The Foundation for Medical Practice Education
Practice-Based Learning for Family Physicians

Headaches In Adults

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INTRODUCTION

Headaches are one of the most frequent reasons for patients to visit their primary care practitioner. Challenges with diagnosis are common due to symptoms and features that overlap in different headache subtypes and patients who meet criteria for multiple headache diagnoses. This can interfere with the ability to identify secondary headaches and adequately manage headache symptoms.

OBJECTIVES

This module will enable clinicians to:

- Apply best evidence to assess and manage both episodic and chronic migraine headaches, using patient-specific nonpharmacologic strategies, and pharmacologic acute/abortive and prophylactic therapy.
- Identify and manage medication-overuse headaches.
- Assess and investigate new-onset headaches, including secondary headache presentations, with a focus on identifying red flags.

CASES

Case 1: Sofie, female, age 27

Sofie has been a patient of yours for the last 5 years and presents to your community office with recurrent headaches for the last 2 to 3 years. Her headaches initially occurred once every few months but now have increased in frequency and occur monthly, prompting today's visit. She usually takes ibuprofen to control them. She does not describe any auras, flashing lights, or visual changes preceding her headaches. She needs to lie down in a cool dark room with the curtains drawn. She describes her headaches as right-sided and pulsatile with sensitivity to light. She has mild nausea but no vomiting. The headaches typically occur around her menstrual period 2 to 3 days in a row and last for 5 to 6 hours before gradually improving. Her menses are regular (every 28–32 days). She takes no other medications and is not on an oral contraceptive pill.

What further information would be helpful?

Part Two

Sofie's headaches do not wake her at night but have escalated in frequency and intensity, although the quality of her headaches remains unchanged. The increased intensity has become more disabling, and she has had to miss work as an elementary school teacher resulting in the use of her sick days more often each month. She currently takes no medication other than ibuprofen occasionally at the onset of her headache, uses no other substances, and is a non-smoker. She is currently using condoms for contraception with her long-term partner. She does not think there are triggers other than her menses, but she has not really been tracking. Sofie does not describe any focal neurologic symptoms. There is no family history of migraines. There has been no clear precipitating event or stressors prior to this change.

Sofie's BP is 117/82. She has a normal fundoscopic exam. Her head and neck exams are normal. A neurological exam (including cranial nerves, motor/sensory, cerebellar, and gait testing) is normal. Brief screens for depression and anxiety are both negative.

What would be your approach to Sofie?

Part Three—Three months later

Sofie returns with the headache diary given to her at her last appointment. It shows that her headaches generally start 1 to 3 days prior to the first day of her menstrual cycle. They continue to be right-sided, with sensitivity to light and mild nausea. There are no other obvious triggers that she can identify. She does not describe any insomnia. She rates her headache intensity as 6 to 7/10. There are no preceding symptoms. She has

taken her frovatriptan (2.5 mg PO) 4 times per month (prescribed at her last appointment) with moderate relief, but her headaches remain functionally limiting. She would like to discuss how to prevent her headaches.

How would you respond to Sofie?

What would you recommend to Sofie if she had questions about contraceptive options?

What would be your approach if Sofie presented with an acute, severe migraine headache unresponsive to her usual abortive regimen?

Case 2: Nora, female, age 45

Nora is new to your practice and booked a same-day appointment at your primary care office complaining of a bad "migraine." This morning she woke up with her typical migraine headache in the left temple region. She describes this as a pressure, pulsing, pounding headache that has now started to dissipate after 3 to 4 hours. It is associated with nausea, vomiting, and photophobia. She does not describe any aura. The headache is usually relieved with zolmitriptan but it was not effective this morning.

She was diagnosed in adolescence with migraine headaches which generally recurred twice a month. These headaches were manageable with zolmitriptan and acetaminophen taken at the onset of the headache. She takes propranolol (20 mg TID) for migraine prevention that was started by her previous primary care clinician 4 years ago.

Nora is also concerned about an increase in her headache frequency. About 6 months ago, her headaches started to recur multiple times per week (5 of 7 days), prompting the increased use of her abortive medication. She started a new administrative job around the time that her headaches intensified. Although she enjoys the change, the hours are longer and she is spending more time on screens. She has also had more trouble falling asleep at night. She states she now takes zolmitriptan most days of the week along with 1 to 2 tablets (400 mg) daily of acetaminophen or ibuprofen.

She has a previous history of breast cancer (3 years ago), treated with radiation. There has been no evidence of recurrence. She was diagnosed with anxiety and takes venlafaxine XL (150 mg) once daily. There is no family history of migraine headache and no history of hypertension. She is a non-smoker and does not drink alcohol.

What further information would be helpful?

Part Two

Other than an increase in frequency, Nora's headaches have been very similar in terms of severity and location. They do not wake her up at night. She does not describe any neurologic findings, visual changes, diplopia, or motor or sensory deficits. She can walk with a normal gait and has no issues with balance. She has not had any fevers, chills, or weight loss. There is no history of trauma or fall.

Her neurologic exam is normal. Her visual fields are intact. Fundoscopic exam is normal. Cranial nerves are generally unremarkable. There is no tenderness over the sinuses, temporomandibular joint (TMJ), or temporal artery region. Motor and sensory exams are normal, and she can walk tandem gait. There is no truncal ataxia. BP is 125/65.

Considering her history of breast cancer and increased headache frequency, a CT scan with contrast was ordered. Results are normal with no evidence of metastatic disease.

What would be your approach for Nora?

Case 3: Bayan, female, age 53

Bayan presents to your urgent care centre with a new 1-week history of bilateral temporal pain. She reports her headache is steady throughout the day and describes it as a "heavy head." She currently lives with her husband and sister-in-law, and has recently moved to your community but has not yet found a primary care clinician.

What further information would you need?

Part Two

Bayan has had the occasional stress-related headache in the past, but never anything like this. With this headache, she occasionally experiences shooting pain into both temples which she describes as a severity of 10 out of 10. Her headache is bilateral but worse on the left side with pain in the temporal area, ear, and jaw. She also reports that her upper jaw hurts on both sides, especially when chewing. She has had posterior neck pain and scalp tenderness when brushing her hair over the last week.

Bayan does not describe any further neurologic deficits or symptoms—flashing lights or visual changes, photophobia, nausea, vomiting, upper respiratory tract symptoms, or fever. There is no history of trauma or fall. She does report increased fatigue over the last 2 to 3 weeks. She describes pain in her right shoulder and left hip (present for months), but no significant morning stiffness.

Her past medical history includes bipolar disorder, anxiety, fibromyalgia, irritable bowel syndrome, osteoporosis, and dyslipidemia. Her medications include quetiapine (300 mg PO at bedtime), rosuvastatin (10 mg PO daily), duloxetine (60 mg PO daily), omeprazole (20 mg PO daily), and denosumab (60 mg subcutaneous every 6 months).

On exam she has pain on palpation of the left temple and pain over her left mastoid. Her visual acuity and visual fields are normal. Cranial nerve exam is unremarkable. She has pain on palpation of her upper cervical spine and mildly restricted movement of her neck laterally to the left due to pain. She has no tenderness over the sinuses but does endorse pain over the left TMJ and over the left temporal region. She has good temporal artery pulses on both sides. Motor exam reveals normal muscle tone, power, coordination, and gait. Romberg sign is negative, and she can walk tandem gait. There is no truncal ataxia or cerebellar dysmetria. Her BP is 130/85.

What would be your next steps?

INFORMATION SECTION

EPIDEMIOLOGY

1. Headaches are one of the most common reasons for patient visits to primary care in Canada, and account for approximately 20% of all work absences.[1]
   a) Lifetime prevalence of primary headache disorders is 66%: 14 to 16% for migraine, 46 to 78% for tension-type headache, and 0.1 to 0.3% for cluster headache.[1]
   b) Migraines are underdiagnosed and undertreated. It is estimated that at least 2.6 million adult women and 1 million adult men experience migraine in Canada.[1]
   c) Migraine headaches have significant impact on disability, employability, and relationships.[2]

CLASSIFICATION

2. The International Headache Society's International Classification of Headache Disorders, 3rd Edition (ICHD-3) recognizes over 200 headache disorders. Each of these disorders is organized into 3 groups:
   - Primary headache disorders—e.g., migraine, tension, and cluster headaches.
   - Secondary headache disorders which have another underlying causative disorder or condition—e.g., medication-overuse headaches, temporal arteritis, central nervous system pathology.
   - Painful cranial neuropathies, other facial pain, and other headaches.[3,4]

   Note: Given their importance and frequency of presentation in primary care, this module will cover migraine as an exemplar of a primary headache disorder, and medication-overuse headache and temporal arteritis as exemplars of secondary headache disorder. This module will not cover headaches from the painful cranial neuropathies category.

The Centre for Effective Practice Core Neck Tool and Headache Navigator is a useful tool to aid diagnosis and management. You can find it at: https://cep.health/clinical-products/core-neck-tool-and-headache-navigator/	

ASSESSMENT AND DIAGNOSIS

Refer to Appendix 1 for an algorithmic approach to the assessment of headache.

3. Assessment of headache includes elements of headache history (Table 1), physical examination (Info point 4), and patient perspective.[1] The identification of red flags for secondary headaches (Table 2; Appendix 1) will inform the need for referral/additional investigations.

Table 1. Elements of Headache History[3]

Factor	Details
Time	• Headache onset—thunderclap, preceding head or neck trauma, pregnancy, or infections. • Previous attacks—progression of symptoms. • Duration of attacks—limited or continuous. • Days per month with headache. Consider asking "How many days are you headache free?"
Characteristics of pain	• Location—e.g., unilateral, bilateral, any associated neck pain. • Severity and quality. • Headache-associated symptoms—e.g., nausea, vomiting, photophobia, phonophobia conjunctival injection, rhinorrhea, eyelid droop.
Cause	• Relationship of headache attacks to precipitating factors—e.g., stress, posture, cough, exertion, straining, neck movement, jaw pain, substances or their withdrawal, medication overuse. • Menstrual association where relevant. • Other systemic symptoms, such as fever, weight loss, rash, jaw claudication. • Visual changes, neurological or musculoskeletal complaints (polymyalgia rheumatica). • Family history (migraine, glaucoma).
Impact	• Headache severity and effect on function.

4. Physical exam includes:[3,5]
   - BP measurement.
   - Screening neurologic exam:
     - General assessment of mental status.
     - Cranial nerve exam, including fundoscopy for papilledema.
     - Assessment of all 4 limbs for unilateral weakness, reflex asymmetry, sensory changes, and evaluation of coordination in the upper and lower limbs.

  - Assessment of gait, including heel–toe walking (tandem gait).
- Focused neurologic examination if indicated by other neurologic symptoms or signs on screening examination (e.g., lower cranial nerve examination in a patient with dysarthria).
- Neck examination.
- ENT exam if associated complaints.
- TMJ exam if associated jaw complaints.
- Palpation of temporal arteries if suspicion for temporal arteritis.

Table 2. Red Flags Indicating More Urgent Investigation or Management[4,6,7]

Symptoms/Findings	Possible Cause(s)
Migraine-like headache, diplopia, loss of peripheral vision, focal neurological deficits, seizures, risk factors for thrombosis, papilledema. Can be sudden onset.	Cerebral venous sinus thrombosis.
Fever, altered mental state, seizures, focal neurologic deficits, travel history, insect bites, meningismus (meningitis).	Encephalitis, meningitis.
Sudden severe rise of BP, diffuse pain, pulsatile quality, aggravated by physical activity.	Hypertensive headache.
Sudden onset vomiting, focal neurologic deficits, altered mental status.	Intracerebral hemorrhage.
Thunderclap headache, vomiting, syncope, obtundation, meningismus. First occurrence of an exertional headache.	Subarachnoid hemorrhage.
Sleepiness, altered mental status, hemiparesis, loss of retinal venous pulsations, papilledema, trauma history.	Subdural hematoma.
Repeated episodes of short, piercing, or stabbing severe pain on one side of lower face.	Trigeminal neuralgia.
Diffuse headache, dizziness, nausea/vomiting, weakness, and confusion in the context of exposure to carbon monoxide.	Carbon monoxide poisoning.
Unilateral frontal or orbital halos around lights, decreased visual acuity, conjunctival injection, vomiting.	Acute angle-closure glaucoma.
Seizures, vomiting, precipitated by Valsalva manoeuvre, altered mental status (eventual), papilledema, focal neurologic deficits, worse on awakening or awakens patient from sleep.	Tumour or mass.
New-onset temporal headache over age 50, scalp tenderness, jaw claudication, visual changes, history of polymyalgia rheumatica.	Temporal arteritis (Info point 21).

5. MRI (if available) is more sensitive for lesions of the posterior fossa and pituitary and for neoplasms, although CT may be used to rule out an expansive lesion if MRI cannot be obtained.
   a) Include contrast (for both CT and MRI) if there is an abnormal neurological exam; history of cancer, HIV, or immunocompromise; or the headache is exertional or aggravated by the Valsalva manoeuvre.
   b) CT angiography (arch to vertex) is best for thunderclap headache to rule out subarachnoid hemorrhage, arterial dissection, and venous thrombosis, as well as other potential causes of thunderclap headache.[8-10]

6. A headache diary is a valuable tool that eliminates recall bias and helps to identify headache frequency, severity, features, and triggers (Info point 23). Various headache diaries can be accessed online (Table 3).[3]
   a) A headache calendar can be used to support the headache diary. While a headache diary captures the descriptive features of a headache, a calendar notes the timing of episodes and related events (e.g., menstruation, medication intake).[3]
   b) Mobile apps may be more useful for patients to record, track, and analyze their migraine headaches. Two apps that are available for free are the Canadian Migraine Tracker (developed by the Canadian Headache Society) and Migraine Buddy (recommended by Healthline; US based). Refer to Table 3.

Table 3. Online Headache Diaries and Apps

Migraine Canada https://migrainecanada.org/diaries/	
	Institute of Health Economics https://www.ihe.ca/advanced-search/ambassador-headache-diary
Migraine Buddy https://migrainebuddy.com Also available for download on the Apple App Store or Google Play.	

Primary Headaches

7. The diagnosis of primary headaches (Appendix 1) can be completed with information collected from patient history and physical (including neurologic) examinations. Neuroimaging (e.g., CT or MRI of the brain), sinus and cervical spine x-ray scans, or electroencephalograms for routine assessments of headache are not recommended.[1]

Migraine

8. Migraine is the most common headache type in patients seeking medical help for headache.[1] A 2019 retrospective study (n=2,829, age 18+) found that a stronger family history of migraine (i.e., 1 or both parents being diagnosed with migraine) is associated with a lower age at onset (p<0.001), higher frequency and number of medication days (p=0.006), and migraine with aura subtype (p=0.03).[11]

9. The mnemonic POUND is an evidence-based tool for migraine diagnosis:
   - **P**ulsatile quality of headache.
   - **O**ne-day duration (4–72 hours if untreated or unsuccessfully treated).
   - **U**nilateral location.
   - **N**ausea or vomiting.
   - **D**isabling intensity.

   In primary care, there is a 92% probability of migraine in patients with at least 4 of the POUND criteria. This decreases to 64% with 3 criteria.[12] Refer to Table 4 for the added diagnostic criteria for migraine with aura.

10. The ID Migraine screening tool (Appendix 1) is a simpler 3-item screen that asks about the presence of nausea, photophobia, and at least 1 disabling headache in the past 3 months.[13]
    a) This screening tool was first validated in a primary care study (n=451 adults) against the gold standard of neurological assessment. Patients were enrolled if they had 2 or more headaches in the past 3 months, at least 1 of which limited function. If any 2 of these 3 characteristics (nausea, photophobia, at least 1 disabling headache in the past 3 months) were present, sensitivity was 0.81 (95% CI 0.77–0.85) and specificity 0.75 (95% CI 0.64–0.84). In this somewhat selected primary care population (329 were eventually diagnosed with migraine), the 3-item screener was found to have a positive predictive value of 93.3 (95% CI 89.9–95.8) and good test–retest reliability.[13]
    b) A subsequent systematic review/meta-analysis (13 studies, n=5,866) found similar results—pooled sensitivity of 0.84 (95% CI 0.75–0.90) and pooled specificity of 0.76 (95% CI 0.69–0.83).[14]

Table 4. Diagnostic Criteria—Migraine with Aura[4]

Recurrent unilateral, fully reversible visual, sensory, or nervous system symptoms lasting 5–60 minutes, followed by migraine headache symptoms (Info point 9) and:
One or more of the following aura symptoms: • Visual. • Sensory. • Speech and/or language. • Motor. • Brainstem. • Retinal.
Additional aura characteristics—at least 3 of the following: • At least 1 aura symptom spreads gradually over ≥ 5 minutes. • 2 or more aura symptoms occur in succession. • At least 1 aura symptom is unilateral. • At least 1 aura symptom is positive.

11. Visual aura is the most common symptom occurring in over 90% of patients as a zigzag distortion with scintillations (positive symptoms) and/or a gradually enlarging scotomata. Next in frequency are sensory symptoms such as pins and needles (positive symptoms) or numbness. Aura symptoms may be multiple and in succession. Motor symptoms may last up to 72 hours.[4]
    Note: Some patients have aura without headache exclusively. In these cases, particularly in those over age 40 with negative symptoms (i.e., hemianopia, sensory or motor loss), central nervous system pathology must be ruled out.[4]

12. Menstrual migraine is diagnosed when, in at least 2 out of 3 cycles, migraine attacks (with or without aura) occur from 2 days prior to 3 days after the onset of menses. It is estimated to occur in about 60% of women with migraine[4] and relates to a drop in estrogen just prior to menstruation, although exact mechanisms are unclear. Menstrual migraine can be more severe, longer in duration, or treatment refractory compared to migraines that occur at other times of the month.[15-17]

13. Chronic migraine is defined as headache occurring on 15 or more days per month for more than 3 months, where over half have the features of migraine.[4] It is often complicated by:
    - Depression and/or anxiety.
    - Low back and/or neck pain.
    - Medication overuse (Info points 18–20).[3,18]

14. It is often difficult to distinguish between chronic migraine and tension-type headache.
    a) Symptoms of migraine such as nausea or photo/phonophobia may be less apparent when the headache becomes chronic in nature.
    b) Additionally, people with migraines who may be overusing medications commonly experience a reduction in typical migraine symptoms and are misdiagnosed with tension-type headache.[19]

15. Cluster headache is more easily distinguished from migraine as it is characterized by short lasting (15 minutes–3 hours), localized, severe pain. It tends to be periorbital with any or all of the typical associated symptoms—restlessness, ipsilateral watery red eye, miosis and ptosis, and nasal congestion or rhinorrhea. It has a circadian (e.g., an attack at 3 pm then another at 2 am) and seasonal pattern (e.g., fall or spring). Cluster headache is more common in men.[3]

Refractory Migraine

16. Although there has been significant progress in migraine management therapies over the last decade, some patients continue to experience migraines despite optimal treatment. These patients are considered to have refractory migraine. The term refractory migraine has been used to describe "a persistent headache that is difficult to treat or fails to respond to standard and/or aggressive treatment." The term has been used to refer to both unresponsive acute and chronic migraine.[20]

17. There is no universally accepted definition of refractory migraine, but based on a 2020 consensus conference, the European Headache Federation (EHF) describes it in the following way (all of the criteria must be met):
    - Diagnosis of migraine with or without aura, or chronic migraine.
    - Debilitating headache* for at least 8 days per month for at least 6 months.
    - Failure with and/or contraindication to migraine prevention therapies, at appropriate dose and duration (Appendix 3).[21]

    *The EHF defines debilitating headache as headache causing serious impairment to activities of daily living despite use of pain-relief medications taken at beginning of attack, and failure of at least 2 different triptans.[22]

Secondary Headaches

Medication-Overuse Headache

18. The frequent and regular intake of medication to treat acute headache episodes can result in increased headache frequency and eventually lead to chronic headaches. This is called medication-overuse headache (MOH).[23]
    a) Migraine is the underlying primary headache disorder in most patients (80%) with MOH.[24]
    b) The use of triptans, opioids, simple analgesics, and combination analgesics is most often associated with this condition. Opioids should be avoided in managing migraine headaches.[23]
    c) Risk factors for MOH include other types of comorbid pain, more severe migraine symptoms, use of sedatives, progressive increase in acute medications for headache, psychiatric comorbidities (particularly anxiety and depression), and female gender.[23]

19. MOH is suspected if:[1,3,4,25]
    - Recurrent headache attacks—occurring on at least 15 days/month in a patient with a pre-existing headache disorder.
    - Regular overuse for > 3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache.
    - Use of prescription medication on at least 10 days/month, or use of acetaminophen or NSAIDs on at least 15 days/month.

    Note: More severe MOH results from overuse of triptans and opiates compared with NSAIDs and simple analgesics.[3,26]

20. The presence of the following conditions should be evaluated in patients with suspected MOH:
    - Psychiatric comorbidities—depression and anxiety.
    - Psychological and physical drug dependence.
    - Use of inappropriate coping strategies.[1]

Temporal Arteritis

Box 1. Scope

A detailed discussion of the assessment of temporal arteritis is beyond the scope of this module. For a more detailed discussion, refer to the PBLP module Polymyalgia Rheumatica (November 2016) available at https://members.fmpe.org/.

21. Temporal arteritis should be suspected in patients > age 50 with new-onset headache (2/3 of patients) and other symptoms of temporal arteritis—unilateral visual loss (about 20% of patients at onset), scalp tenderness, jaw claudication, and systemic symptoms such as fatigue, night sweats, and weight loss.[5,27,28]
    a) History may include older age, polymyalgia rheumatica (PMR), and female gender.[29]
    b) Physical exam findings may include tenderness along the temporal bone or scalp, reduction/loss of temporal artery pulse or thickening of artery on palpation, papilledema, and decreased strength of proximal muscles (with PMR).[29]

MANAGEMENT

22. The disability of the headache should be evaluated and quantified to inform decisions regarding pain management. The Migraine Disability Assessment (MIDAS) is a 7-item, validated, self-administered questionnaire.[13,30] It can

measure the impact that migraines have on a patient's life (including level of pain and disability) and help to identify optimal treatment. The Headache Under-Response to Treatment (HURT) Questionnaire—an 8-item, self-administered tool—is designed to help assess and improve outcomes.[31] Refer to Table 5 for details on accessing these tools.

Table 5. Management of Headache: Clinical Tools

MIDAS https://headaches.org/wp-content/uploads/2018/02/MIDAS.pdf	
	HURT Questionnaire https://link.springer.com/article/10.1007/s11916-012-0263-1/figures/1

Nonpharmacologic Treatment

23. Common triggers for primary headaches include dehydration, irregular meals or skipped meals, sleep disorders (irregular or too little), stress, lack of exercise, weather changes, hormonal changes, and dietary triggers.[5,32-38] Advise patients to try adjusting any behaviours or other identified triggers that may exacerbate their headache.[5] A headache diary may help to identify these factors (Table 3).
    a) The mnemonic SEEDS (sleep, exercise, eating, headache diary, stress) may be helpful to guide counselling related to triggers and behaviours.[39]
    b) Evidence to support specific nonpharmacologic therapies is outlined in Table 6.

Table 6. Nonpharmacologic Options

Options	Indications/Evidence
Acupuncture	A 2017 Cochrane review found that acupuncture reduced the frequency of episodic migraine by at least 50% compared to usual care—number needed to treat (NNT) = 4 [Moderate Evidence].[41]
Mindfulness-based therapies	A 2018 meta-analysis (10 RCTs, 1 controlled clinical trial, n=315) found that mindfulness meditation improved pain intensity and frequency of migraine and tension-type headache when compared to controls. However, the authors concluded that larger sample sizes and higher quality designs are needed to conclusively determine the role of mindfulness meditation in headache.[42]
Exercise	An umbrella mapping review (18 systematic reviews, 95 original studies, n=9,188)[43] found that: • Aerobic exercise showed a small to moderate clinical effect on pain intensity and medication use in patients with migraine [Low to Very Low Evidence]. • Strength training showed a moderate clinical effect for tension-type headache [Very Low Evidence].
Hydration	While hydration alone has not been shown to provide pain relief, dehydration may exacerbate a primary or secondary headache disorder,[45] and rehydration is important for those who experience nausea and vomiting due to headache pain.[29]
Neuromodulation and biobehavioural therapies	Very limited evidence (small, open label studies) supports the efficacy of transcranial supraorbital and magnetic stimulation for both acute and preventive treatment. Similarly, there is limited evidence for the use of biofeedback, cognitive behavioural therapy (CBT), and relaxation therapy.[46] These options are best reserved for patients who decline, or for those who are intolerant or unresponsive to therapy that has more supporting evidence.

Pharmacologic treatment

Migraine

Acute/Abortive Therapy (Appendix 2)

24. Patients will often take acetaminophen or NSAIDs as a first line of defence against headaches. If NSAIDs are ineffective, medications such as triptans, ergots, or antiemetics can be trialled.[1]

25. All triptans have strong evidence for effectiveness—sumatriptan is the most widely studied. Few head-to-head comparisons have been conducted.[12] A 2015 systematic review/meta-analysis (133 RCTs) of 7 triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) found that:
    - Standard-dose triptans were more effective in relieving migraines (relieved pain within 2 hours in 42–76% of patients) than ergots (38%), NSAIDs (including ASA), and acetaminophen (46–52%).[47] Triptans provided complete pain relief at 2 hours in 18 to 50%.[46]
    - Standard-dose triptans alone were slightly worse than combination therapies (triptan + NSAID or acetaminophen).[47]

    Overall NNTs for the outcome of pain-free at 2 hours in those with moderate to severe pain range from ~8 to 10 for ASA/NSAIDs, 12 for acetaminophen, and ~5 to 6 for oral triptans when taken in recommended doses (Appendix 3).[48]

26. Triptans are equivalent in efficacy and safety and share a common mechanism of action but differ with regards to routes of administration, cost, and pharmacokinetics.[12] The choice will depend on individual patient factors such as cost and convenience (Table 7).

Table 7. Triptans: How to Choose[17]

Patient Factors/Needs	Options
Fastest relief	10–15 minutes for any SC or nasal formulation.
Best efficacy at 2 hours	Likely SC sumatriptan—highest % of the maximum daily dose as the first dose (NNT = 2 at 2 hours versus NNT = 3 for oral/nasal sumatriptan). Lowest efficacy at 2 hours—naratriptan or frovatriptan due to slower onset.
Best tolerability	Naratriptan or frovatriptan—slow onset and lowest % of the maximum daily dose as the first dose results in reduced adverse effects, but may also reduce effectiveness of the first dose.
Vomiting	Any SC, nasal, or rectal suppository formulation, or add antiemetic (e.g., metoclopramide).
Long-lasting attacks/ Menstrual migraine	Naratriptan or frovatriptan (long half-life).
Privacy	Any oral-dissolving tablet since it can be taken without water.
Cost	Lower cost for PO formulations of almotriptan, sumatriptan, zolmitriptan, rizatriptan. Higher cost for SC and nasal formulations.

SC = subcutaneous

27. Patient education about triptan use is important.
    a) Triptans should be used less than 10 times per month to avoid MOH.[26,49] Patients should be monitored for this condition (Info points 18–20).
    b) If a patient generally needs to repeat dosing within 24 hours, taking the maximum dose once is more effective than taking a lower dose twice.[26,49]
    c) Optimal results occur when triptans are taken early in an attack.[26,49]
    d) For migraine with aura, best results are achieved by taking the triptan at the onset of pain rather than the onset of aura, although taking a triptan during a typical aura appears to be safe.[12]

28. Response (or lack of response) to one triptan does not predict a response to another. If the patient is not responding to a specific triptan, try a higher dose, an alternative triptan, or an alternative formulation.[26,49]

29. For acute migraine, combination therapy may be considered.[26,49] A 2016 update[50] of a Cochrane Review (13 RCTs, n≈9,300)[51] found sumatriptan plus naproxen was superior to placebo and to monotherapy with either agent alone. Compared to placebo, the primary outcomes of pain-free and headache relief at 2 hours showed NNT ≈ 3 when baseline pain was mild and NNT ≈ 5 when baseline pain was moderate/severe [High Evidence].
    a) Three studies (n=3,869) compared combination therapy (sumatriptan + naproxen) to monotherapy for moderate to severe pain. Combination therapy was significantly better than monotherapy for headache relief at 2 hours:
        - Relative benefit of combination versus sumatriptan alone: NNT ≈ 10.
        - Relative benefit of combination versus naproxen alone: NNT = 5.5 [Moderate Evidence].
    b) Combination therapy can include triptan (max 9 days/month) +/– NSAID (max 14 days/month) +/– antiemetic.[49]
    c) A meta-analysis (8 RCTs, n=905) found that combining a steroid such as dexamethasone (DMX—dose range: 10–24 mg IV or IM) with standard abortive migraine therapy reduces the risk of migraine recurrence by 30% within the first 72 hours. Studies that used ≥ 15 mg showed a stronger treatment effect. Two of the studies (n=78) included patients who received oral steroid treatment (range: DMX 8 mg once–prednisone 40 mg for 2 days), allowing for a subgroup comparison with those who received parenteral treatment. For the primary outcome of moderate or severe migraine headaches, no significant difference was found between oral administration and parenteral administration of steroids.[52]

30. If acute migraine does not respond to standard treatment, consider referring the patient to an acute care setting where they can receive IV or IM medication (refer to Appendix 2 for medication options).[53,54]

Prophylactic Therapy (Appendix 3)

31. Consider prophylactic therapy for migraines if the patient has any 1 of the following:
    - 6 headache days/month or 3 headache days/month and medications not effective.
    - Risk of MOH.
    - Migraines severe enough to decrease quality of life.
    - Attacks that fail to respond adequately to acute/abortive therapy.
    - Contraindications to acute/abortive therapy.
    - Recurrent attacks with prolonged aura.[1,49]

32. Considerations before prescribing prophylactic therapies include:
    - Educating the patient on the need to take therapy daily and according to prescribed frequency and dosage.
    - Ensuring the patient has realistic expectations:
        - Headaches will likely not be eliminated.
        - Success = reduction in headache frequency by 50%.
        - Substantial benefit will not be seen until 4 to 12 weeks after initiation.
    - Evaluating effectiveness of therapy using a headache diary (Info point 6; Table 3).
    - Depending on the medication, start with a low dose and increase gradually to minimize side effects. Increase dosage until:
        - The drug is effective.
        - There are dose-limiting side effects.
        - A target dose is reached.
    - Ensuring therapy is taken for an adequate drug trial (at least 12 weeks).[1]

33. Although supporting evidence is less robust, magnesium, riboflavin, or coenzyme Q10 may be reasonable initial options to consider for prophylaxis given their relative safety, lower cost, and side effect profile.
    a) A 2017 systematic review (5 RCTs, n=253, age 18–65) found a statistically significant reduction in the number of migraines (22–43%) with oral magnesium when compared to placebo [Low Evidence].[55]
    b) A 2021 meta-analysis of coenzyme Q10 (6 RCTs, n=371) showed a reduction in frequency and duration of headache attacks compared with placebo—mean decrease (MD) −1.52 times per month (95% CI −2.40 to −0.65) and MD −0.19 hour of headache during an attack per month (95% CI −0.27 to −0.11) respectively. Dose range in the trials was 100 to 800 mg with 400 mg the most common.[56]
    c) A 2017 systematic review of riboflavin as a single agent (5 small trials in adults, n=23–100, only one of which was placebo-controlled and double-blind) showed a reduction in the number of monthly migraines as well as headache severity [Low Evidence].[57]

34. Onabotulinum toxin A (Botox) injections may be beneficial in preventing chronic migraine for patients experiencing more than 15 migraine days per month. A therapeutic benefit typically takes 6 to 9 months, and the success rate is approximately 50%. Botox is not recommended for prophylaxis of episodic migraine or tension-type headache.[2,3,17,58,59]

35. Menstrual migraine may respond to either a long-acting triptan (e.g., naratriptan or frovatriptan BID) started 2 days prior to menstrual onset and continued for a total of 7 days [Very Low Evidence].[15,16]
    - Women who have menstrual migraine without aura may have reduced migraine frequency by using extended (12 weeks with 1 week off) or continuous monophasic (12 months) low dose (20 mcg of ethinyl estradiol) combined oral contraceptives (COCs) to minimize hormonal fluctuations. If women experience migraine during the period off COCs, consideration can be given to using a very low dose (10 mcg) formulation during this time to minimize the drop in estrogen [Very Low Evidence].[15,16,60]

36. A newer class of injectable drugs—calcitonin gene-related peptide binding monoclonal antibodies (CGRP mAbs)—has shown efficacy and tolerability in migraine prophylaxis in both episodic and chronic migraine.
    a) A 2020 systematic review/meta-analysis of 11 high quality RCTs (n=4,402, mean baseline migraine days/month range 6–9) showed a reduction in monthly migraine days—weighted mean difference –1.44 (95% CI –1.68 to –1.19). Follow-up was 12 to 24 weeks. Significantly more trial participants had a 50% reduction in monthly migraine—relative risk (RR) 1.51 (95% CI 1.37–1.66). Injection site pain was the only adverse event seen more often in the CGRP mAbs group compared with placebo. These medications offer the potential advantage of a monthly injection but are significantly more costly than the alternatives (Appendix 3).[61]
    b) A 2022 EHF guideline recommends the following in patients who have failed or are intolerant to at least 2 standard prophylactic treatments:
        - For episodic migraine prophylaxis: erenumab, fremanezumab, and galcanezumab [High Evidence for all agents and doses].
        - For chronic migraine prophylaxis:
            - Erenumab—70 mg [High Evidence], 140 mg [Moderate Evidence].
            - Fremanezumab—225 mg [Moderate Evidence], 675 mg [High Evidence].
            - Galcanezumab—120 mg and 240 mg [High Evidence].[62]
    c) There are no head-to-head trials comparing CGRP mAbs to other prophylactic options. However, an indirect systematic review/meta-analysis of CGRP mAbs versus topiramate suggested equal efficacy (NNT = 6 and 7 respectively for a 50% reduction in migraine frequency) but a lower risk of side effects for CGRP mAbs (NNH = 130 and 12 respectively).[63] Refer to Appendix 3 for details and dosing.

37. There is some controversy regarding the use of COCs in women with migraine with aura (of any type—refer to Table 4), although most organizations—including the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG)—recommend that these women should avoid COC use due to an increased risk of stroke.[60,64,65] Overall, studies are small and observational (carrying a high risk of bias), and they did not differentiate risk based on estrogen dose. There are no studies estimating risk with the lower dose (10–30 mcg) formulations.
    a) A 2018 systematic review included 15 studies—11 were case-control; only 1 specifically examined stroke risk in migraine with aura. This trial (n=1,884 women with a stroke diagnosis) found an odds ratio (OR) of 6.1 (95% CI 3.1–12.1) for women with migraine with aura, compared with an OR of 1.77 (95% CI 1.09–2.88) in women with migraine without aura. All participants had used COCs within 90 days prior to their stroke diagnosis.[66]
    b) The EHF and European Society of Contraception and Reproductive Health (ESC) estimated in a consensus statement that the absolute stroke risk of COCs was 36.9/100,000 in women who have migraine with aura, 25.4/100,000 in women who have migraine without aura, and 6.3/100,000 in women without migraine.[67]

    Note: COCs containing < 35 mcg of ethinyl estradiol are considered an acceptable option by the EHF/ESC, SOGC, and ACOG in women who have migraine without aura, although women should be monitored for a worsening headache or new aura, prompting discontinuation of COCs.

38. Intrauterine devices (IUDs), including the levonorgestrel-releasing IUD, and progesterone-only oral and injectable contraceptives are safe and reasonable options in women with migraine with and without aura.[68,69]

Refractory Migraine

39. There are several reasons why standard migraine treatments fail. A systematic review of factors associated with refractory migraine should be performed and include:[20]
    a) Revisiting the diagnosis—a primary headache may be misdiagnosed, a secondary headache may be undiagnosed, or more than 1 headache disorder may be present.[20]
    b) Reassessing for MOH (Info points 18–20).
    c) Reviewing other exacerbating factors and comorbidities that may have been missed—e.g., dietary or behavioural triggers, use of other medications that can trigger headaches (e.g., nitrates), psychiatric comorbidities, and sleep disorders (e.g., sleep apnea, insomnia).[5,20]
    d) Reinforcing the role of behavioural factors. "Rather than making a long list of things to avoid, patients should be encouraged to have regular habits."[20]
    e) Optimizing acute/abortive therapy (Appendix 2) and preventive therapy (Appendix 3). Consider a CGRP mAbs depending on the patient's medication coverage (Info point 36). Preventive therapy is particularly important to review in refractory migraine, as patients often report that multiple preventive therapies have failed when, in fact, these medications were never used appropriately. Initiate a discussion of side effects (which are mostly self-limiting and resolve over time) and realistic expectations of success.[20]
    f) Considering biobehavioural therapies—e.g., CBT, biofeedback, relaxation therapies (Table 6).[20]
    g) Considering neuromodulation, both non-invasive and invasive.[20] Electrical peripheral nerve stimulation (particularly occipital nerve stimulation) has been used but evidence is limited (Table 6).[5]

    Note: Several of the options listed above will require specialist consultation, such as psychiatry, pain medicine, or neurosurgery.[20]

40. First-choice parenteral treatment of an acute refractory migraine in the ER (or similar settings) includes metoclopramide or prochlorperazine (with or without prior diphenhydramine), and ketorolac. If the patient has not taken another triptan in the previous 24 hours, subcutaneous sumatriptan (6 mg) could also be considered. Adequate hydration and a stress-free environment are helpful.[5] In the office setting, other medications that avoid the oral route (for those with GI symptoms) include diclofenac, indomethacin, or naproxen suppository; and zolmitriptan or sumatriptan nasal spray.[54]

Table 8. Management of MOH[5,23,48,70]

Strategy	Details
Step 1 Educate the patient.	Discuss with the patient that: • Acute medication overuse can increase headache frequency. • When medication overuse is stopped, headaches may worsen and withdrawal symptoms may occur. • Long-term headache frequency reduces after ceasing medication overuse in most patients. • Prophylactic medications may become more effective. • Education alone is not suitable for patients who overuse opioids or sedatives (benzodiazepines), have had previous relapses to MOH, or have not stopped overuse following education. [Low Evidence].
Step 2 Consider preventive medication.	Consider prophylactic medication, started *prior to or during medication withdrawal*. Agents with the best evidence in chronic migraine are: • Onabotulinum toxin A [Moderate Evidence]—given by clinicians experienced in its use for headache). • CGRP mAbs [Moderate to High Evidence]. • Topiramate [Low Evidence]. Refer to Appendix 3 for dosing.
Step 3 Initiate withdrawal from overused medication.	There is low to very low evidence on how to best perform medication withdrawal. Based on the Towards Optimized Practice (TOP) and SIGN guidelines, consider: • Abrupt withdrawal for MOH caused by simple analgesics or triptans, although gradual withdrawal is an option. • Gradual withdrawal for MOH caused by opioids and opioid-containing analgesics. • In-hospital withdrawal may be required for patients with relevant comorbidities, opioid or polydrug overuse, and/or previous unsuccessful attempts at withdrawal.
Step 4 Treat withdrawal symptoms.	Several medications can be used to treat withdrawal symptoms: • Antiemetics—e.g., metoclopramide (10 mg IM or PO 3 times daily) or equivalent: chlorpromazine, prochlorperazine, domperidone. • Analgesics (maximum of 3 days within the first week)—e.g., acetaminophen (1,000 mg PO or PR), naproxen (500 mg PO). Avoid the same drug class previously overused for the rescue medication.
Step 5 Treat remaining headache.	Take headache medication at a maximum of 2 days per week, avoiding the same drug class previously overused. Select the medication based upon the patient's medical history, headache characteristics, and past therapeutic experiences.
Step 6 Support the patient.	The majority of relapses occur within the first year after withdrawal. Studies report relapse rates of 0–41% after 6 months.[23] • Regular follow-up is important to monitor drug intake. • Continuous treatment with onabotulinum toxin A, short-term psychotherapy, and mindfulness-based training may help to prevent relapse.

PR = per rectum

Medication-Overuse Headache

41. Most patients with MOH improve after the overused medication is discontinued, with an episodic pattern of headache restored for prolonged periods. There are, however, very few placebo- or sham-controlled, double-blind trials to guide specific treatment of this condition.[23] Management generally utilizes a multi-step approach that includes patient education about overuse, withdrawal of the overused medication, treatment of withdrawal symptoms or rescue therapy, and initiation of preventive therapy (Table 8).[5,25]

Temporal Arteritis

Box 2. Scope

A detailed discussion of the management of temporal arteritis is beyond the scope of this module. For a more detailed discussion, refer to the PBLP module Polymyalgia Rheumatica (Nov 2016).

42. If temporal arteritis is suspected, urgent evaluation (hours–days) would include testing of C-reactive protein and erythrocyte sedimentation rate, as well as temporal artery biopsy or imaging (if indicated). This will likely require urgent consultation and early systemic corticosteroid treatment (prednisone 50–60 mg) to prevent blindness.[5,29] It is important to obtain the biopsy within 2 weeks of starting steroid therapy due to risks of false negative results.

KEY POINTS

- Common primary headache disorders can be identified WITHOUT the use of imaging, using diagnostic criteria and ruling out red flags for secondary headache.
- Triptans have strong evidence to support their efficacy in acute migraine treatment.
- All patients with migraine can benefit from identification and management of triggers. Consider preventative medications if > 4 to 6 migraines per month, with significant severity and impact on quality of life.
- Consider onabotulinum toxin A or CGRP mAbs in patients with chronic migraine who are unresponsive to usual preventive therapy.
- To avoid MOH, counsel patients to use abortive treatment ≤ 10 days/month with prescription medication or ≤ 15 days/month with OTC medication.
- Management of MOH includes educating patients, withdrawing analgesics, considering prophylactic treatment during withdrawal, and limiting ongoing analgesic use to prevent recurrence.

CASE COMMENTARIES

Case 1: Sofie, female, age 27

What further information would be helpful?

To begin a discussion with Sofie regarding her headaches, you would want to establish a clear understanding of her baseline headache characteristics, assess any changes from this baseline, and rule out any red flags that might suggest a more serious cause (Info point 3; Tables 1, 2; Appendix 1). Focus on previous and current headache timing (onset, pattern of attacks, duration, days per month headache free). What pain characteristics is she presenting with now and how do these differ from previous presentations? What precipitates her headaches now and in the past?

A few key things to keep in mind in your discussion:

- Was there a precipitating event such as trauma, infection, new medications, or behavioural factors that may have contributed to this change?
- Are there any other potential headache triggers, such as psychosocial factors, changes in sleep patterns, or enviromental factors?
- Is she experiencing any neurological symptoms, and do they wake her at night? (Refer to Table 2 for red flags with nocturnal wakening.)
- Have any of her headache characteristics (severity, duration, associated symptoms) changed over time?
- How do these headaches impact her function, and how has this changed more recently?
- How does she currently manage her headaches, including what medication she uses, dose, and frequency—e.g., is she using more ibuprofen more frequently?
- Does she have a family history of migraine?

A physical exam would include BP and BMI; neurologic exam (cranial nerves, funduscopic exam, motor/sensory, coordination/gait); head and neck assessment; as well as a brief screen for depression and anxiety (Info point 4).

Part Two

What would be your approach to Sofie?

Sofie's presentation of nausea and photophobia with at least 1 disabling migraine in the last month meets the ID Migraine screening tool criteria (Info point 10; Appendix 1) as well as 4 of the POUND criteria for migraine headache (Info point 9). There are no red flags to suggest the need for imaging (Table 2; Info point 5).

You could begin a conversation about tracking her headaches and provide her with information about how to fill out a headache diary or download an app such as Migraine Buddy (Info point 6; Table 3). You could discuss how to avoid potential headache triggers that she identifies (Info point 23). It would also be helpful to review behavioural strategies that may be beneficial, such as exercise, mindfulness, and hydration (Table 6).

If Sofie decides to pursue pharmacologic treatment, she could be started on acute/abortive therapy such as a triptan (Info points 25–27; Table 7; Appendix 2). Given their relative safety and tolerability, you could discuss the benefits of magnesium and, possibly, coenzyme Q10 and riboflavin for prevention (Info point 33, Appendix 3).

Part Three—Three months later

How would you respond to Sofie?

You could reinforce your earlier discussion with Sofie related to behavioural changes that may help to prevent her headaches (Table 6) as well as her use of the recommended acute/abortive therapy (how much is she using and how often?). You could also review whether she has tried the prophylactic vitamin options you reviewed with her (Info point 33; Appendix 3). It would be important to determine Sofie's goals for headache pain management and if she has drug coverage.

Sofie may benefit from a trial of a beta blocker—for example, propranolol starting at 20 mg PO BID or topiramate starting at 25 mg. Discuss the potential side effects (Appendix 3). The medication can be titrated up over the next few weeks. Alternatively, if Sofie did have symptoms of depression or if she suffered from insomnia, she could be started on amitriptyline or nortriptyline as first-line migraine prophylaxis with the option of titrating up as directed (Appendix 3).

What would you recommend to Sofie if she had questions about contraceptive options?

As Sofie does not have migraine with aura and no other risk factors for stroke, she could be offered COCs, an IUD (including the levonorgestrel-containing IUD), or oral or injectable progesterone-only contraception, depending on her preferences. If she chooses a COC, you may wish to use a lower estrogen formulation. Although there is some controversy and differing guidelines, migraine with aura is generally considered a contraindication to COC use (Info points 37–38).

What would be your approach if Sofie presented with an acute, severe migraine headache unresponsive to her usual abortive regimen?

It would be important to ensure that Sofie's headache is similar in quality to her previous migraine and there are no additional associated red flag symptoms. Assuming this is the case, you could consider giving her the option of going to the ER/urgent care for management (Info point 40). Options for acute refractory migraine management in the office setting might include medications that bypass the gastrointestinal tract such as NSAID suppositories and triptan nasal spray formulations (Info point 40; Appendix 2).

When Sofie's acute headache subsides, it will be important to revisit her use of prophylactic medications to ensure that she is using these as directed. Consider CGRP mAbs if she is unresponsive to the usual prophylactic options and her coverage allows (Info point 36). It would be important to consider revisiting the headache diagnosis in the case of refractory migraines and to assess for MOH (Info point 39).

Case 2: Nora, female, age 45

What further information would be helpful?

In addition to a thorough headache history (timing, characteristics of pain, causes and impact on function), medication history, and mental health screen, it would be helpful to inquire about any red flags for secondary headache disorders (Tables 1, 2; Appendix 1). Conduct careful neurologic, head and neck, motor, and sensory exams (Info point 4). You could consider sending Nora for imaging given her history of breast cancer and increased headache frequency. Due to her cancer history, contrast should be included when ordering either CT or MRI (Info point 5).

Part Two

What would be your approach for Nora?

Nora's increased headache frequency is due, at least in part, to medication overuse given her analgesic use (Info points 18–20). Consider educating Nora on MOH and discuss how to prevent it (Info point 41). Abrupt withdrawal of her triptans and simple analgesics would be appropriate. Starting another prophylactic medication (e.g., topiramate) prior to withdrawal of medication may be helpful (Table 8). You could provide Nora with information on self-management and nonpharmacologic techniques (e.g., exercise, mindfulness-based therapies) for managing both her migraines and her withdrawal headaches (Table 6).

Case 3: Bayan, female, age 53

What further information would you need?

It would be important to ask about the key elements of her headache history and how these differ from any previous headaches she may have had (Table 1). It would be essential to include a full review of red flag symptoms (Tables 2):

- Her pain characteristics—nature, location, severity.
- Other associated neurological symptoms.
- Any morning stiffness or musculoskeletal symptoms.
- Visual changes.
- Fever, fatigue, other intercurrent illness.
- History of trauma or falls.
- Past history of headaches.
- Current medications and any recent changes to them.
- Her current mental health status to understand if stress may be a factor in her headache presentation.
- Headache impact on her current function. Is it functionally limiting?

A physical examination would include neurological, motor/sensory, and ENT exams, as well as an assessment of her temporal artery pulses and TMJ (Info point 4).

Part Two

What would be your next steps?

Bayan's presentation is highly suspicious for temporal arteritis (Info point 21). If accessible, it would be important to review your findings with an on-call rheumatologist or consultant in your area. It would also be important to ensure that you have timely access to labs including a CRP and ESR. Depending on your access to consultation, consider prescribing high-dose steroids.

The next steps would be an urgent referral to the rheumatologist and/or internist to ensure imaging of the temporal artery, and/or a temporal artery biopsy (Info point 42). For more information on temporal arteritis, refer to the PBLP module Polymyalgia Rheumatica (November 2016) available at http://www.members.fmpe.org.

We always welcome your input. If you would like to provide feedback on this module, the following link will take you to an electronic survey: **http://members.fmpe.org/modulefeedback**.

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LEVELS OF EVIDENCE

Evidence Level	Type of Evidence Included
High Study conclusions are unlikely to be strongly affected by information from future studies.	• Systematic reviews/meta-analyses that include a wide range of well-designed studies (few limitations/risk of bias, directly applicable to target population, summary estimate has a narrow confidence interval). • Large, well-designed, multi-centre RCTs.
Moderate Study conclusions might be affected by additional information from future studies.	• Systematic reviews/meta-analyses of studies with more limitations/risk of bias (less well-designed RCTs, cohort, case-control studies; summary estimate has a wide confidence interval). • Single, moderate-sized well-designed RCTs. • Well-designed, consistent, controlled but not randomized trials/studies. • Large cohort studies.
Low Study conclusions could likely be affected by additional information from future studies.	• Small RCTs with a high risk of bias. • Controlled or cohort studies with significant limitations/risk of bias, significant variation between study results, or not directly applicable to target population.
Very Low Evidence from appropriately sized studies in representative populations is lacking or insufficient.	• Individual case reports or series. • One or more studies with very severe limitations/risk of bias.

In addition to the categorization above, when the body of evidence on a specific issue is limited, we may cite expert opinion as the highest available level of evidence.

Sources:

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2) US Preventive Services Task Force Grade Definitions. May 2008. https://www.uspreventiveservicestaskforce.org/uspstf/grade-definitions.

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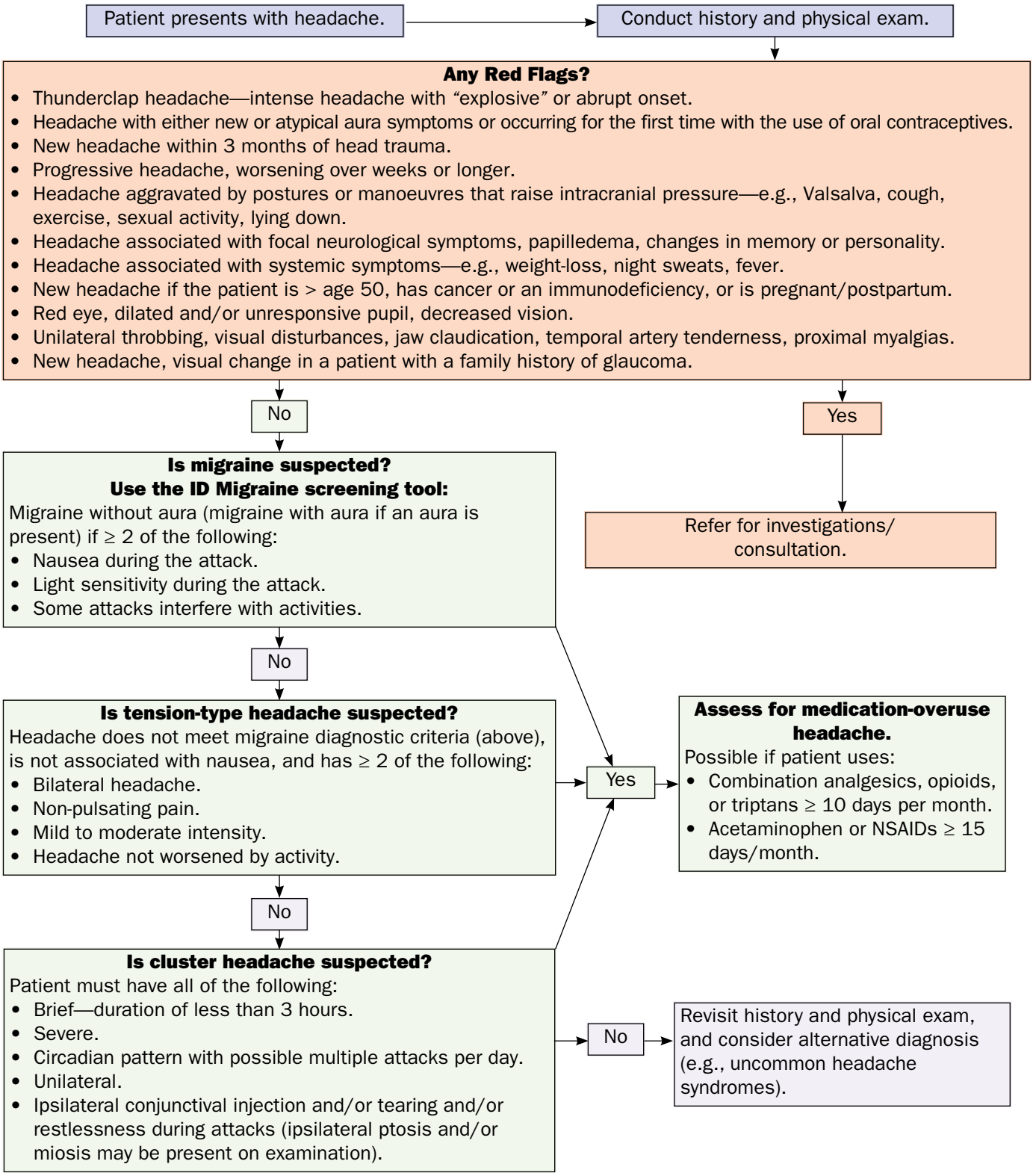
APPENDIX 1. Assessment of Headache in Adults



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APPENDIX 2. Acute/Abortive Therapy for Headache

Class	Generic Name (Trade Name)	Dose			Side Effects	Cost per 6 doses (except where indicated)
		Initial Range	May repeat	Max/ 24 hours		
NSAIDs	Ibuprofen (Advil/Motrin)	400–800 mg PO	4–6 h	3.2 g	GI disturbances, hemorrhagic syndrome, hypersensitivity reaction, drowsiness, tinnitus, acute kidney injury, hypertension, edema.	$3
	ASA (Aspirin)	650–1,300 mg PO	4 h	4 g		$3
	Naproxen Sodium (Anaprox, Aleve)	Lower dose: 220 or 275 mg PO 375 mg PO 500 mg PO/PR (may load with 1,000 mg)	4–6 h 6–8 h 8–12 h	1.5 g		$7
	Ketorolac	30 mg IV 60 mg IM	6 h 8 h	120 mg 120 mg	As above, plus dyspepsia, dizziness.	$94/30 days
Aceta-minophen	Acetaminophen (Tylenol)	500–1,000 mg PO	4 h	4 g	GI disturbances.	$3
Triptans	Sumatriptan (Imitrex)	50–100 mg PO	2 h	200 mg	Nausea, facial flushing, tingling, paresthesia, dizziness, fatigue, somnolence, chest discomfort or tightness +/– palpitations, serotonin syndrome, coronary vasospasm, dysgeusia (≤ 25%) with nasal spray.	$27–28
		5 mg or 20 mg in 1 nostril	2 h	40 mg		$117–120
		6 mg SC*	1 h	12 mg		$250
	Rizatriptan (Maxalt)	5–10 mg PO	2 h	20 mg		$34
	Almotriptan (Axert)	6.25–12.5 mg PO	2 h	25 mg		$25–57
	Zolmitriptan (Zomig)	1.25–2.5 mg PO	2 h	10 mg		$22–33
		2.5–5 mg in 1 nostril	2 h	10 mg		$207
	Eletriptan (Relpax)	20–40 mg PO	2 h	80 mg		$80
	Frovatriptan (Frova)	2.5 mg PO	2 h	5 mg		$97
	Naratriptan (Amerge)	1 mg or 2.5 mg PO	4 h	5 mg		$51–92
Ergot	Dihydroergotamine (Migranal)	0.5–1 mg SC/IM/IV	1 h	3 mg (6 mg/wk)	Nausea, tingling, paresthesia, drowsiness, dizziness, chest discomfort, diarrhea, muscle cramps, serotonin syndrome, Raynaud. Local irritation (30–52%); rhinitis (26%)	$51–92
		1 spray (0.5 mg) into each nostril	15 min	4 sprays		$65/4 sprays

APPENDIX 2. Acute/Abortive Therapy for Headache (cont'd)

Class	Generic Name (Trade Name)	Dose	Side Effects	Cost per 6 doses (except where indicated)
Antiemetics	Metoclopramide (Maxeran)	5–10 mg PO or 10–20 mg SC/IV once (maximum TID)	Drowsiness/ fatigue, diarrhea, hyperprolactinemia, akathisia, extrapyramidal side effects, tardive dyskinesia.	$18–30/ 30 days
	Domperidone (Motilium)	10 mg PO TID or 20 mg rectal TID–QID	Dry mouth, abdominal cramps, diarrhea, hyperprolactinemia, QT interval prolongation (> 30 mg/day).	$12–21/ 30 days
	Prochlorperazine (Stemetil)	5–10 mg PO, 25 mg rectal, or 5–10 mg IV q8 h	Anticholinergic effects, akathisia, extrapyramidal side effects.	$29–41/ 30 days
	Diphenhydramine (Benadryl)	50 mg PO or 25 mg IV q4–6 h	Sedation, anticholinergic symptoms, paradoxical stimulation.	$13/ 1 package (60 tablets)
Steroid	Dexamethasone	4–8 mg PO or 10 mg IV once	Proximal muscle weakness, hyperglycemia, fluid retention, insomnia, psychosis, anxiety, gastric pain, poor wound healing.	$30–90/ 30 days

*If no other triptan has been used in the previous 24 hours.
q = every; SC = subcutaneous

Sources:

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APPENDIX 3. Prophylactic Therapy for Migraine

Generic Name	Drug (Trade Name)	Dosing (starting–max)	Side Effects	Cost/month
At Least Moderate Evidence to Support Efficacy and Recommended				
TCAs	Amitriptyline (Elavil)	10–100 mg PO daily	Dry mouth, constipation, dizziness, drowsiness, fatigue, postural hypotension, weight gain.	$13–26
	Nortriptyline (Aventyl)	10–150 mg PO at bedtime	Drowsiness, dry mouth, weight gain. Less anticholinergic than amitriptyline.	$40–143
Beta-Blockers	Propranolol (Inderal)	40–240 mg PO daily	Fatigue, bradycardia, hypotension, coldness of extremities, depression, impotence, sleep disturbance, bronchospasm, nausea. Avoid in asthma or if pregnancy planned.	$18–50
	Metoprolol (Lopresor)	50–200 mg PO daily		$15–21
	Timolol (Blocadren)	10–30 mg PO daily		$32–43
	Nadolol (Corgard)	20–160 mg PO daily		$23–55
CCB	Flunarizine (Sibelium)	5–10 mg PO daily	Fatigue, weight gain, Parkinson-like side effects. Use with caution in those at risk of or with history of depression.	$61
Anticonvulsant	Topiramate (Topamax)	25–100 mg PO daily (max 200 mg)—start low, go slow	URTI, nausea, anorexia, renal calculi, paresthesia, acute glaucoma, CNS (dizziness, tremor, sedation, cognitive impairment, depression), weight loss, and metabolic acidosis. Avoid if pregnancy planned.	$37
Calcitonin gene-related monoclonal antibodies (CGRP mAbs)	Erenumab (Aimovig)	70–140 mg SC monthly	Injection site reactions, constipation (3% serious complications), hypertension. Avoid in active vascular disease [Expert Opinion]. Less common: hot flashes, hair loss, brain fog, joint pain, nausea, fatigue. Third- or fourth-line for those that have failed other prophylactic medications.	$600
	Fremanezumab (Ajovy)	225 mg SC q4 weeks **or** 675 mg q12 weeks		$630
	Galcanezumab (Emgality)	240 mg SC load, then 120 mg SC monthly		$700
Botulinum Toxin Consider when > 15 migraines/ month.	Onabotulinum toxin A (Botox)	100–200 units every 3 months by injection given by clinicians experienced in its use for headache	Injection pain, drooping eyelid, facial paresis, myalgias; "wears off" days to weeks prior to the next scheduled injection, with an increase in headache.	$195–242
Vitamins	Magnesium	300–600 mg PO daily	Diarrhea (more common with the oxide and hydroxide salts). Less common: dizziness, fainting, flushing. At toxic doses (5,000 mg/day): muscle paralysis, trouble breathing, cardiac arrest. Caution with reduced renal function.	$12
	Coenzyme Q10	100–800 mg PO daily (400 mg most common in trials)	Few side effects.	$25

APPENDIX 3. Prophylactic Therapy for Migraine (cont'd)

Generic Name	Drug (Trade Name)	Dosing (starting–max)	Side Effects	Cost/month
Lower Evidence to Support Efficacy *or* Significant Side Effects/Cost, but can be considered for prophylaxis				
ARB	Candesartan	4–16 mg PO daily	Hypotension, hyperkalemia, acute kidney injury, URTI, dizziness. Avoid if pregnancy planned.	$17
SNRIs	Venlafaxine (Effexor)	37.5–150 mg PO daily	Increased blood pressure and heart rate, tremor, agitation, insomnia, sweating, nausea, decreased appetite, fatigue, anticholinergic effects.	$13–16
	Duloxetine (Cymbalta)	30–120 mg PO daily		$27–58
CCB	Verapamil (Isoptin)	120–360 mg PO daily	Bradycardia, hypotension, constipation, nausea, edema, headache.	$25–38
Anti-convulsants	Valproic acid (Epival)	500–1,500 mg PO daily	Nausea, vomiting, anorexia, abdominal pain, tremor, weight gain, alopecia, increased hepatic enzymes, blood dyscrasias, diplopia. Avoid if pregnancy planned.	$21–65
	Gabapentin (Neurontin)	600–2,400 mg PO daily	Dizziness, drowsiness, fatigue, ataxia, weight gain, tremor.	$20–33
5-HT2	Pizotifen (Sandomigran)	0.5–6 mg PO at bedtime	Weight gain, increased appetite, fatigue, weak anticholinergic effects.	$23–47
Vitamin	Riboflavin	400 mg PO daily (can take several months for benefit)	Yellow discolouration of urine, diarrhea.	$15

NOTE: Order of recommendation balances the level of evidence to support the medication, adverse effects, and cost.
SC = subcutaneous; URTI = upper respiratory tract infection; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker

Sources:

1) Toward Optimized Practice (TOP) Headache Working Group. *Primary care management of headache in adults: clinical practice guideline: 2nd edition*. 2016. http://www.topalbertadoctors.org/cpgs/10065;
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