. Medications that are possibly effective, with less certainty than the previous groups, include lisinopril, candesartan, clonidine, guanfacine, carbamazepine, nebivolol, pindolol, and cyproheptadine. Authors highlight that treatment selection depends on patient comorbidities and tolerability, as many of these medications have other pharmacological effects and indications.<sup>26</sup>

The 2015 guideline by the National Institute for Health and Care Excellence (NICE) recommends topiramate, propranolol, or amitriptyline for the prevention of migraine, without specifying a particular preference for one over another.<sup>41</sup> Divalproex and timolol are not mentioned among the guideline.

Regarding chronic migraine, guidelines have not been developed specifically for this indication. Thus, neurologist experts (Amaal Starling, MD, and David Dodick, MD) of the Mayo Clinic developed an evidence-based “best-practices” guide.<sup>10</sup> In addition, the AAN published a guideline in 2016 focusing on appropriate uses of botulinum toxins.<sup>11</sup> In the best-practice guide (2015), authors explain that besides OBTA, topiramate was the only other agent shown to be efficacious in randomized, placebo-controlled trials of patients with chronic migraine.<sup>10,42,43</sup> The 2016 AAN guideline for the use of OBTA recommends that OBTA should be offered to patients with CM to reduce the number of headache days and improve health-related quality of life. Furthermore, authors concluded that there is insufficient evidence comparing OBTA to topiramate for chronic migraine.<sup>11</sup>

#### I.a Treatment of Pediatric Patients

The National Institute for Health and Care Excellence (NICE) provides a guideline for migraine prophylaxis in pediatric patients over 12 years old, last updated in 2015. The committee recommends offering topiramate, propranolol, or amitriptyline based on the patient’s preference, comorbidities and the risk of adverse events.

The AAN last published a guideline for migraine management in the pediatric population (for ages 3 to 18 years) in 2004, which is currently being updated. In the 2004 guideline, authors found insufficient evidence to support or refute the use of amitriptyline, divalproex sodium, topiramate, or levetiracetam for migraine prophylaxis. Evidence at that time was conflicting for preventative therapy with propranolol or trazodone, so no recommendations were offered regarding these medications.

Table 2 provides a summary of the recommended therapies in treatment guidelines for migraine prophylaxis. All were published prior to the approval of the CGRP antagonist monoclonal antibodies. Please refer to the publication for additional guidance regarding use of other off-label medications.

Table 2. Guidelines for Migraine Prophylaxis

Professional Organization ❖ Guideline Title	Statements
<p><b>American Academy of Neurology and the American Headache Society</b></p> <p>❖ Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults<sup>26</sup> (2012)</p>	<p style="text-align: center;"><b>Guideline Background</b></p> <p>A literature search in MEDLINE, PsycINFO, and CINAHL from 1999 to May 2007 to identify RCTs to determine the following:</p> <ul style="list-style-type: none"> <li>• Define pharmacologic therapies that are proven effective for migraine prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?</li> <li>• Define the safety profile of these pharmacological treatment options</li> </ul> <p>The literature search was updated through May 2009 in MELINE only.</p> <p style="text-align: center;"><b>Recommendations</b></p> <p>Medications with <b>Level A evidence</b> (established as effective; with ≥2 Class I trials) and that should be offered for migraine prevention: divalproex sodium, sodium valproate, topiramate metoprolol, propranolol, timolol</p> <ul style="list-style-type: none"> <li>- For short-term menstrual migraine prevention: frovatriptan</li> </ul> <p>Medications with <b>Level B evidence</b> (probably effective; 1 Class I or 2 Class II studies) and that should be considered for migraine prevention: amitriptyline, venlafaxine, atenolol, nadolol</p> <ul style="list-style-type: none"> <li>- For short-term menstrual migraine prevention: naratriptan and zolmitriptan</li> </ul> <p>Medications with <b>Level C evidence</b> (possibly effective; 1 Class II study) and may be considered for migraine prevention: lisinopril, candesartan, clonidine, guanfacine, carbamazepine, nebivolol, pindolol, and cyproheptadine</p> <p>See the full guideline for other groupings of agents classified as having inadequate or conflicting data, and medications that are possibly/probably ineffective</p>
<p><b>National Institute for Health and Care Excellence</b></p> <p>❖ Headaches in over 12s: diagnosis and management; CG150<sup>41</sup> (2012, updated in 2015)</p>	<p style="text-align: center;"><b>Migraine (with or without aura) Prophylactic Therapy</b></p> <ul style="list-style-type: none"> <li>- The following medications should be offered and the decision should be based on the patient’s preference, comorbidities and risk of adverse events:             <ul style="list-style-type: none"> <li>• Topiramate (warn about the risk of fetal malformations and reduction of the effectiveness of hormonal contraceptives with this medication)</li> <li>• Propranolol</li> <li>• Amitriptyline</li> </ul> </li> <li>- If patients are already on another form of prophylaxis that is effective for them, continue the current treatment</li> <li>- Do not offer gabapentin for the prophylactic treatment of migraine</li> <li>- If both topiramate and propranolol are inappropriate, consider acupuncture</li> <li>- Re-assess the need for prophylactic therapy 6 months after initiation</li> </ul>

Table 2. Guidelines for Migraine Prophylaxis

Professional Organization ❖ Guideline Title	Statements
<p><b>Canadian Health Society Guideline for Migraine Prophylaxis</b></p> <p>❖ Canadian Headache Society Guideline for Migraine Prophylaxis<sup>44</sup> (2012)</p>	<p>This guideline applies to patients with episodic migraine (headache on no more than 14 days a month) who suffer from a significant degree of disability from these attacks and for whom abortive medications do not provide sufficient relief to minimize migraine-related disability or who are at high risk of medication overuse headache or intolerable side-effects due to use of acute treatments.</p> <p>Prophylactic options with <u>high-quality evidence showing benefit</u>:</p> <ul style="list-style-type: none"> <li>• Beta-blockers: Propranolol (target dose 80 to 160 mg/d), and metoprolol (target dose 100 to 200 mg/d); both with “strong recommendation”</li> <li>• Topiramate (target dose of 100 mg/d): authors assign a “strong recommendation” for use of this drug, since its risk benefit profile is positive</li> <li>• Amitriptyline (10 to 100 mg/d); “strong recommendation”</li> <li>• Divalproex (500 to 1500 mg/d); authors assign a “weak recommendation” to this drug due to the risk benefit profile of divalproex. Some adverse effects include weight gain and may cause reversible tremor and hair loss, and teratogenicity</li> </ul> <p>Prophylactic options with <u>moderate-quality evidence showing benefit</u>:</p> <ul style="list-style-type: none"> <li>○ Gabapentin (at least 1,200 mg/d) : “strong recommendation”</li> <li>○ Nadolol (80 to 160 mg/d): “strong recommendation”</li> <li>○ Candesartan (16 mg/d): “strong recommendation”</li> </ul> <p>Prophylactic options with <u>low-quality evidence showing benefit</u>: venlafaxine, verapamil, lisinopril</p>
<p><b>American Academy of Neurology</b></p> <p>❖ Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents (2004)<sup>40</sup></p>	<p style="text-align: center;"><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>- “There is insufficient evidence to make any recommendations concerning the use amitriptyline, divalproex sodium, topiramate, or levetiracetam...”</li> <li>- Recommendations were not made concerning propranolol or trazodone for preventive therapy as the evidence is conflicting.</li> <li>- Pizotifen and nimodipine and clonidine lack have supportive evidence for efficacy and are not recommended.</li> </ul>

Table 2. Guidelines for Migraine Prophylaxis

Professional Organization ❖ Guideline Title	Statements
<b>Guidance for the Use of OnabotulinumtoxinA</b>	
<b>American Academy of Neurology</b>  ❖ Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache <sup>11</sup> (2016)	OBTA is effective and safe for the reduction of headache days and probably effective for improving quality of life for patients with chronic migraine. Authors state that there is insufficient evidence comparing OBTA to topiramate for chronic migraine.
<b>National Institute for Health and Care Excellence</b>  • Botulinum toxin type A for the prevention of headaches in adults with chronic migraine; Technology appraisal guidance [TA260] <sup>45</sup> (2012, updated 2015)	OnabotulinumtoxinA is a recommended option for the treatment of chronic migraine that has not responded to at least three prior pharmacological prophylactic therapies (only if the patient is appropriately managed for medication overuse) - Chronic migraine is defined as having headaches on at least 15 days per month of which at least 8 days are with migraine Treatment with OBTA should be stopped if there is not at least a 30% reduction in headache days per month after two treatment cycles, or if the patient’s symptoms have not changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months. Nonetheless, patients should have the option to continue treatment until they and their clinician consider it appropriate to stop if the circumstance falls outside of these recommendations.

Abbreviations: OBTA, onabotulinumtoxinA, RCT, randomized controlled trial

## Pharmacology and Special Populations

Migraine pathogenesis involves a dysfunction in the monoaminergic sensory systems of the brain and hypothalamus.<sup>46</sup> The approved agents for migraine prophylaxis have the ability to stabilize neuronal signals through mechanisms that aren't entirely clear. The newly approved monoclonal antibodies (mAb) have been developed specifically for the pathway involving calcitonin gene-related peptide (CGRP) that is implicated as part of migraine pathogenesis.<sup>7,15</sup> Erenumab binds to the CGRP receptor and antagonizes CGRP effects.<sup>7</sup> Fremanezumab and galcanezumab, bind to CGRP ligand, antagonizing its action at the CGRP receptor.<sup>15,17</sup> Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract and is thought to primarily work by increasing gamma-aminobutyric acid (GABA) in the brain.<sup>22</sup> Topiramate blocks voltage-gated sodium channels, inhibits glutamate-mediated neurotransmission, and enhances the effect of endogenous GABA.<sup>36</sup>

Pharmacokinetic parameters for the approved migraine-prophylactic agents are found in **Table 3**. The monoclonal antibodies and OBTA have a duration of action that allows for monthly to quarterly dosing frequencies; whereas, the oral agents must be taken daily. Divalproex is highly metabolized in the liver and should be avoided in patients with significant liver impairment. Patients with liver impairment should be monitored more closely while receiving topiramate or the beta-blockers since plasma drug concentrations may increase; however, there are no hepatic dose adjustments outlined in the labeling for these products. Renal dose adjustments are recommended in the labeling only for topiramate. No renal or hepatic dosage adjustments are necessary for the monoclonal antibodies or for OBTA. Further information regarding the use of these agents in special populations is summarized in **Table 4**.

Table 3. Pharmacokinetics of Migraine Prophylactic Agents

Generic Name	Metabolism	Excretion	Half-life
<b>Divalproex</b> <sup>22,27</sup>	Extensive via hepatic glucuronide conjugation (30-50% of dose) and mitochondrial beta-oxidation (40% of dose)	Renal: 30-50% of dose as glucuronide conjugate	9-16 hours (per package inserts for both Depakote ER and Depakote DR which apply for age 10 years and over)
<b>Erenumab-aooe</b> <sup>16</sup>	Not metabolized by CYP-P450 enzymes	Eliminated through saturable binding with the calcitonin gene-related peptide (CGRP) receptor and via non-specific, non-saturable proteolytic pathways	28 days
<b>Fremanezumab-vfrm</b> <sup>15</sup>	Not metabolized by CYP-P450 enzymes	Eliminated through proteolysis	31 days
<b>Galcanezumab-gnlm</b> <sup>17</sup>	Not metabolized by CYP-P450 enzymes	Eliminated through proteolysis	27 days
<b>Onabotulinum-toxinA</b> <sup>33</sup>	Not detected in the peripheral blood following intramuscular injection at the recommended doses		



Table 3. Pharmacokinetics of Migraine Prophylactic Agents

Generic Name	Metabolism	Excretion	Half-life
<b>Propranolol</b> <sup>28-30</sup>	Extensive hepatic metabolism via CYP2D6, CYP1A2, CYP2C19, and P-glycoprotein	Primarily excreted renally as metabolites	Oral IR tablet and solution: 3-6 hours (adults) Oral ER: 8-20 hours
<b>Timolol</b> <sup>31</sup>	Hepatic, via CYP2D6 metabolism; 50% via first pass	Renally, as timolol and metabolites	4 hours
<b>Topiramate</b> <sup>23,34-36</sup>	Not extensively metabolized No active metabolites	Renally excreted, 70% as unchanged drug	Oral, IR: 21 hours Oral, ER: 31 hours Trokendi XR: 31 hours Qudexy XR: 56 hours

Abbreviations: CYP, cytochrome P450 enzyme; ER, extended release; IR, immediate release

Table 4. Special Population Considerations

Generic Name	Pregnancy and Nursing	Pediatrics	Hepatic and Renal Impairment
<b>Divalproex</b> <sup>22,27</sup>	Pregnancy category X: Contraindicated in pregnancy for the treatment of migraines due to the risk of neural tube defects, other major malformations, and decreased IQ  Valproate is excreted into human milk; use with caution	Indicated down to 10 years old for epilepsy; however, the package insert states that efficacy was not established for the pediatric population for migraine indication  Children under the age of two years are at considerably higher risk of fatal hepatotoxicity	Contraindicated with hepatic disease or significant hepatic dysfunction  The free fraction of drug can increase in patients with hepatic and renal disease; use with caution in the elderly
<b>Erenumab-aooe</b> <sup>16</sup>	No data in pregnant women/offspring, but animal-model data is positive as no adverse effects in offspring were observed	Safety and effectiveness in the pediatric population have not been established	Renal or hepatic impairment is not expected to affect the pharmacokinetics
<b>Fremanezumab-vfrm</b> <sup>15</sup>	No data on lactation excretion		
<b>Galcanezumab-gnlm</b> <sup>17</sup>	No data on lactation excretion		
<b>Onabotulinum-toxinA</b> <sup>33</sup>	May cause fetal harm based on animal studies; there are no adequate studies in pregnant women  No data on lactation excretion	Safety and efficacy not established for under <18 years old for chronic migraine. The product is indicated down to 12 years old for other indications, namely blepharospasm and strabismus	Drug is not detected in the peripheral blood following intramuscular injection at the recommended doses

Table 4. Special Population Considerations

Generic Name	Pregnancy and Nursing	Pediatrics	Hepatic and Renal Impairment
<b>Propranolol</b> <sup>28</sup>	Pregnancy category C, based on embryotoxicity and neonatal toxicity in animal models; there are no adequate studies in pregnant women but adverse-effects (eg, bradycardia, hypoglycemia, and respiratory depression) have been reported in neonates of mothers in parturition receiving beta-blockers		Use with caution in patients with hepatic or renal impairment since these disease states increase the plasma concentration of propranolol. Consider dose adjustments (specific adjustments are not detailed in product labeling)
<b>Timolol</b> <sup>31</sup>	Some excretion into human milk occurs; use with caution	Safety and effectiveness in pediatric patients have not been established	
<b>Topiramate</b> <sup>23,34-36</sup>	Can cause fetal harm (eg, cleft lip/palate and small birth weight) Topiramate is excreted into human breast milk; the developmental effects on the child are unknown	Safety and effectiveness in pediatric patients below the age of 12 years have not been established for the prophylactic treatment of migraine headache Indicated for seizures in patients at least 6 years old	For creatinine clearance less than 70 mL/min/1.73m <sup>2</sup> , use half of the usual dose Use caution with hepatic impairment and avoid use with alcohol (stop alcohol 6 days prior to starting topiramate)

Abbreviations: ER, extended release; IR, immediate release

## Efficacy of Migraine Prophylactic Agents in Pivotal Clinical Trials

This section provides information from placebo-controlled trials and summaries from FDA advisors who reviewed these trials. It is important to keep in mind that it is unscientific to make direct comparisons of outcomes across placebo-controlled trials because there are key differences in patient populations, trial designs, and outcomes that are not accounted for. Nonetheless, we are providing this information at Medicaid's request. Please see the next section as well (*Direct Comparative Evidence*), which summarizes treatment-effect differences between migraine prophylactic agents based on head-to-head studies of active arms.

When examining efficacy comparisons from placebo-controlled trials, it is important to consider the *difference in effect* between the active and placebo arms because there is usually a strong placebo effect in migraine-prophylaxis studies.<sup>47-49</sup>

### I. Episodic Migraine

The oral agents (divalproex, topiramate, propranolol and timolol) were FDA-approved for migraine prophylaxis prior to the diagnostic distinction between chronic and episodic migraine; approvals were based on data from study populations primarily with episodic migraine.<sup>7</sup> Information on reduced monthly migraine days (MMDs) is reported for some of the agents in the product labeling; for other agents, reduced MMDs is not reported, likely because MMD is a more recent endpoint of interest in the disease state. Standards for drug labeling, study design, and endpoint definitions for migraine prophylaxis drug trials have changed considerably since the early development of the oral agents.<sup>7,47,49-51</sup>

- The anticonvulsants, topiramate and divalproex, reduced MMDs by about 1 to 2 more days compared placebo in pivotal clinical trials; changes from baseline for the anticonvulsants were between 1 and 3 MMDs.<sup>23,34,50</sup>
- The labeling for propranolol products simply reports that propranolol significantly reduced the severity of headache compared to placebo.<sup>28-30</sup> A reduction of MMDs endpoint was not reported.
- The efficacy of timolol for migraine is not described thoroughly in the labeling. Only the following information is provided: "Approximately 50 percent of patients who received timolol had a reduction in the frequency of migraine headache of at least 50 percent, compared to a similar decrease in frequency in 30 percent of patients receiving placebo."<sup>31</sup>
- In pivotal clinical trials leading to the approval of the CGRP antagonists, treatment generally led to about 1 to 2 fewer mean monthly migraine days (mMMD) compared to placebo, for patients with EM.<sup>15-17</sup> Changes from baseline ranged from about 3 to 5 mMMD for the CGRP antagonists.

### II. Chronic Migraine

- Regarding the pivotal placebo-controlled studies for OBTA (Botox), with a treatment period of 6 months, OBTA treatment led to about 2 fewer monthly migraine/possible migraine days compared to placebo.<sup>52</sup>

- Topiramate has been studied in a randomized, placebo-controlled trial in patients with chronic migraine. Compared to placebo, topiramate-treated patients experienced about 2 fewer monthly migraine/migrainous days, with 4 months of treatment.<sup>15,43</sup>
- In pivotal trials of the CGRP antagonists, compared to placebo, active treatment generally led to about 2 to 3 fewer MMD for patients with CM, over a treatment period of 3 months.<sup>15-17</sup> Changes from baseline ranged from about 5 to 7 mMMD for the CGRP antagonists.

### III. Additional Efficacy Information for CGRP Antagonists

#### III.a. Episodic Migraine

##### ERENUMAB

In the two pivotal clinical trials of patients with EM, treatment with erenumab led to about 1 to 2 fewer mMMD compared to placebo. Treatment arms improved by about 3 to 4 mMMD from baseline, while placebo arms improved by about 2 mMMD from baseline.<sup>16,53,54</sup> Forty to 50% of patients receiving erenumab experienced at least a 50% reduction in mMMD (10% to 23% difference from placebo). One study involved a treatment duration of 6 months and the other was 3 months.<sup>16</sup> Treatment and placebo groups had a baseline rate of about 8 MMD and a subset of patients was allowed to use up to one prophylactic migraine medication concomitantly.<sup>16,53,54</sup> The FDA summary review for erenumab notes that “[t]he treatment effect size (the difference between erenumab and placebo; approximately 2 fewer migraine headache days/month) was similar to that observed with drugs already approved for episodic migraine [oral agents].”<sup>7</sup>

##### FREMANEZUMAB

In the pivotal clinical trial of patients with EM, treatment with fremanezumab led to about 1 to 2 fewer mMMD compared to placebo. Treatment arms improved by about 3 to 4 mMMD from baseline, while the placebo arm improved by about 2 mMMD from baseline. Forty five to 48% of patients receiving fremanezumab experienced at least a 50% reduction in mMMD (17% to 20% difference from placebo), over a 3 month treatment period.<sup>15,55</sup> Treatment and placebo groups had a baseline rate of about 9 MMD and a subset of patients was allowed to use up to one prophylactic migraine medication concomitantly. The FDA summary review for fremanezumab notes “[t]he treatment effect size (the difference between fremanezumab and placebo; approximately 2 fewer migraine headache days/month) was similar to that observed with drugs already approved for episodic migraine [oral agents and erenumab].”<sup>50</sup>

##### GALCANEZUMAB

In the two pivotal trials of patients with EM, treatment with galcanezumab led to about 2 fewer mMMD, compared to placebo. Treatment arms improved by about 4 to 5 mMMD from baseline, while the placebo arms improved by about 2 to 3 mMMD from baseline. Sixty to 62% of patients experienced at least a 50% reduction in mMMD (23% difference from placebo), over a 6 month treatment period.<sup>17</sup> Study arms had a baseline rate of about

9 MMD and studies *excluded* patients on other migraine prophylactic therapies.<sup>17</sup> The FDA summary review notes that the effect size of galcanezumab, with respect to the difference in mMMD reduction compared to placebo, appears similar to other drugs already approved for episodic migraine prophylaxis (eg, the oral agents, erenumab, and fremanezumab).<sup>56</sup>

Additional responder secondary endpoints were evaluated including the proportion of patients with at least a 75% or 100% reduction in mMMD: 34% to 39% of patients experienced a 75% mMMD reduction from baseline (16% to 20% difference from placebo), and 12% to 16% of patients experienced a 100% mMMD reduction from baseline (6% to 10% difference from placebo).

### III.b. Chronic Migraine

#### ERENUMAB

In the pivotal clinical trial of patients with CM, compared to placebo, treatment with erenumab led to about 2.5 fewer mMMD, and about 16% to 17% more patients experienced at least a 50% reduction in mMMD over a 3 month treatment period.<sup>16</sup> Treatment arms improved by about 7 mMMD from baseline, while the placebo arm improved by about 4 mMMD from baseline. The baseline MMD was about 18 for all study arms.<sup>16,57</sup> FDA summary reviews described the treatment effect of erenumab to be similar to that of onabotulinumtoxinA and fremanezumab.<sup>7,50</sup>

#### FREMANEZUMAB

In the pivotal clinical trial of patients with CM, compared to placebo, treatment with fremanezumab led to about 2 fewer mMMD over a 3 month treatment period.<sup>15</sup> The treatment arms improved by about 5 mMMD from baseline, while the placebo arm improved by about 3 mMMD from baseline. The baseline mMMD was about 16 for the study arms.<sup>58</sup> Between 20% and 23% more patients experienced at least a 50% reduction in monthly average number of headache days (aMHD) of at least moderate intensity compared to placebo. The FDA summary review described the treatment effect of fremanezumab to be similar to the two previously approved drugs for CM, erenumab and onabotulinumtoxinA.

#### GALCANEZUMAB

In the pivotal clinical trial of patients with CM, compared to placebo, treatment with galcanezumab led to about 2 fewer mMMD, and approximately 13% more patients experienced at least a 50% reduction in mMMD over a 3 month treatment period.<sup>17</sup> The treatment arm improved by about 5 mMMD from baseline, while the placebo arm improved by about 3 mMMD from baseline. The baseline mMMD was about 19 for the study arms.<sup>17</sup> The FDA summary review notes that the effect size of galcanezumab, with respect to the difference in MMD reduction compared to placebo, appears similar to other drugs already approved for chronic migraine prophylaxis (OBTA, erenumab, and fremanezumab).<sup>56</sup>

## Direct Comparative Evidence

*Section format*—The first subsection (*I. Summary Points*) condenses the comparative evidence findings. The following section (*II. Systematic Review Evidence for the Prophylaxis of Migraine*) and Table 1 of Appendix C describe the included SRs and relevant RCTs in greater detail. Drug comparisons are ordered alphabetically and according to the study population for which they apply. In the second subsection, drugs are abbreviated by the first three letters of their generic name. Numerical values follow the drug abbreviation to indicate the daily dosages compared (e.g. PRO 80 versus TOP 100 means propranolol 80 mg/day versus topiramate 100 mg/day).

### I. Summary Points

#### I.a Pediatric Population

For migraine prophylaxis in pediatric patients, it is unknown whether topiramate or propranolol is more effective because evidence is limited and conflicting.<sup>8,9</sup> No other head-to-head comparisons have been evaluated in randomized studies for this population.

#### II.b Adult Population

##### Divalproex Comparisons

Head-to-head comparisons involving divalproex include propranolol or OBTA comparator arms. Divalproex performed similarly compared to these agents; however, one small study (N=59) suggests that OBTA is better tolerated than divalproex.

- Several systematic reviews cite only 1 small (N=37) head-to-head RCT involving divalproex versus propranolol for the prevention of episodic migraine.<sup>12,39,59</sup> No significant differences in response or tolerability were found when divalproex (target dose of 1,500 mg/day) was compared to propranolol (target dose of 180 mg/day) for the outcome of  $\geq 50\%$  reduction in migraine frequency or mean migraine days over 12 weeks.<sup>60</sup>
- One small RCT (N=59) suggested that divalproex and OBTA are similarly effective for migraine prevention in a mixed population with episodic and chronic migraine; however, there were significantly lower adverse event-related discontinuation rates with OBTA compared to treatment with divalproex (evidence rated as very low quality by Cochrane review authors).<sup>13</sup>

##### Monoclonal Antibody Comparisons (erenumab, fremanezumab, galcanezumab)

No head-to-head RCTs are available for any monoclonal antibody versus another active comparator.

##### OnabotulinumtoxinA Comparisons

OBTA head-to-head comparisons include divalproex or topiramate comparator arms. OBTA performed similarly compared to divalproex and topiramate; although tolerability appeared better with OBTA.

- A 2018 Cochrane review and 2013 Agency for Healthcare Research and Quality (AHRQ) SR<sup>14</sup> found no major efficacy differences between OBTA versus topiramate for adults diagnosed with chronic migraine. Adverse event-related discontinuations with OBTA were numerically lower compared to topiramate, while individual adverse-effect rates for depression, mood disturbance, weight loss, paresthesia, and cognitive deficits were significantly more common with topiramate.<sup>14</sup> The Cochrane review authors rated the evidence as very low quality.<sup>13</sup>

#### Propranolol Comparisons

Head-to-head comparison studies involving propranolol include timolol or topiramate comparator arms; propranolol appeared similarly effective compared to these agents. A 2017 meta-analysis also showed that propranolol is better tolerated compared to topiramate, with a significantly lower rate of composite adverse events and rate of withdrawal due to adverse events.<sup>12</sup>

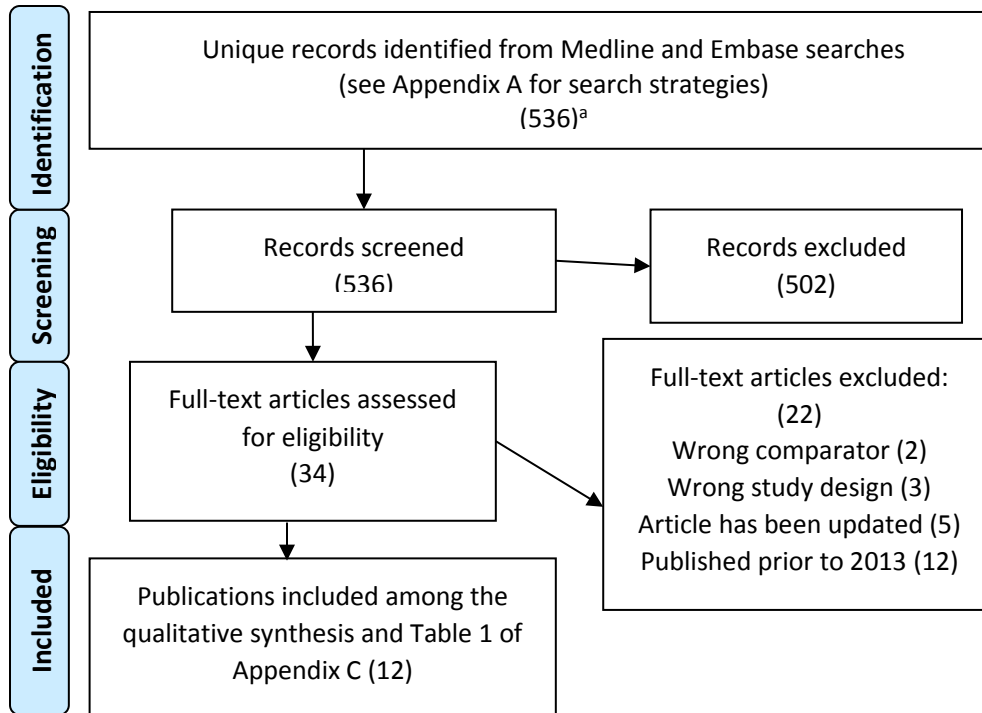
- Propranolol and topiramate appear similarly effective for the reduction of migraine frequency and total headache days based on a 2017 meta-analysis of 2 RCTs.<sup>12</sup>
- There is limited evidence available suggesting propranolol and timolol are similarly efficacious (1 small RCT conducted in 1984 in patients with 2 to 6 migraine attacks per month); data was insufficient to determine whether there were significant differences with respect to adverse events.

## II. Systematic Review Evidence for the Prophylaxis of Migraine

### II.a PRISMA

Our literature search for SRs and RCTs yielded a total of 536 unique titles. Twelve SRs were selected for inclusion. **Figure 1** displays the PRISMA flow chart for the publication screening process. Appendix B provides a list of studies excluded in the full-text review stage and the list of SRs included.

Figure 1. PRISMA Flow chart for Publication Screening



<sup>a</sup> Combined results from Medline and Embase search strategies after duplicates removed in Covidence®



## II.b Drug Comparisons

### Pediatric Population

#### **Propranolol (PRO) versus Topiramate (TOP)**

Barnes et al (2015), an SR, included comparative evidence for migraine preventive therapies used in the pediatric population. After finding 2 inconsistent RCTs of “very low quality evidence,” authors concluded that evidence is inconclusive regarding a difference in efficacy between PRO and TOP.<sup>8</sup>

One RCT (N=565) was found by Mulleners et al 2015 SR, which included adolescent patients; however, the study population primarily included adults.<sup>9,61</sup> This RCT by Diener et al was conducted in patients between 14 and 66 years of age (median age of 41 years) and after 26 weeks of treatment found that both TOP 100 and PRO 160 were similarly effective for the reduction of migraine frequency, migraine days, and use of rescue medication.<sup>61</sup>

### Adult Population

#### DIVALPROEX

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#### **Divalproex (DIV) versus Propranolol (PRO)**

Several SRs (He et al 2017, Jackson et al 2015, and Linde et al 2013) identified 1 RCT for this comparison.<sup>12,39,59</sup> The 1997 RCT by Kaniecki et al randomized patients to receive DIV or sustained release PRO, and titrated to target doses of DIV 1,500 mg/day and PRO 180 mg/day, respectively. After 8 and 12 weeks of treatment, both active-treatment arms demonstrated similar response rates. Response was defined as at least a 50% reduction in migraine frequency or mean migraine days.<sup>60</sup> These medications were tolerated similarly as there were no differences in total adverse events or adverse event-related withdrawals.<sup>12</sup> This RCT was limited by a small study population number of only 37 patients.<sup>62</sup>

#### **Divalproex (DIV) versus OnabotulinumtoxinA (OBTA)**

Only 1 RCT (Blumenfeld et al 2008)<sup>63</sup> has been identified for this comparison (captured in the SRs by Herd et al 2018<sup>13</sup> and Shamliyan et al 2013<sup>14</sup>). The patients included in this trial either had episodic migraine (n=45) or chronic migraine (n=14), and the distribution of patients according to migraine type was balanced in each treatment arm. While there were no significant differences in efficacy between the 2 treatment arms after 9 months of therapy with respect to the number of headache days per month, responder rates, headache intensity, or disability assessment scores (eg, Migraine Disability Assessment [MIDAS] and Headache Impact Test-6 [HIT-6]), OBTA appeared to be better tolerated compared to divalproex. Significantly more patients treated with DIV reported adverse events possibly related to treatment compared to the OBTA arm (DIV 75.8% versus OBTA 50%, P = .04) and more patients reported discontinuing the DIV because of adverse events

(DIV 27.6% versus OBTA 3.3%,  $P = .012$ ).<sup>63</sup> The Cochrane review authors (Herd et al) judged the quality of evidence from this study to be very low because this was a small trial ( $N=59$ , mostly of patients diagnosed with episodic migraine) and the risk of bias assessment showed unclear or high risk for various bias measures.<sup>13</sup>

#### MONOCLONAL ANTIBODIES (ERENUMAB, GALCANEZUMAB, FREMANEZUMAB)

A systematic review by Khan et al showed no RCTs comparing erenumab to other alternatives.<sup>64</sup> Only the pivotal placebo-controlled studies for migraine prevention were identified. Since Khan et al searched only one database (PubMed), we designed our literature search to amend this potential limitation; however, did not find any head-to-head evidence involving erenumab, or any of the other monoclonal antibodies.

#### ONABOTULINUMTOXINA

##### *OnabotulinumtoxinA (OBTA) versus Topiramate (TOP)*

A Cochrane systematic review by Herd et al, 2018, found no significant difference in efficacy between OBTA and TOP in terms of the number of migraine or headache days per month, the use of rescue medication, or the Migraine Disability Assessment score.<sup>13</sup> These findings were based on 2 RCTs (Cady 2011, and Mathew 2009) that included adult patients diagnosed with chronic migraine.<sup>65,66</sup> No additional head-to-head RCTs published more recently than the search dates of the Cochrane review (ie, 2017 onward) were found from our literature search.

The 2013 AHRQ SR is consistent with the Cochrane review findings, as authors found the same 2 RCTs.<sup>14</sup> The AHRQ report also highlights that there are less frequent (significance level unknown) discontinuations with OBTA compared to TOP and particular adverse effects were significantly more common with topiramate: depression, mood disturbance, weight loss, paresthesias and cognitive deficits.<sup>14</sup>

#### PROPRANOLOL

##### *Propranolol (PRO) versus Topiramate (TOP)*

A 2017 SR by He et al included a pairwise meta-analysis which resulted in no significant differences for PRO versus TOP with respect to migraine headache days or headache frequency based on 2 RCTs (Diener et al and Ashtari et al).<sup>12,39</sup> Other SRs (Jackson et al 2015, Mulleners et al 2015, and Lind et al 2013) are also consistent with these findings.<sup>9,39,67</sup> The meta-analysis also shows that propranolol is better tolerated compared to topiramate, with significantly lower total adverse-events and rate of withdrawal due to adverse events.<sup>12</sup>

- Diener et al 2004 compared TOP 100 or 200 versus PRO 160 or placebo after 26 weeks of treatment.<sup>61</sup> The population included patients with episodic migraine

between 14 and 66 years of age.<sup>67</sup> There was no significant difference in the change of monthly migraine frequency, migraine days, or rescue medication use between TOP 200 compared to placebo, likely due to the high dropout rates from intolerability of this high dose. Propranolol 160 and TOP 100 performed better than placebo and were similarly effective (ie, no significant difference between active-drug arms).<sup>61</sup>

- Ashtari et al 2008 compared low-dose TOP 50 to PRO 80 after 8 weeks of treatment in adults with a history of migraine for at least 1 year who experienced at least 3 attacks per month.<sup>68</sup> Topiramate was more effective for the reduction of migraine frequency, intensity, and duration.<sup>68</sup>

#### *Propranolol (PRO) versus Timolol (TIM)*

Two publications for 1 RCT<sup>69,70</sup> were identified for this comparison (via SRs, Jackson et al 2015<sup>39</sup> and Shamliyan et al 2013<sup>14,71</sup>). The 1984 publication assessed data from multiple treatment sites. The RCT was a crossover study, by Tfelt-Hansen et al, conducted in 83 adult patients suffering from 2 to 6 migraine attacks per month. This criteria for migraine diagnosis used in the study differs from currently used criteria (ie, ICHD-III). After 12 weeks of therapy with either TIM 20 or PRO 160, there were no significant efficacy differences for endpoints such as frequency of attacks, duration of attacks, percentage of patients with  $\geq 50\%$  reduction in frequency.<sup>70</sup> The 1982 publication by Standnes et al reported only the Norwegian study-site results for this RCT. Findings were consistent with those seen in the larger population, as propranolol and timolol performed similarly for the reduction of migraine attack frequency.<sup>69</sup>

## Safety

The SR by He et al, 2017, suggests propranolol is better tolerated than topiramate, with lower adverse-event rates and adverse event-related treatment discontinuations.<sup>12</sup> No head-to-head evidence was found comparing the tolerability of topiramate versus divalproex. There is RCT evidence suggesting OBTA is better tolerated compared to the anticonvulsants divalproex and topiramate; however, this evidence was rated as very low quality according to the Cochrane review authors.<sup>14,62</sup>

Long-term adherence to the oral migraine prophylactic agents is low in patients with chronic migraine (29% at 6 months, and 20% at 12 months)<sup>18</sup> due to a mix of factors including adverse reactions and in-adequate response to therapy. Poor persistence and adherence to oral migraine-prophylactic agents remains a topic of discussion; there is much room for improvement.<sup>18-21</sup> The anticonvulsants, divalproex and topiramate, can produce neurological and gastrointestinal side effects, and can cause fetal harm (black box warning for divalproex).<sup>22,23</sup> Paresthesia is common with topiramate, although, cognitive dysfunction is the main adverse event-related reason for discontinuation (eg, confusion, psychomotor slowing, impaired concentration and memory, word-finding difficulty).<sup>24</sup> In placebo-controlled trials, 20% of topiramate-treated patients withdraw due to adverse events.<sup>67</sup> Weight gain, tremor, and alopecia can occur with long-term use of divalproex, while gastrointestinal events can cause significant distress early on (but may lessen after 6 months of use and with slow titration).<sup>25</sup> Common adverse events involved with beta-blockers include fatigue, reduced exercise tolerance, hypotension, sexual dysfunction, sleep disturbance, lightheadedness, disorientation, and gastrointestinal side effects. Interestingly, a 2017 meta-analysis found that topiramate- and propranolol-treated patients were significantly more likely to withdrawal from studies due to adverse events compared to placebo; but, for divalproex versus placebo, there was no significance difference in adverse event-related withdrawals.<sup>12</sup>

Regarding the injectable medications, no major safety issues surfaced from the clinical trials involving the monoclonal antibodies.<sup>7,50</sup> The most common adverse event was injection-site reaction with the CGRP antagonists. Constipation was also more common with the 140 mg/month maintenance dose regimen of erenumab compared to placebo. Overall, the monoclonal antibodies were well tolerated with low study drop-out rates ( $\leq 2\%$ ) due to adverse events in the double-blind pivotal trials,<sup>15-17,50</sup> suggesting perhaps they may have tolerability advantages compared to some of the oral prophylactic products available. Confirmatory head-to-head studies are needed.

Similarly, OBTA was also well tolerated, with low discontinuation rates due to adverse events of about 4% in pivotal studies.<sup>33</sup> Labeled adverse events occurring in 5% or more of patients and more often compared to placebo include neck pain and headache (significance not reported for the difference).<sup>33</sup>

**Table 5** summarizes the common adverse reactions for each product. Labeled warnings are summarized in **Table 6**.

Table 5. Adverse Reactions and Clinical Concerns<sup>15-17,44</sup>

	May be inappropriate or intolerable for the patients with the following	May be preferred for patients with migraine and the following co-morbidity or issue	Common Adverse Reactions <sup>15-17,22,23,27-36</sup>
<b>Divalproex</b>	Liver disease, bleeding disorders, alcoholism, obesity, pregnancy/peripartum	Epilepsy, mania, anxiety	Reported in >5%: abdominal pain, alopecia, amblyopia/blurred vision, amnesia, anorexia, asthenia, ataxia, constipation, depression, diarrhea, diplopia, dizziness, dyspnea, emotional lability, headache, increased appetite, insomnia, nausea, nervousness, nystagmus, peripheral edema, pharyngitis, rash, somnolence, thinking abnormal, thrombocytopenia, tinnitus, tremor, vomiting, weight gain, weight loss
<b>Erenumab-aooe</b>			Reported in >3% of patients and more often than placebo: injection site reaction and constipation
<b>Fremanezumab-vfrm</b>	No labeled contraindications	Intolerance or contraindications to the oral options	Reported in ≥5% and greater than event rate in placebo arm: injection site reactions
<b>Galcanezumab-gnlm</b>			Reported in ≥2% and at least 2% greater than event rate in placebo arm: injection site reactions
<b>Onabotulinum-toxinA</b>	Episodic migraine (approved for patients with chronic migraine)	Intolerance or contraindications to the oral options	Reported in >5% of patients treated for chronic migraine and more often than in the placebo group: neck pain and headache
<b>Propranolol</b>	Asthma, heart block, CHF, hypotension, bradycardia, peripheral vascular disease, depression, highly active in aerobic activities	Hypertension, angina	Fatigue, bradycardia, intensification of CHF or AV block, reduced exercise tolerance, hypotension, bronchospasm, sexual dysfunction, sleep disturbance, light-headedness, vivid dreams, disorientation, GI side effects
<b>Timolol</b>			Fatigue, bradycardia, intensification of CHF or AV block, reduced exercise tolerance, hypotension, bronchospasm, sexual dysfunction, sleep disturbance
<b>Topiramate</b>	Kidney stones, kidney failure, angle closure glaucoma, pregnancy;	Epilepsy, obesity, mania, anxiety, essential tremor, alcohol dependence	Reported in ≥5% more frequent than placebo: paresthesia, anorexia, weight loss, difficulty with memory, taste perversion, diarrhea, hypoesthesia, nausea, abdominal pain and upper respiratory tract infection

Table 6. Warnings, Precautions, and Drug-drug Interaction Labeling<sup>15-17,22,23,27-36,,a</sup>

<p><b>Divalproex</b></p>	<p><b>Black Box Warning</b></p> <ul style="list-style-type: none"> <li>Life-threatening hepatotoxicity usually during the first 6 months of treatment. Children under years of age and patients with mitochondrial disorders are at higher risk of hepatotoxicity</li> <li>Fetal risk (eg, neural tube defect, major malformations, and decreased IQ)</li> <li>Pancreatitis, including life-threatening hemorrhagic cases</li> </ul> <p><b>Contraindicated</b> in hepatic disease or significant dysfunction, certain mitochondrial disorders, urea cycle disorders, and during pregnancy</p> <p>Other Warnings</p> <ul style="list-style-type: none"> <li>Increased risk of suicidal ideation or behavior</li> <li>Bleeding or other hematopoietic disorders</li> <li>Hyperammonemia</li> <li>Hypothermia</li> <li>Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity</li> </ul>	<p>Drug Interactions</p> <ul style="list-style-type: none"> <li>Hepatic enzyme inducing or inhibiting drugs<sup>b</sup></li> <li>Aspirin, carbapenem antibiotics, estrogens</li> <li>Concomitant topiramate use may increase risk of hyperammonemia</li> <li>Dose adjustments may be needed for some concomitant drugs such as amitriptyline and warfarin</li> <li>CNS depressants (eg, opioids, benzodiazepines, alcohol)</li> </ul>
<p><b>Erenumab-aooe</b></p>	<ul style="list-style-type: none"> <li>Immunogenicity potential or development of inhibitors (ie, neutralizing antibodies)</li> </ul>	<p>No clinical significant drug interactions are known of</p>
<p><b>Fremanezumab-vfrm</b></p>	<ul style="list-style-type: none"> <li>Hypersensitivity reactions</li> <li>Immunogenicity potential or development of inhibitors (ie, neutralizing antibodies)</li> </ul>	<p>No clinical significant drug interactions are known of</p>
<p><b>Galcanezumab-gnlm</b></p>	<ul style="list-style-type: none"> <li>Hypersensitivity reactions</li> <li>Immunogenicity potential or development of inhibitors (ie, neutralizing antibodies)</li> </ul>	<p>No clinical significant drug interactions are known of</p>
<p><b>Onabotulinum-toxinA</b></p>	<p>Contraindicated if infection is present at the proposed injection site</p> <p>Warnings</p> <ul style="list-style-type: none"> <li>Spread of toxin effects that may be life-threatening</li> <li>Concomitant neuromuscular disorder may exacerbate clinical effects of treatment</li> <li>Use with caution in patients with compromised respiratory function</li> </ul>	<p>Drug Interactions</p> <ul style="list-style-type: none"> <li>Use caution and monitor more closely if there is concomitant use with aminoglycosides or other agents affecting neuromuscular transmission or skeletal relaxants</li> </ul>
<p><b>Propranolol</b></p>	<p><b>Contraindicated</b> in cardiogenic shock; sinus bradycardia, bronchial asthma</p> <p>Warnings</p> <ul style="list-style-type: none"> <li>Abrupt discontinuation can cause or exacerbate angina pectoris and potential for MI in patients with cardiovascular disease. Medication must be tapered-off gradually instead of abruptly discontinuing</li> </ul>	<p>Drug Interactions<sup>b,c</sup></p> <ul style="list-style-type: none"> <li>Use caution with strong inhibitors or inducers of CYP2D6, CYP1A2, CYP2C19, or inducers of hepatic drug metabolism. Propranolol can also inhibit substrate metabolism at these mentioned CYP enzymes</li> <li>The exposure of both zolmitriptan or rizatriptan</li> </ul>

Table 6. Warnings, Precautions, and Drug-drug Interaction Labeling<sup>15-17,22,23,27-36,,a</sup>

	<ul style="list-style-type: none"> <li>• Hypersensitivity and skin reactions</li> <li>• Cardiac failure</li> <li>• Non-allergic bronchospasm</li> <li>• Hypoglycemia in diabetes</li> <li>• Thyrotoxicosis</li> <li>• Bradycardia</li> </ul>	<p>increases with concomitant use of propranolol</p>
<p><b>Timolol</b></p>	<p><b>Black box warning:</b> Exacerbation of ischemic heart disease following abrupt withdrawal</p> <p><b>Contraindicated</b> with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock;</p> <p>Warnings</p> <ul style="list-style-type: none"> <li>• Abrupt discontinuation can cause or exacerbate angina pectoris and potential for MI in patients with cardiovascular disease. Medication must be tapered-off gradually instead of abruptly discontinuing</li> <li>• Cardiac failure</li> <li>• Bronchospasm</li> <li>• Hypoglycemia in diabetes</li> <li>• Thyrotoxicosis</li> <li>• Bradycardia</li> </ul>	<p>Drug Interactions<sup>b,c</sup></p> <ul style="list-style-type: none"> <li>• Use caution with strong inhibitors or inducers of CYP2D6</li> <li>• Calcium channel blockers, digitals</li> <li>• Clonidine</li> <li>• Caution with use of catecholamine depleting drugs (eg. reserpine)</li> </ul>
<p><b>Topiramate</b></p>	<p><b>Contraindicated</b> with recent alcohol use (within 6 hours prior to after taking topiramate ER)</p> <p>Warnings</p> <ul style="list-style-type: none"> <li>• Acute myopia and secondary angle closure glaucoma; Visual field defects</li> <li>• Oligohydrosis and hyperthermia</li> <li>• Metabolic acidosis</li> <li>• Suicidal behavior and ideation</li> <li>• Cognitive/neuropsychiatric</li> <li>• Fetal toxicity</li> <li>• Withdrawal symptoms upon abrupt discontinuation</li> <li>• Hyperammonemia/encephalopathy</li> <li>• Kidney stone</li> </ul>	<p><b>Drug interactions</b></p> <ul style="list-style-type: none"> <li>• Alcohol</li> <li>• Antiepileptic drugs</li> <li>• Carbonic anhydrase inhibitors</li> <li>• CNS depressants (eg, opioids, benzodiazepines, alcohol)</li> </ul>

<sup>a</sup> Refer to package inserts for full labeling of these sections

<sup>b</sup> Hepatic enzyme inducers include phenytoin, carbamazepine, phenobarbital, primidone, rifampin; hepatic inhibitors include felbamate;

<sup>c</sup> CYP2D6 substrates(eg, amiodarone, fluoxetine, paroxetine, and ritonavir); CYP1A4 substrates (eg, imipramine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan); CYP2C19 substrates (eg, fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide; no interaction observed with omeprazole)

## Summary

### Pediatric Population

The only FDA-approved medication for migraine prophylaxis in the pediatric population is topiramate (for adolescents 12 years and older). Barnes et al (SR) conclude that there is limited evidence to support the use of beta-blockers in pediatric patients; however, because propranolol has a good safety profile in patients without respiratory or cardiovascular co-morbidities, it may be reasonable to try, with the understanding that only some patients respond adequately. Authors concluded that topiramate is potentially beneficial compared to placebo; however, evidence is limited. It is unknown whether topiramate or propranolol is more effective because there is limited and conflicting evidence.<sup>8,9</sup> The guidelines by the American Academy of Neurology are currently being updated and are anticipated to be published soon. Their last pediatric guideline was published in 2004 at which time they could not make strong recommendations for or against divalproex, topiramate, or propranolol.

### Adults

SRs published between 2013 and 2018 were included, which contained head-to-head comparative evidence available for the migraine prophylactic agents. The following comparisons were found: *divalproex* versus propranolol or OBTA; *OBTA* versus divalproex or topiramate; and *propranolol* versus timolol or topiramate.

Divalproex appears similarly effective compared to propranolol and OBTA; however, one small study suggested divalproex is less tolerable compared to OBTA. OBTA also performed similarly compared to topiramate; however, the anticonvulsant also appears less tolerable compared to OBTA. Head-to-head comparison studies involving propranolol versus timolol or topiramate comparator arms suggest similar efficacy. A meta-analysis suggests that propranolol is better tolerated compared to topiramate.

No head-to-head RCTs are available for the monoclonal antibodies versus each other or another active comparator. FDA reviewers have highlighted that the treatment effect of the CGRP antagonists, with respect to the difference in mMMD reduction from placebo, appears similar compared to other agents already approved.<sup>7,50,56</sup> Nonetheless, differences in study populations and study procedures are not accounted for when making such an observational, indirect comparison across trials and yields a preliminary hypothesis that needs head-to-head confirmatory data.



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## Appendix A: Literature Search Strategies

Table 1. Ovid Medline Literature Search Strategy	
<b>Systematic Review Search</b>	
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily <1946 to July 31, 2018>	
1	(eptinezumab or erenumab or fremanezumab or galcanezumab or monoclonal?antibod*).ti,ab,kw,kf. (3757)
2	(divalproex or propranolol or timolol or topiramate or onabotulinum* or botulin* or beta?blocker* or beta?antagonist* or anticonvulsant*).ti,ab,kw,kf. (82080)
3	Antibodies, Monoclonal, Humanized/ or Adrenergic beta-Antagonists/ or exp Botulinum Toxins, Type A/ or exp Botulinum Toxins/ or Valproic Acid/ or Propranolol/ or Timolol/ or Anticonvulsants/ (167304)
4	1 or 2 or 3 (199927)
5	Migraine Disorders/ or migraine*.ti,ab,kw,kf. (35607)
6	(MEDLINE or systematic review).tw. or meta analysis.pt. (217117) [McMaster review filter; maximized specify]
7	4 and 5 and 6 (111)
8	exp animals/ not humans.sh. (4479745)
9	(7 not 8) and English.la. (109)___ <a href="#">Systematic Review Results</a>
<b>Randomized Controlled Trials Search</b>	
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to August 15, 2018>	
1	Migraine Disorders/ or migraine*.ti,ab,kw,kf. (35667)
2	exp animals/ not humans.sh. (4487838)
3	(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. (1166965) [Cochrane RCT filter (2008 revision)]

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- 4 (onabotulinum\* or botulin\*).ti,ab,kw,kf. or Botulinum Toxins, Type A/ or \*Botulinum Toxins/ (20237)
  - 5 1 and 3 and 4 (177)
  - 6 (5 not 2) and English.la. (158)
  - 7 limit 5 to yr="2017 -Current" (14)
  - 8 (eptinezumab or erenumab or fremanezumab or galcanezumab or monoclonal?antibod\*).ti,ab,kw,kf. or Antibodies, Monoclonal, Humanized/ or Calcitonin Gene-Related Peptide/ (46951)
  - 9 1 and 3 and 8 (94)
  - 10 (9 not 2) and English.la. (84)
  - 11 (propranolol or timolol or beta?blocker\* or beta?antagonist\*).ti,ab,kw,kf. or Propranolol/ or Timolol/ or \*Adrenergic beta-Antagonists/ (64014)
  - 12 1 and 3 and 11 (212)
  - 13 exp animals/ not humans.sh. (4487838)
  - 14 (12 not 13) and English.la. (187)
  - 15 limit 14 to yr="2014 -Current" (22)
  - 16 (divalproex or topiramate or anticonvulsant\*).ti,ab,kw,kf. or Anticonvulsant/ or Valproic Acid/ (35986)
  - 17 1 and 3 and 16 (306)
  - 18 (17 not 13) and English.la. (288)
  - 19 limit 18 to yr="2014 -Current" (58)
  - 20 7 or 10 or 15 or 19 (165)\_\_\_ [Total RCTs with year limits](#)
-

Table 2. EMBASE Search Strategy

**SR Search performed on July 30<sup>th</sup> 2018\_ Results 194**

('eptinezumab'/exp OR 'erenumab'/exp OR 'fremanezumab'/exp OR 'galcanezumab'/exp OR 'calcitonin gene related peptide receptor antagonist'/exp OR 'valproate semisodium'/exp OR 'anticonvulsive agent'/exp OR 'topiramate'/exp OR 'timolol maleate'/exp OR 'timolol'/exp OR 'propranolol'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'botulinum toxin a'/exp OR divalproex:ti,ab,kw OR topiramate:ti,ab,kw OR timolol:ti,ab,kw OR propranolol:ti,ab,kw OR ((beta NEAR/4 block\*):ti,ab,kw) OR ((beta NEAR/4 antagonist):ti,ab,kw) OR eptinezumab:ti,ab,kw OR erenumab:ti,ab,kw OR fremanezumab:ti,ab,kw OR galcanezumab:ti,ab,kw OR botulin\*:ti,ab,kw OR onabotulinum\*:ti,ab,kw) AND ('migraine'/exp OR migraine\*:ti,ab,kw) AND (cochrane\*:jt OR 'systematic review\*':jt OR 'meta analysis'/mj OR 'systematic review'/mj OR ((systematic NEAR/3 review):ti) OR 'meta analys\*':ti,ab,kw OR metaanalys\*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it) AND [english]/lim

#1 'eptinezumab'/exp OR 'erenumab'/exp OR 'fremanezumab'/exp OR 'galcanezumab'/exp OR 'calcitonin gene related peptide receptor antagonist'/exp 2002

#2 'valproate semisodium'/exp OR 'anticonvulsive agent'/exp OR 'topiramate'/exp OR 'timolol maleate'/exp OR 'timolol'/exp OR 'propranolol'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'botulinum toxin a'/exp 654492

#3 divalproex:ti,ab,kw OR topiramate:ti,ab,kw OR timolol:ti,ab,kw OR propranolol:ti,ab,kw OR ((beta NEAR/4 block\*):ti,ab,kw) OR ((beta NEAR/4 antagonist):ti,ab,kw) OR botulin\*:ti,ab,kw 80807

#4 eptinezumab:ti,ab,kw OR erenumab:ti,ab,kw OR fremanezumab:ti,ab,kw OR galcanezumab:ti,ab,kw 239

#5 botulin\*:ti,ab,kw OR onabotulinum\*:ti,ab,kw 26233

#6 #1 OR #2 OR #3 OR #4 OR #5 674818

#7 'migraine'/exp OR migraine\*:ti,ab,kw 63918

#8 'valproate semisodium'/exp OR 'topiramate'/exp OR 'timolol maleate'/exp OR 'timolol'/exp OR 'propranolol'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'botulinum toxin a'/exp July 30th 320723 --- got rid of the broad anticonvulsant term

#9 #1 OR #3 OR #4 OR #5 OR #8 341771

#10 (cochrane\*:jt OR 'systematic review\*':jt OR 'meta analysis'/mj OR 'systematic review'/mj OR ((systematic NEAR/3 review):ti) OR 'meta analys\*':ti,ab,kw OR metaanalys\*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it) AND [english]/lim July 30th 189902

#11 #7 AND #9 AND #10 135

#12 #6 AND #7 AND #10 194

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**RCT Search performed on August 24, 2018\_ 269 Results**

#1	'migraine'/exp OR migraine*:ti,ab,kw	64143
#2	'eptinezumab'/exp OR 'erenumab'/exp OR 'fremanezumab'/exp OR 'galcanezumab'/exp OR 'calcitonin gene related peptide receptor antagonist'/exp	2023
#3	eptinezumab:ti,ab,kw OR erenumab:ti,ab,kw OR fremanezumab:ti,ab,kw OR galcanezumab:ti,ab,kw	253
#4	('clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR (((clinical OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ti,ab) OR placebo:ab,ti OR 'head to head':ti,ab) AND [english]/lim	900772
#5	'conference abstract'/it OR 'conference review'/it	3138703
#6	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	6547282
#7	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	2653151
#8	#4 NOT (#5 OR #6 OR #7)	629593
#9	#1 AND (#2 OR #3) AND #8	104
#10	'botulinum toxin a'/exp OR botulin*:ti,ab,kw OR onabotulinum*:ti,ab,kw	31663
#11	#1 AND #8 AND #10 AND (2017\$:py OR 2018\$:py)	14
#12	divalproex:ti,ab,kw OR topiramate:ti,ab,kw OR timolol:ti,ab,kw OR propranolol:ti,ab,kw OR ((beta NEAR/4 block*):ti,ab,kw) OR (beta NEAR/4 antagonist):ti,ab,kw)	56106
#13	'valproate semisodium'/exp OR 'anticonvulsive agent'/exp OR 'topiramate'/exp OR 'timolol maleate'/exp OR 'timolol'/exp OR 'propranolol'/exp OR 'beta adrenergic receptor blocking agent'/exp	638741
#14	#1 AND #8 AND (#12 OR #13) AND (2014\$:py OR 2015\$:py OR 2016\$:py OR 2017\$:py OR 2018\$:py)	161
#15	#9 OR #11 OR #14	269

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## Appendix B: Included and Excluded Studies

### Included Studies

1. Barnes NP. Migraine headache in children. *BMJ clinical evidence*. 2015;2015.
2. El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: A meta-analysis. *JAMA Pediatrics*. 2013;167(3):250-258.
3. He A, Song D, Zhang L, Li C. Unveiling the relative efficacy, safety and tolerability of prophylactic medications for migraine: pairwise and network-meta analysis. *The journal of headache and pain*. 2017;18(1):26.
4. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *The Cochrane database of systematic reviews*. 2018;6:CD011616.
5. Jackson JL, Cogbill E, Santana-Davila R, et al. A comparative effectiveness meta-analysis of drugs for the prophylaxis of migraine headache. *PLoS ONE*. 2015;10(7).
6. Khan S, Olesen A, Ashina M. CGRP, a target for preventive therapy in migraine and cluster headache: Systematic review of clinical data. *Cephalalgia : an international journal of headache*. 2017;333102417741297.
7. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *The Cochrane database of systematic reviews*. 2013(6):CD010611.
8. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. *The Cochrane database of systematic reviews*. 2013(6):CD010610.
9. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia : an international journal of headache*. 2015;35(1):51-62.
10. Shamlivan TA, Kane RL, Taylor FR. *Comparative Effectiveness Review Number 103. Migraine in Adults: Preventive Pharmacologic Treatments. Effective health Care Program*. Minneapolis, MN: Agency for Healthcare Research and Quality (US), Minnesota Evidence-based Practice Center;2013.
11. Shamlivan TA, Kane RL, Ramakrishnan R, Taylor FR. *Comparative Effectiveness Review Number 108. Migraine in Children: Preventive Pharmacologic Treatments* Minneapolis, MN: Agency for Healthcare Research and Quality (US), Minnesota Evidence-based Practice Center;2013.
12. Shamlivan TA, Choi J-Y, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults. *Journal of general internal medicine*. 2013;28(9):1225-1237.

### Excluded Studies

#### Wrong Comparator

1. Le K, Yu D, Wang J, Ali AI, Guo Y. Is topiramate effective for migraine prevention in patients less than 18 years of age? A meta-analysis of randomized controlled trials. *Journal of Headache and Pain*. 2017;18(1)
  - Contains placebo comparisons only
2. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. *The Cochrane database of systematic reviews*. 2013(6):CD010608.

#### Wrong Study Design

3. Silberstein SD. Topiramate in Migraine Prevention: A 2016 Perspective. *Headache*. 2017;57(1):165-178.
  - Lacking systematic search
4. Hougaard A, Tfelt-Hansen P. General lack of use of placebo in prophylactic, randomised, controlled trials in adult migraine. A systematic review. *Cephalalgia*. 2016;36(10):960-969.
5. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache*. 2012;52(6):930-945.

#### SR has been updated

6. Barnes NP. Migraine headache in children. *BMJ clinical evidence*. 2011;2011.

7. Barnes NP, James EK. Migraine headache in children. *BMJ clinical evidence*. 2009;2009
  - Included Barnes et al 2015 with updated search dates
8. Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. *Cochrane Database of Systematic Reviews*. 2004;2004(3).
9. Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. *Cochrane Database of Systematic Reviews*. 2016;2016(5).
10. Gray RN, Goslin RE, McCrory DC, Eberlein K, Tulsy J, Hasselblad V. *Technical Reviews No. 2.3: Drug Treatments for the Prevention of Migraine Headache* Rockville, MD: Agency for Health Care Policy and Research (US);1999.
  - Included two 2013 AHRQ reports of SRs in adults and children by Shamiyan et al

Published prior to 2013

11. Adelman JU, Adelman RD. Current options for the prevention and treatment of migraine. *Clinical therapeutics*. 2001;23(6):772-771
  - Authors only searched 1 database (Medline)
12. Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. *Cephalalgia: an international journal of headache*. 2006;26(5):497-505.
  - Authors did not find head-to-head trials of interest to compare drugs in Table 1 of this review
13. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacology bulletin*. 2003;37 Suppl 2:98-115.
14. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. *JAMA - Journal of the American Medical Association*. 2012;307(16):1736-1745.
15. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine. *CNS drugs*. 2002;16(9):611-634.
16. Linde K, Rosnagel K. Propranolol for migraine prophylaxis. *The Cochrane database of systematic reviews*. 2004(2):CD003225.
  - Authors did not find head-to-head trials of interest to compare drugs in Table 1 of this review
17. Pringsheim T, Davenport WJ, Becker WJ. Prophylaxis of migraine headache. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2010;182(7):E269-276.
18. Pringsheim T, Davenport WJ, MacKie G, et al. Systematic review: Medications for migraine prophylaxis - Section II. *Canadian Journal of Neurological Sciences*. 2012;39(2):S8-S28.
19. Tfelt-Hansen P. A review of evidence-based medicine and meta-analytic reviews in migraine. *Cephalalgia*. 2006;26(11):1265-1274.
  - Authors do not specify databases searched or appear to have a systematic review process
20. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. *The Cochrane database of systematic reviews*. 2003(4):CD002761.
  - Authors did not find head-to-head trials of interest to compare drugs in Table 1 of this review
21. Victor S, Ryan S, Hobson A. Drugs for preventing migraine headaches in children. *Cochrane Database of Systematic Reviews*. 2014;2014(7).
  - This title is a notice of withdrawal of the original 2003 publication since Cochrane states it is now out of date
22. Wenzel RG, Schwarz K, Padiyara RS. Topiramate for migraine prevention. *Pharmacotherapy*. 2006;26(3):375-387.

## Appendix C: Systematic Reviews

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
Herd 2018 <sup>13</sup>	<p>Study objective: “To assess the effects of botulinum toxins versus placebo or active treatment for the prevention or reduction in frequency of chronic or episodic migraine in <u>adults</u>.”</p> <p>Searched CENTRAL, Medline (1946 to Dec. 7<sup>th</sup>, 2017), and EMBASE (up to week 49 of 2017)</p> <p>Considered prospective, randomized and quasi-randomized, double-blind, controlled trials of all sero-types of botulinumtoxin</p>	<p>Head-to-head studies included:</p> <ul style="list-style-type: none"> <li>• RCTs Botox vs topiramate (Mathew 2009, and Cady 2011); Botox 100 U fixed dose plus an optional 100 U or less versus topiramate at a maximum dose of 200 mg per day</li> <li>• RCT Botox vs valproate (Blumenfeld 2008); Botox 100 U or less versus sodium valproate 250 mg twice daily</li> </ul> <p>“It was not possible to carry out any analysis on migraine or headache frequency outcomes, severity of migraine, headache index, duration of migraine or the use of rescue medication outcome measures for head-to-head comparisons between botulinum toxin and other established agents due to lack of available data”</p> <p><b>Botox vs. topiramate (Very low quality evidence)</b>  <b>Number of migraine days per month:</b> No significant differences found between Botox vs. topiramate (1 RCT, Mathew 2009)  <b>Number of headache days per month:</b> No significant differences found between Botox vs. topiramate (1 RCT, Cady 2011)  <b>Use of rescue medication:</b> No difference found between Botox vs. topiramate (1 RCT, Mathew 2009)  <b>Headache intensity:</b> small difference in favor of topiramate, versus Botox (1 RCT, Mathew 2009); however, this evidence was based on a five point scale and was judged by the Cochrane authors to be of very low quality (eg, high risk for selection, performance, detection and attrition bias)  <b>MIDAS:</b> no difference found between Botox vs. topiramate (2 RCTs, Mathew 2009 and Cady 2011)</p> <p><b>Botox (up to 100 U) vs. divalproex ( up to 500 mg twice daily)</b>  <b>Number of headache days per month:</b> No significant difference found (1 RCT, Blumenfeld 2008)  <b>Headache intensity medication:</b> No significant difference found (1 RCT, Blumenfeld 2008)  <b>MIDAS:</b> No significant difference found (1 RCT, Blumenfeld 2008)</p>

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
Khan 2017 <sup>64</sup>	<p>Study objective: Review current clinical data on anti-CGRP mAbs for treatment of migraine and cluster headache</p> <p>Searched PubMed on August 7, 2017. Also searched clinicaltrials.gov and cgrpforum.org on August 7, 2017</p> <p>Considered RCTs on treatment and prevention of migraine and cluster headache</p>	<p>Authors report many placebo controlled trials of anti-CGRP mAbs used for treatment and prevention of migraine headache, however no studies comparing anti-CGRP mAbs with treatment alternatives were identified.</p>
He 2017 <sup>12</sup>	<p>Study objective: compare different treatments used for migraine prophylaxis via pairwise- and network- meta analysis</p> <p>Searched PubMed and Embase; however, authors did not report search dates. Most recent RCT included had a publication date of 2015</p> <p>Studies must meet the following criteria to be included: trial must be randomized, with blinding procedures, and have a sample size of 30 or greater. Patients must have migraine diagnosis and there must be comparisons between different treatments, had relevant clinical outcomes</p> <p>Studies were excluded if they only included treatments that didn't form a closed network (in the context of a network-meta analysis)</p> <p>Note that the patient population was not explicit (ie, authors did not limit to adults). Thus it appears that authors would have included studies with pediatric patients if they met criteria and had been available.</p>	<p><b>Pairwise meta-analysis: random effects modeling</b></p> <p><b>Propranolol vs. Topiramate (2 RCTs)<sup>61,68</sup></b></p> <ul style="list-style-type: none"> <li>• Efficacy: No significant difference found for migraine headache days and headache frequency</li> <li>• Safety: A significant difference in favor of propranolol was found for the “all-adverse events” summary point (OR 0.57 (0.36, 0.90) and for the “withdrawal due to AEs” summary point (OR 0.58 (0.37, 0.91). However, there were no differences in individual safety assessments including nausea, somnolence, and dizziness.</li> </ul> <p><b>Propranolol vs. divalproex</b></p> <ul style="list-style-type: none"> <li>• Efficacy: There were no studies found addressing migraine headache days or frequency for this comparison</li> <li>• Safety: The study that was available for this comparison (Kaniecki 1997) reported no significant difference in “all-adverse events,” “withdrawal due to AEs” or in individual safety assessments including nausea, somnolence, and dizziness</li> </ul> <p><b>Topiramate vs. valproate</b></p> <ul style="list-style-type: none"> <li>• Efficacy: There were no studies found addressing migraine headache days or frequency for this comparison</li> <li>• Safety: The study that was available for this comparisons addressed tolerability and reported no significant difference in “all-adverse events,” “withdrawal due to AEs” or in</li> </ul>

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
		<p>individual safety assessments including nausea, somnolence, and dizziness</p> <p>Topiramate vs. amitriptyline</p> <ul style="list-style-type: none"> <li>• Efficacy: No significant difference found for migraine headache days</li> <li>• Safety: No differences in tolerability was found</li> </ul>
Mulleners 2015 <sup>9</sup>	<p>Objective: to compare different antiepileptics with placebo, with each other, or alternatives for the prevention of migraine for patients <u>16 years of age or older</u></p> <p>Searched the Cochrane Central Register of Controlled Trials, PubMed/MEDLINE (1966 to January 15, 2013), MEDLINE In-Process (current week, January 15, 2013), and EMBASE (1974 to January 15, 2013) and handsearched Headache and Cephalalgia through January 2013.</p> <p>Considered prospective, controlled trials employing <u>antiepileptic therapy</u> to prevent of migraine attacks in adults, or to improve migraine-related quality of life</p>	<p>Mulleners et al identified 3 key head-to-head trials that apply to our review including the following and consistent with He et al 2017.</p> <ul style="list-style-type: none"> <li>• Ashtari et al 2008 comparing PRO vs. TOP in adults</li> <li>• Diener et al 2004, comparing PRO vs. TOP in patients between 12 to 65 years of age</li> <li>• Kaniecki et al 1997 comparing DIV vs. TOP</li> </ul>
Jackson 2015 <sup>39</sup>	<p>Objective: to perform a meta-analysis that describes the comparative effectiveness and side effects of the oral prophylactic treatment options available for migraine prevention in <u>adults</u></p> <p>Searched Medline, Embase, and CENTRAL through November 7, 2014</p> <p>Considered published RCTs of adults with migraine of a least 4 weeks duration. Comparisons included placebo-controlled or active comparator arms</p>	<p>Jackson et al identified 4 key head-to-head trials that apply to our review. One crossover RCT (Tfelt-Hansen et al) provides information for PRO vs. TIM, and was not found by SRs listed in this table with more recent publication dates than Jackson et al.</p> <ul style="list-style-type: none"> <li>• Ashtari et al 2008 comparing PRO vs. TOP</li> <li>• Diener et al 2004, comparing PRO vs. TOP</li> <li>• Kaniecki et al 1997 comparing DIV vs. TOP</li> <li>• Tfelt-Hansen et al 1984 comparing PRO vs TIM <ul style="list-style-type: none"> <li>○ There was no significant difference in frequency of migraine attacks, and various headache indexes<sup>70</sup></li> </ul> </li> </ul>

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
Barnes 2015 <sup>8</sup>	<p>Objective: compare the effectiveness and adverse effects of migraine prophylactic medications for <u>children</u></p> <p>Searched Pubmed, Embase, CENTRAL through May 18, 2014</p> <p>Considered RCTs of adults with a history of migraine for at least 4 weeks</p>	<p>Author's classify the following drugs by "Unknown effectiveness" since evidence is weak and largely inconclusive: beta-blockers, flunarizine, pizotifen, and topiramate.</p> <ul style="list-style-type: none"> <li>• Topiramate may be useful but evidence is limited. Authors concluded that it is unknown whether efficacy of topiramate differs from propranolol since evidence from 2 RCTs was inconsistent.</li> <li>• Authors found SR by El Chammas et al<sup>72</sup> of 3 RCTs concluded no significant difference between propranolol and placebo; there were no studies for timolol vs. placebo</li> </ul> <p><b>Clinical guidance:</b></p> <ul style="list-style-type: none"> <li>• Authors state that it is reasonable to try beta-blockers considering their safety profile in otherwise healthy patients; however, there is a paucity of data on their efficacy. Topiramate is potentially beneficial for migraine prophylaxis, however, evidence is limited.</li> <li>• Authors comment that prophylactic agents should be avoided if possible. However, if initiated, response should be evaluated around 3 months of use. If there is no improvement at that time, the agent should be discontinued and an alternative considered. There should also be an annual trial of discontinuation of an agent with apparent benefit to see if the patient can do without prophylaxis at that later point.</li> </ul>
Lind 2013 <sup>59</sup>	<p>Objective: review comparative effectiveness and tolerability of valproate in <u>adults</u> for migraine prevention</p> <p>Searched Medline, Embase, CENTRAL, and the journals <i>Headache</i> and <i>Cephalgia</i> up to January 2013</p> <p>Considered controlled trials of valproate taken regularly to reduce migraine attack frequency, or to improve migraine related quality of life</p>	<p>Authors identified 1 randomized cross-over trial for <b>divalproex vs. propranolol</b> (Kaniecki et al): There was insufficient data for Lind et al to calculate their objective outcome measure, mean difference in headache frequency. The reported results showed no significant difference between treatments in the proportion of responders</p> <p>No other head-to-head studies comparing agents in Table 1 of our report were identified.</p>

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
Lind 2013 <sup>67</sup>	<p>Objective: review comparative effectiveness and tolerability of topiramate in <u>adults</u> for migraine prevention</p> <p>Searched Medline, Embase, CENTRAL, and the journals <i>Headache</i> and <i>Cephalalgia</i> up to January 2013</p> <p>Considered controlled trials of topiramate taken regularly.</p>	<p><b>Topiramate vs. propranolol</b> (2 RCTs; Ashtari 2008 and Diener 2004). Pooled results from these two trials did not indicate a significant difference between treatment with topiramate or propranolol with respect to headache frequency.</p> <ul style="list-style-type: none"> <li>Ashtari et al (N=60) compared topiramate 50 mg vs. propranolol 80 mg. There was no significant difference in <u>mean headache frequency</u> during treatment</li> <li>Diener et al (N=282) compared propranolol 160 mg versus either topiramate 200 mg or 100 mg; there was also a placebo arm. There was no significant difference in the change of headache frequency from baseline or the proportion of responders in topiramate 100 mg and propranolol arms.</li> </ul>
Shamliyan 2013 <sup>73</sup>	<p>Objective: review comparative effectiveness and safety of preventive medications for <u>children</u> with episodic or chronic migraine</p> <p>Searched Medline and CENTRAL up to May 2012</p> <p>Considered RCTs to evaluate treatment benefits, and both RCTs and observational studies to evaluate treatment harms.</p>	<ul style="list-style-type: none"> <li>“Limited evidence from individual RCTs suggested no differences in migraine prevention with examined drugs including propranolol, valproate, and topiramate.”</li> <li>Authors found 3 head-to-head studies that involved sodium valproate comparisons only. Authors did not find the 2 RCTs with propranolol vs. topiramate found by Barnes et al 2015.</li> </ul>
Shamliyan 2013 <sup>14</sup>	<p>Objective: compare the effectiveness of migraine preventive medications for <u>adults</u> with episodic or chronic migraine</p> <p>Searched Medline, CENTRAL, SCIRUS up to May 2012</p> <p>To evaluate drug effectiveness RCTs were considered; to assess adverse effects and treatment discontinuation due to adverse effects, RCTs and nonrandomized studies were considered</p>	<p><b>Chronic Migraine:</b> authors found no significant differences between OBTA and topiramate with respect to migraine prevention or improvement in migraine disability assessment (authors do not have in-text citations to studies)</p> <p>No differences were found between DIV vs. OBTA in terms of migraine prevention, migraine-related disability, or quality of life. (authors do not have in-text citations to studies)</p> <p><b>Episodic Migraine:</b></p> <ul style="list-style-type: none"> <li>No difference in responder rates (at least a 50% in headache frequency) found between propranolol versus timolol. (studies ranked as low quality evidence)</li> </ul>
Shamliyan 2013 <sup>71</sup>	<p>Objective: compare the effectiveness of migraine preventive medications for <u>adults</u> with episodic migraine</p>	<ul style="list-style-type: none"> <li>No difference in responder rates found between propranolol versus timolol.</li> </ul>

Table 1. Systematic Reviews

Study lead author, year	Methods	Results
	<p>Searched Medline, CENTRAL, FDA website and WHO clinical trials registry up to May 2012</p> <p>Considered RCTs reporting on quality of life, or responder rates (with responder defined of having at least a 50% reduction in monthly migraine frequency)</p>	
<p>El Chammas 2013<sup>72</sup></p>	<p>Objective: to assess the effectiveness of prophylactic headache treatment in <u>children and adolescents</u>. Note that authors selected studies addressing episodic migraine or chronic daily headache</p> <p>Searched Pubmed, Embase, and CENTRAL up to August 11, 2012</p> <p>Considered RCTs in children and adolescent evaluating the efficacy migraine prophylaxis for the reduction of headache frequency or severity</p>	<ul style="list-style-type: none"> <li>No head-to-head studies between products in Table 1 of this report were found</li> </ul>

Abbreviations: AEs, adverse events; CENTRAL, Cochrane Central Register of Controlled Trials; CGRP, calcitonin gene-related peptide; DIV, divalproex sodium; DR, delayed release; MA, meta-analysis; mAbs, monoclonal antibodies; MIDAS, Migraine; Disability Assessment; NSD, no significant difference, OR, odds ratio; PRO, propranolol; RCT, randomized controlled trial; TIM, timolol; TOP, topiramate