**Inclusion Criteria**
- ≥ 6 years with migraine or headache

**Exclusion Criteria**
- Age < 6 years, abnormal neurologic exam, intracranial shunt, fever, malignancy, closed head injury/truma within 24 hours, seizure, signs of increased ICP, sudden-onset headache reaching maximum intensity within 5 minutes

**Signs of Cushing Triad**
- Bradycardia, hypertension, abnormal breathing pattern
- Notify ED attending if present

**Clinical Warning Signs**
- GCS Score ≤ 13
- Anisocoria (unequal pupil size)
- Abnormal neurological exam
- Fever or meningeal signs
- Chronic/progressive headache, morning headaches, or headache waking from sleep

**Begin Clinical Assessment**
- Complete pain assessment
- **Physical exam with complete neurologic exam** (attempt fundoscopic exam when possible)
- Initiate headache care and print patient education

**Evaluate for Cushing’s Triad and clinical warning signs**

**Urgent Care Transfer Criteria**
- Patients unable to tolerate PO
- Persistent HA after dose of IN Sumatriptan and oral rehydration
- Administer dose of IN Sumatriptan before transferring to ED
  - "Transfer via POV unless otherwise indicated"

**Pain Assessment**
- **Pain Assessment Tool – English**
- **Pain Assessment Tool – Spanish**

**Definition of Improvements**
- Significant (≥ 2 points) pain score reduction
- Family or patient reports improvement in headache and/or pain

**Differential Diagnosis**
- Stroke or hemorrhage
- Intracranial mass
- Vascular malformation
- Shunt Malfunction
- Meningitis/encephalitis
- Trauma/concussion

**Migraine v5.0: General Assessment**

**PHASE I: ED**

**Print Patient Education**
- **Headache Log**
- **Headache Help For Your Child or Teen**

**Nursing Headache Care and Education**
- Dim lights
- Oral rehydration if tolerating PO
- Heat or ice packs
- Decrease stimulation (recommend no electronics)

**0-10 SCALE for children over age 7**

On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, what number are you feeling right now?

<table>
<thead>
<tr>
<th>No pain</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10 Worst pain</th>
</tr>
</thead>
</table>

**Faces PAIN SCALE - REVISED (FPS-R) for children over age 3**

Point to the face that shows how much you hurt.

These faces show how much something can hurt. The left-most face shows no pain. The faces show more and more pain up to the right-most face – it shows very much pain.

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For questions concerning this pathway, contact: migraine@seattlechildrens.org

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Last Updated: April 2022
Next Expected Revision: October 2021
**PHASE I: ED**

**Assess if combination therapy is indicated:**
Are any of the below true?
- Patient has already taken Ibuprofen or a triptan for this headache?
- Patient has severe pain (i.e., pain score ≥7)?
- Patient vomiting/not tolerating PO?

**Definition of HA Improvement**
- Significant (≥ 2 points) pain score reduction
- Family or patient reports improvement in headache and/or pain

**Combination Therapy Recommended**
- **IN Sumatriptan** (if greater than 2 hours since last dose, max 2 dose in 24 hours)

**PAUSE and reassess pain** (~30 min), if improved hold IV therapies. If persistent, place PIV and continue with:
- **NS bolus**
- **Prochlorperazine IV**
- **Diphenhydramine IV**
- **Ketorolac** (if > 6 hours since last NSAID dose)

**Reassess 45 minutes**
- Improved
- Significant HA persists

**IV Magnesium Sulfate**
- **2nd NS bolus**

**Reassess 45 minutes**
- Improved
- Significant HA persists

If 12 years and older, may give IV valproic acid initial dose and reassess in 30-60 minutes

**If no improvement, consider alternative diagnosis**

**For children not improving on migraine pathway, consider alternative diagnosis and neurology consult**

**Administer**
- **Ibuprofen**
- Oral rehydration
- **PO caffeine**

**Discharge Bundle**
- Follow-up with PCP
- Follow-up with neuro if consulted in ED

If received Sumatriptan in the ED, prescribe:
- 3 doses Sumatriptan (PO for home)

**Significant HA persists**

**Last Updated: April 2022**
**Next Expected Revision: October 2021**
### Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye Opening Response</th>
<th>Spontaneous--open with blinking at baseline</th>
<th>4 points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Opens to verbal command, speech, or shout</td>
<td>3 points</td>
</tr>
<tr>
<td></td>
<td>Opens to pain, not applied to face</td>
<td>2 points</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1 point</td>
</tr>
<tr>
<td>Verbal Response</td>
<td>Oriented</td>
<td>5 points</td>
</tr>
<tr>
<td></td>
<td>Confused conversation, but able to answer questions</td>
<td>4 points</td>
</tr>
<tr>
<td></td>
<td>Inappropriate responses, words discernible</td>
<td>3 points</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible speech</td>
<td>2 points</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1 point</td>
</tr>
<tr>
<td>Motor Response</td>
<td>Obeys commands for movement</td>
<td>6 points</td>
</tr>
<tr>
<td></td>
<td>Purposeful movement to painful stimulus</td>
<td>5 points</td>
</tr>
<tr>
<td></td>
<td>Withdraws from pain</td>
<td>4 points</td>
</tr>
<tr>
<td></td>
<td>Abnormal (spastic) flexion, decorticate posture</td>
<td>3 points</td>
</tr>
<tr>
<td></td>
<td>Extensor (rigid) response, decerebrate posture</td>
<td>2 points</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1 point</td>
</tr>
</tbody>
</table>

**Verbal response criteria for children under 5 years.**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>2 to 5 years</th>
<th>0 to 23 Months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Appropriate words or phrases</td>
<td>Smiles or coos appropriately</td>
</tr>
<tr>
<td>4</td>
<td>Inappropriate words</td>
<td>Cries and consolable</td>
</tr>
<tr>
<td>3</td>
<td>Persistent cries and/or screams</td>
<td>Persistent inappropriate crying &amp;/or screaming</td>
</tr>
<tr>
<td>2</td>
<td>Grunts</td>
<td>Grunts or is agitated or restless</td>
</tr>
<tr>
<td>1</td>
<td>No response</td>
<td>No response</td>
</tr>
</tbody>
</table>
The Glasgow Coma Scale (GCS) is an objective measurement, readily available, and is not dependent on the history of illness. The score is a sum of the best eye, verbal and motor response as listed in the table.

Patients with a GCS score of < 13 should be excluded from the migraine pathway an extended differential diagnosis should be considered.

<table>
<thead>
<tr>
<th>Eyes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Opens Eyes Spontaneously</td>
</tr>
<tr>
<td>3</td>
<td>Opens Eyes in Response to Voice</td>
</tr>
<tr>
<td>2</td>
<td>Opens Eyes in Response to Painful Stimuli</td>
</tr>
<tr>
<td>1</td>
<td>Does Not Open Eyes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Oriented, Converses Normally</td>
</tr>
<tr>
<td>4</td>
<td>Confused, Disoriented</td>
</tr>
<tr>
<td>3</td>
<td>Utters Inappropriate Words</td>
</tr>
<tr>
<td>2</td>
<td>Incomprehensible Sounds</td>
</tr>
<tr>
<td>1</td>
<td>Makes No Sounds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Obeys Commands</td>
</tr>
<tr>
<td>5</td>
<td>Localizes Painful Stimuli</td>
</tr>
<tr>
<td>4</td>
<td>Flexion / Withdrawal to Painful Stimuli</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal Flexion to Painful Stimuli (Decorticate)</td>
</tr>
<tr>
<td>2</td>
<td>Extension to Painful Stimuli (Decerebrate)</td>
</tr>
<tr>
<td>1</td>
<td>Makes No Movements</td>
</tr>
</tbody>
</table>
Differential Diagnosis: Causes of Intracranial Hypertension

- Traumatic brain injury/intracranial hemorrhage
- Subdural, epidural, or intraparenchymal hemorrhage
- Ruptured aneurysm
- Diffuse axonal injury
- Arteriovenous malformation or other vascular anomalies
- Central nervous system infections (e.g. encephalitis, meningitis, abscess)
- Ischemic stroke
- Neoplasm
- Vasculitis
- Hydrocephalus or intracranial shunt malfunction
- Idiopathic intracranial hypertension (pseudotumor cerebri)
- Idiopathic
Cushing Triad and Clinical Warning Signs

- **Cushing’s Triad:** hypertension, bradycardia, and abnormal respiration; it is a late sign of brainstem compression and suggests impending herniation.

- **Clinical warning signs** that warrant further investigation for secondary headache:
  - Preschool age
  - Seizure
  -Abrupt alteration in mental status or respiratory effort
  - Focal neurologic deficit
  - Nuchal rigidity or meningismus
  - First/worst headache with sudden “thunderclap” onset
  - Progressively increasing severity or frequency
  - Sleep arousal from headache; exclusive early morning or late night occurrence
  - Severe vomiting, particularly in the early morning
  - Association with straining during Valsalva
  - Poor response to ongoing therapy
  - High-risk populations (sickle cell disease, immunodeficiency, malignancy, coagulopathy, pregnancy, neurocutaneous syndromes, congenital heart disease, or recent head trauma)
  - Persistent vital sign derangement (fever, hypertension with bradycardia)
  - Petechial rash or lesions associated with neurocutaneous disease (ash-leaf spots or café au lait spots)

A physical exam should be done with special attention to vital signs, pupillary response, reflexes, focal deficit, and baseline level of consciousness.

For most primary headaches, including migraines, the physical exam will be normal (Conicella 2008).

The exam should include at least the following evaluations:

- Assessment of patient’s mental status
- Ophthalmological examination to include pupillary symmetry and reactivity, optic fundi, visual fields, and ocular motility
- Cranial nerve examination to include corneal reflexes, facial sensation, and facial symmetry
- Symmetry of muscle tone, strength (may be as subtle as arm or leg drift), or deep tendon reflexes
- Sensation
- Plantar responses
- Gait, arm and leg coordination
Diagnostic Considerations

- Routine imaging is not recommended (Conicella 2008, Beithon 2013)

- The diagnosis of migraine is a clinical diagnosis
  - “Additional testing in patients without atypical symptoms or an abnormal neurologic examination is unlikely to be helpful” (Conicella 2008, Beithon 2013)
  - For most migraines, the physical exam will be normal (Conicella 2008)

- A thorough history and physical examination should identify patients who require further diagnostic testing (Conicella 2008, Beithon 2013)
  - Further investigation for secondary headache causes should be considered for patients meeting exclusion criteria or those with atypical symptoms, clinical warning signs on HPI or family history, an abnormal neurologic examination, GCS of 13 or less, abnormal vital signs, or for children that are not improving on the migraine pathway

For children not improving on migraine pathway, consider an alternative diagnosis
Medication Use: Ibuprofen or Ketorolac

Several high quality guidelines and systematic reviews demonstrate the benefit of ibuprofen in the management of pediatric headaches

• Ibuprofen 10mg/kg is effective for acute migraine or benign primary headache [LOE: ⭐⭐⭐⭐ High Quality (Patniyot 2016, Bonfert 2013, AAN practice parameter Winner 2015)]
  • Ibuprofen is superior to acetaminophen in having completely aborted migraine after 2 hours [Bonfert 2013, NICE guideline, AAN practice parameter]

• Combining an NSAID with a triptan exerts greater efficacy than either agent alone [LOE: ⭐⭐⭐⭐ (Patniyot 2016, Bonfert 2013, Winner 2015)]

• Consider IV Ketorolac in patients that are not tolerating PO
  • There is no evidence that IV Ketorolac is superior to Ibuprofen (Patniyot 2016)
Medication Use: Sumatriptan

- Use intranasal sumatriptan as a migraine-specific agent in patients whose headaches respond poorly to nonsteroidal anti-inflammatory drugs. In patients naïve to triptans, these are the first-line option next to analgesics in the ED. [NICE guideline 2013; Bonfert 2013; Barnes 2015; 2004 AAN Practice parameter]

- Several high quality guidelines and systematic review demonstrate benefit with use of sumatriptan in patients 12 years of age and older [NICE guideline 2013; Bonfert 2013; Barnes 2015]

- The American Academy of Neurology practice parameter on the pharmacologic treatment of migraine headache in children and adolescents recommends the use of intranasal sumatriptan as a migraine-specific agent in patients whose headache respond poorly to NSAIDS or acetaminophen [LOE: Guideline/High Quality (Ref ID 68, Ref ID 361)]

- There is limited evidence for patients < 12 years of age. However, based on review of pediatric consensus statements and expert opinion, use of triptans is also recommended in patients 6-11 years of age
Triptan Contraindications

- Triptans are vascular serotonin 5-HT1 receptor agonists, producing vasoconstriction

- Triptans are contraindicated in patients with a history of organ transplant, stroke, cardiovascular disease or peripheral vascular syndromes (e.g. stroke, TIA, ischemic bowel disease), severe hepatic impairment, patients with signs or symptoms of ischemic heart disease, MI, uncontrolled hypertension, concomitant use of ergotamine derivatives (within last 24 hours), vasoconstrictive drugs, methysergide, or MAO inhibitors, use of MAO inhibitors within past 2 weeks, management of hemiplegic or basilar migraine

- They may not be used within 24 hours of ergot preparations

Medication Use: Prochlorperazine

- Consider an antiemetic (prochlorperazine) in addition to other acute treatment for migraine even in the absence of nausea and vomiting [(NICE guideline 2013) (Patniyot 2016)]

- “The combination of IV prochlorperazine and ketorolac may be more effective than each agent alone” (Patniyot 2016)

- A prospective randomized, double-blind study trial of children ages 5-17 years presenting to the ED with migraine concluded that intravenous prochlorperazine is more effective than intravenous ketorolac (Brousseau 2004)

- Side effects of prochlorperazine include extrapyramidal symptoms such as akathisia and dystonic reactions, which can be treated with antihistamines

NOTE: All medications in this class have the potential to prolong the QTc

Return to General Assessment

Return to ED Management
Co-administration of diphenhydramine is recommended when treating acute migraine with a prochlorperazine to prevent extrapyramidal side effects [LOE: Expert Opinion/Low Quality Evidence ☆☆☆☆ (Patniyot 2016, Leung 2013)]

“Based on the available studies, the potential benefits outweigh the risks of using diphenhydramine with phenothiazines (prochlorperazine) to prevent potential extrapyramidal side effects” (Patniyot 2016)

Side effects of prochlorperazine include extrapyramidal symptoms such as akathisia and dystonic reactions, which can be treated with antihistaminines; co-administration of diphenhydramine is recommended when treating acute migraine with prochlorperazine
Combination Management

- Offer combination therapy with a triptan and an NSAID, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events [LOE: ★☆★☆☆☆ (NICE guideline 2013, Leung 2013, Winner 2015, Bonfert 2013)]

- Consider an anti-emetic (prochlorperazine) in addition to other acute treatment for migraine even in the absence of nausea and vomiting [LOE: ★☆★☆☆☆ (NICE guideline 2013; ref ID 812) (Patniyot 2016; ref ID 815)]

- “The combination of IV prochlorperazine and ketorolac may be more effective than each agent alone” (NICE guideline 2013, Patniyot 2016)
- Combining an NSAID with a triptan exerts greater efficacy than either agent alone (Patniyot 2016, Bonfert 2013, Winner 2015)
- Co-administration of diphenhydramine is recommended when treating acute migraine with a prochlorperazine to prevent extrapyramidal side effects (Patniyot 2016, Leung 2013)
Acute Migraine Management: Opioids

- “Do not offer opioids for the acute treatment of migraine” [LOE: Expert Opinion (NICE guideline 2013; ref ID 812. Patniyot 2016)]

- “There are no studies evaluating opioids for use in acute treatment of pediatric migraine. There is concern that opioids facilitate sensitization of the central nervous system to pain, and they are implicated in the progression of episodic to chronic migraine in adults” (Patniyot 2016)

- Opioids are not part of the American Academy of Neurology (AAN) practice parameter for pediatric pharmacologic treatment of migraine headache (2004 guideline)
• Offer oral caffeine as adjuvant therapy for patients tolerating PO [LOE: Expert Opinion (American Headache Society Headache Toolbox 2012 -Ref ID 818)]

NOTE: Before ordering, consider the time of day to prevent potential sleep disruption
Nursing Headache Care includes dimming the lights, providing heat or ice packs, and decreasing stimulation (recommend no electronics/TV use in the ED). Oral rehydration should be initiated if patient is tolerating PO.

The Headache Log and Patient Education Packet should be printed for parents/patient (links provided in pathway and available on CHILD).

Psychological treatments, principally relaxation and cognitive behavioral therapies are effective adjunct treatments of childhood headache (Beithon 2013).
For migraines refractory to medications listed above, administer IV magnesium [LOE: Expert Opinion/Very low quality (NICE guideline 2013; ref ID 812) (Patniyot 2016; ref ID 815)]

- Magnesium oral supplements have been studied in pediatric migraine prevention and found to lower severity (Wang 2004)
- There is one retrospective pediatric chart review study evaluating IV magnesium for acute treatment for headaches (Gertsch 2014)
- The authors reviewed 20 patients aged 13 to 18-years old who received IV magnesium sulfate based of 30 mg/kg with a maximum dose of 2000 mg. Pain improvement was defined as a decrease in perceived pain from severe to moderate, or a decrease of 3 points or more on a 10-point pain rating scale. Of the 7 (35%) patients who showed a favorable response, 5 of them were in status migrainosus, 1 was diagnosed with migraine, and 1 with tension type headache

NOTE: Potential side effects of magnesium include hypotension, flushing, and burning.
Preferred Route of Administration

• Offer intranasal (IN) sumatriptan in preference to an oral triptan [LOE: ★★★★★ NICE guideline 2013, AAN 2004 AAN Practice parameter]

• “For people in whom oral preparations (or nasal preparations) for the acute treatment of migraine are ineffective or not tolerated, offer a non-oral preparation of prochlorperazine and a non-oral NSAID (ketorolac). Consider adding a non-oral NSAID or triptan if these have not been tried.” [Expert Opinion/Guideline]

• There is no evidence to support a benefit of IV hydration in comparison to oral rehydration in a patient tolerating PO
Acute Management: Hydration

• Initiate either oral or IV rehydration [LOE: Expert Opinion/ Low Quality]: Patniyot 2016)
  • IV: 20mL/kg normal saline bolus (max 1L/bolus)
  • PO fluid replacement: 24 to 32 ounces at onset

• There is no evidence to support a benefit of IV hydration in comparison to oral rehydration in a patient tolerating PO

• There is only one single-blind, randomized parallel-group trial assessing efficacy of a 10 mL/kg IV normal saline bolus in patients between the ages of 5 and 17 years presenting to the ED with migraine (Richer 2014); no statistical difference between the two groups was found. However, on multivariate analysis, their findings suggest that “fluids do have a beneficial effect for some, perhaps in those with associated symptoms of nausea and emesis who may be more susceptible to the effects of dehydration” (Patniyot 2016)
Indications for Neurology Consultation

• Consider consultation with neurology if a significant headache persists despite treatment with IV hydration and administration of an NSAID, triptan, prochlorperazine, and IV Magnesium (unless contraindicated)

• Do not administer DHE or Valproic acid without neurology consultation

• Consult neurology service for patients followed by SCH outpatient neurology for management of chronic migraines that present to the ED for management of a migraine refractory to home regimen

• There are no clear guidelines for inpatient admission criteria
  • Neurology should be consulted prior to admission for status migranosis (Expert Opinion)
  • “Inpatient admission should be avoided. It includes many downsides including significant sleep disruption and likely exacerbations of photophobia and phonophobia. Furthermore, admitting the patient provides no guarantee that the headache will resolve.” [LOE: Expert Opinion (Bonfert 2013)]

For children not improving on migraine pathway, consider an alternative diagnosis.
Admission Criteria

• There are no clear guidelines for inpatient admission criteria

• Neurology should be consulted prior to admission for status migranosis (Expert Opinion)

• “Inpatient admission should be avoided. It includes many downsides including significant sleep disruption and likely exacerbations of photophobia and phonophobia. Furthermore, admitting the patient provides no guarantee that the headache will resolve.” [LOE: Expert Opinion (Bonfert 2013)]

For children not improving on migraine pathway, consider an alternative diagnosis
• Consider prescribing at least 1 rescue dose of oral sumatriptan if the medication was administered in the ED without adverse effect
  • Rx for PO Sumatriptan preferred because IN formulation of Sumatriptan is usually not approved by insurance

• The “Headache Log” and “Patient Education Packet” should be printed from pathway link and reviewed with patient/family

• There are no clear guidelines regarding indication to prescribe abortive migraine medications at time of discharge from the ED

• “At discharge, patients must be provided with at least one rescue treatment option that is appropriate for their level of migraine severity” [LOE: Expert Opinion (Ref ID 68)]
• “By virtue of presenting at the ED, these children have demonstrated that they are capable of experiencing at least moderately severe migraine attacks, and hence receiving only nonspecific analgesics for home rescue options may not be appropriate.” (Ref ID 68)
Urgent Care Transfer Recommendations

• Patients unable to tolerate PO
  o Administer dose of IN Sumatriptan before transferring to ED
• Persistent HA after dose of IN Sumatriptan and oral rehydration
• Transfer via POV unless otherwise indicated
Approved by the CSW Migraine team for October 12, 2016 go-live

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This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94.):

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Guideline – Recommendation is from a published guideline that used methodology deemed acceptable by the team.

Expert Opinion – Our expert opinion is based on available evidence that does not meet GRADE criteria (for example, case-control studies).

**Quality of Evidence:**
- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Low quality
- 🌟🌟 Low quality
- 🌟🌟🌟🌟 Very low quality

Guideline
Expert Opinion
**Summary of Version Changes**

- **Version 1.0 (10/12/2016):** Go live.
- **Version 2.0 (6/16/2017):** Changes include
  - Urgent care transfer criteria
  - Additional caution regarding bradycardia, hypertension, altered mental status
  - Specification under “normal neurologic exam” for routine funduscopic exam
- **Version 3.0 (3/16/2018):** Added the following verbiage to Phase I: ED, Clinical Warning Signs box “Chronic/progressive headache, morning headaches, or headache waking from sleep.”
- **Version 4.0 (3/2/2020):** Modified ED Management phase to clarify when combination therapy is indicated for migraine management.
- **Version 5.0 (4/19/2022):** Added IV valproic acid for management of refractory migraine in children 12 and older and adults.
Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian in September, 2015. 814 articles were identified through database searching, which were reviewed by title and abstract.

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535
Included Studies and Additional References


