Common Outpatient Headache Treatments; Practical Recommendations

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Introduction

- Headache:
  - Common condition,
  - Huge number of (specialist) office visits annually
  - Mostly: primary type

ICHD3

- Migraine
- Tension-type headache (TTH)
- Trigeminal autonomic cephalalgias
- Other primary headache disorders

Migraine Headache

- Highly disabling primary headache
- One year prevalence :~15% in the general population
- Second-most prevalent neurological disorder
- Clinical Manifestation: recurrent attacks of headache with a range of accompanying symptoms

Migraine Classification

- Migraine without Aura,
- Migraine with Aura,
- Chronic migraine

- Migraine with and without aura can coexist

Migraine without aura

- Recurrent headache attacks, last 4–72 h .
- Attack typical features
  - Unilateral location,
  - Pulsating quality,
  - Moderate or severe pain intensity,
  - Aggravation by routine physical activity
- Bilateral pain is not uncommon;

Migraine without aura

- Most common associated symptoms:
  - Photophobia,
  - Phonophobia,
  - Nausea and vomiting

Migraine without aura

- Prodromal symptoms:
  - Depressed mood,
  - Yawning,
  - Fatigue
  - Cravings for specific foods

Migraine without aura

- Postdromal symptoms : 48 h
  - Tiredness,
  - Concentration difficulties
  - Neck stiffness

Migraine **with** aura

- One-third experience aura
- With every attack or with some attacks.

Migraine **with** aura

- Aura :
  - Transient focal neurological symptoms
  - >90% of affected individuals: Manifest visually classically as fortification spectra
  - Usually precede, but sometimes accompany (headache phase of a migraine attack)
  - Sensory symptoms
    - predominantly unilateral paraesthesia (pins and needles and/or numbness) that spreads gradually in the face or arm

Chronic Migraine

- Definition: ≥15 headache days per month for >3 months and fulfilment of ICHD-3 criteria for migraine on ≥8 days per month

Diagnosis of Migraine

- The medical history : mainstay of migraine diagnosis
- adequate medical history :
  - Age at onset of headache;
  - Duration of Migraine episodes
  - Frequency of headache episodes;
  - Pain characteristics (location, quality, severity, aggravating factors and relieving factors);
  - Accompanying symptoms (photophobia, phonophobia, nausea and vomiting);
  - Aura symptoms (if any);
  - History of acute and preventive medication use

Education and patient centricity

- Explain both the disease and the principles of effective management
- Instruction on the correct use of medication,
- Potential adverse effects, what to do about them,
- Importance of avoiding medication overuse

Migraine Treatment

- Acute medications
- Preventive medications
- A range of non-pharmacological therapies

Treatment strategy

- Individualized therapy:
  - Objective: each patient receives the therapy that provides the best personal outcome

Acute treatment, introduction

- Migraine attacks: disabling and require treatment
- Ineffective treatment:
  - Increase emergency department visits
  - Place the patient at increased risk for chronic migraine
- Early acute treatment is mandatory
- Patients with nausea or vomiting or rapid-onset attacks: nonoral route is preferred

Nonpharmacologic Treatments for Acute Attacks

- Rest in a dark, quiet space
- Hydration
- Ice pack/ice hat/ice helmet/ice cap
- Creams containing menthol, camphor, lidocaine, or essential oils
- Deep breathing
- Guided meditation
- Biofeedback; need to be trained before the attack

Acute treatment

- Level A evidence for the acute treatment of migraine
  - Triptans,
  - Acetaminophen,
  - Aspirin,
  - Ibuprofen,
  - Naproxen,
  - Diclofenac sodium

NONSPECIFIC TREATMENT

- first-line treatment for mild to moderate migraine attacks
- Acetaminophen: 1000 mg oral
- Nonsteroidal Anti-inflammatory Drugs:
  - Aspirin (900 mg),
  - Diclofenac (50 mg, 100 mg, and oral dissolvable powder),
  - Ibuprofen (200 mg, 400 mg),
  - Naproxen (500 mg, 550 mg)

Nonspecific Treatment

- Opioids and Butalbital-containing Products
  - Should not be prescribed for long periods of time
  - Should not be prescribed as a first-line treatment for people with migraine

Migraine-Specific Treatment

- Triptans: first-line treatment for moderate to severe migraine attacks
- Which triptan? consider:
  - Attack duration: longer attacks may benefit from a medication with a longer half-life
  - Attack onset speed: rapid-onset attacks benefit from a nonoral route of medication
- Triptans contraindication: people with vascular disease.

Migraine-Specific Treatment

- Most favorable outcomes:
  - Subcutaneous sumatriptan,
  - Rizatriptan orally disintegrating tablet,
  - Zolmitriptan orally disintegrating tablet,
  - Eletriptan tablets

Migraine-Specific Treatment

- Note: Combining a triptan with aspirin or acetaminophen or using a nonoral formulation may produce better outcomes

Ergots

- Dihydroergotamine: effective early or late in a migraine attack
- Triptan is ineffective? consider dihydroergotamine
- DHE should be avoided: in patients with;
  - Peripheral vascular disease,
  - Cardiovascular disease,
  - Uncontrolled hypertension

Ditans

- Selective 5-HT1F receptor agonists
- Act on the trigeminal system but;
  - Do not cause vasoconstriction because of their low affinity for 5-HT1B receptors

Ditans

- Lasmiditan 50 mg, 100 mg, or 200 mg;
  - Can be considered in patients with cardiovascular contraindications to triptans.
  - Side effects:
    - Dizziness,
    - Fatigue,
    - Paresthesia,
    - Sedation
- Lasmiditan user: must be instructed not to drive for 8 hours after taking medication

Gepants

- CGRP receptor antagonists
- CGRP: play an important role in migraine pathophysiology
- Blocking its activity may abort and reduce the migraine attacks in frequency
- FDA approved Gepants: for the acute treatment of migraine in adults;
  - Ubrogepant
  - Rimegepant

summary

- Offer acute medication to everyone who experiences migraine attacks.
- Advise use of acute medications early in the headache phase of the attack, as effectiveness depends on timely use with the correct dose.
- Advise patients that frequent, repeated use of acute medication risks development of MOH.
- Use NSAIDs (acetylsalicylic acid, ibuprofen or diclofenac potassium) as first-line medication.
- Use triptans as second-line medication.
- Consider combining triptans with fast-acting NSAIDs to avert recurrent relapse.
- Consider ditans and gepants as third-line medications.
- Use prokinetic antiemetics (domperidone or metoclopramide) as adjunct oral medications for nausea and/or vomiting.
- Avoid oral ergot alkaloids, opioids and barbiturates

Neuromodulation

- External trigeminal nerve stimulation,
- Single-pulse transcranial magnetic stimulation,
- Noninvasive vagus nerve stimulation,
- Remote electrical neuromodulation

Device	Dosing	Side effects
External trigeminal stimulation	1 hour during migraine attack	Paresthesia
Single-pulse transcranial magnetic stimulation	Three pulses up to 3 times per attack as needed	Lightheaded, tingling, tinnitus
Noninvasive vagus nerve stimulation	Bilateral 120 seconds to right and left of neck within 20 minutes of onset of attack; repeat once after 15 minutes	Application site discomfort, nasopharyngitis
Remote electrical neuromodulation	To upper arm for 45 minutes within 1 hour of onset; increase stimulation until perceptible but nonpainful	Transient warmth, redness, or tingling sensation into the arm

- How it works?
- Who is candidate: patients with;
  - Side effects to current therapy,
  - Prefer nondrug therapy,
  - Overusing acute medications

Preventive treatment

- Reduced disability
- Improved quality of life

Preventive treatment

- Good response to treatment: reduction in headache frequency of 50% or more
- Effective preventive medication
  - Reduce the severity or duration of headache attacks,
  - Reduce the need for acute treatment,
  - Improve efficacy of acute treatments
- Headache frequency is one of the strongest predictors for transformation from episodic migraine to chronic migraine

Preventive treatment

- Commonly used criteria for considering Preventive Therapy:
  - Two severe or disabling or four less disabling migraine attacks per month
  - Acute migraine treatment is ineffective or contraindicated
  - Medication-overuse headache is present
  - Highly disabling migraine attacks (eg, hemiplegic migraine or migraine with brainstem aura)
    - Patient preference

Preventive treatment

- Withdrawing preventive treatment: when?
  - One approach is to wait for 3 to 6 months of headache freedom before attempting a slow taper of prevention,

Oral Pharmacologic Prevention

- Migraine prevention:
  - Secondary indication for most drugs currently in use as oral preventive agents.
- Common Preventive medications: according to guidelines;
  - Sodium valproate,
  - Topiramate,
  - Propranolol,
  - Metoprolol
  - Amitriptyline: according to European and Canadian guidelines.

Antidepressant Medications

- Amitriptyline: well tolerated.
- Nortriptyline: often used because of its lower anticholinergic profile
- SNRI:
  - Venlafaxine:
    - Level B evidence for prevention of migraine
    - Can have a significant withdrawal syndrome
  - Duloxetine: less severe withdrawal symptoms than venlafaxine

- Amitriptyline and venlafaxine: best evidence for prevention of migraine

Antihypertensive Medications

- Propranolol: Most prescribed antihypertensive agent
- Metoprolol: cardioselective
- Verapamil:
  - CCB,
  - Benign side effect profile
  - Helpful in patients with migraine aura,
    - particularly prolonged, bothersome, or brainstem aura, and hemiplegic migraine
- ACE inhibitors and angiotensin receptor blockers:
  - Specifically, lisinopril and candesartan

- Propranolol and verapamil:
  - most used antihypertensive for migraine prevention and are generally well tolerated
- Recent evidence:
  - Lisinopril and candesartan: effective migraine preventives with a good side effect profile

Antiepileptic Medications

- Antiepileptic drugs:
  - Higher side effect profile
  - Greater efficacy
- Topiramate:
  - Level A evidence
  - First-line preventive.
  - Bothersome side effect : cognitive slowing;
    - Perceived memory deficits and word-finding difficulties.

Antiepileptic Medications

- Sodium valproate:
  - Highly effective
  - High side effect burden;
    - Somnolence,
    - Weight gain,
    - Hair loss,
    - Possible hepatotoxicity and thrombocytopenia.
  - highly teratogenic: avoided in people who could become pregnant

Antiepileptic Medications

- Topiramate and sodium valproate :
  - Potent migraine preventives
  - Higher side effect burden than other preventives
- Antiepileptic drugs sometimes used for prevention :
  - Gabapentin,
  - Pregabalin,
  - Zonisamide.

- Oral medication choice depends on
  - Effectiveness,
  - Side effect profile,
  - Contraindications,
  - Patient preference

CGRP Monoclonal Antibodies

- CGRP monoclonal antibodies are effective treatments for both episodic and chronic migraine
- Four (CGRP) monoclonal antibodies are now US Food and Drug Administration approved for migraine prevention.
- given monthly or quarterly, either subcutaneously or intravenously.
- effective for refractory migraine and sustain efficacy over several years.

Antibodies to Calcitonin Gene-Related Peptide or Its Receptor[a]

TABLE 4-4

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Target	Ligand	Receptor	Ligand	Ligand
Subclass	Humanized	Human	Humanized	Humanized
Production	Yeast	Chinese hamster ovary	Chinese hamster ovary	Chinese hamster ovary
Dose	100-300 mg IV every 3 months	70 or 140 mg subcutaneous monthly	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly
Time to maximum (T_{max})	2-5 hours	5.5 days	5-7 days	7-13 days
Half-life	27 days	21-23 days	31 days	28 days
Notes	IV administration leads to fastest onset of efficacy	Clinical experience suggests higher risk of constipation than with other monoclonal antibodies	Higher risk of injection site reactions than for erenumab; quarterly dosing may be convenient for some patients	Higher risk of injection site reactions than for erenumab

CGRP Monoclonal Antibodies

- Faster onset of action than oral preventives
- Limitations of CGRP monoclonal antibody:
  - Cost and access issues,
  - Long duration of any side effects that may occur,
  - Need to avoid use during pregnancy
  - Not considered first-line treatments at this time

Preventive Treatment of Chronic Migraine and Medication-Overuse Headache

- Prevention of chronic migraine:
  - OnabotulinumtoxinA,
  - Topiramate,
  - CGRP monoclonal antibodies

- OnabotulinumtoxinA
  - FDA approved: only chronic migraine
  - Level A evidence for prevention of chronic migraine
- Topiramate: high level of evidence for efficacy

MOH

- Many patients with chronic migraine have comorbid medication overuse or medication-overuse headache, or both
- Complicate preventive treatment
- Diagnosis:
  - When a patient uses a triptan, ergot, opioid, combination analgesic, or any combination of acute treatments **more than 10 days a month**, or
  - Acetaminophen or NSAIDs **more than 15 days a month**.

MOH

- Treatment:
  - Combination of discontinuation of the overused medication and starting preventive medication.
- OnabotulinumtoxinA and topiramate:
  - Best evidence for prevention in patients with medication overuse

- multidisciplinary approach
  - Important lifestyle factors to consider in people with migraine :
    - getting adequate and good-quality sleep,
    - Maintaining good hydration,
    - Eating well-balanced frequent meals,
    - Avoiding alcohol,
    - Keeping caffeine to a modest level and at a regular time each morning,
    - Managing stress,
    - Participating in regular physical activity

Herbal and Nutritional Supplements

- Supplements with the best evidence for migraine prevention:
  - Magnesium
  - Riboflavin

Mind/Body and Behavioral Interventions

- Behavioral therapies with good evidence for migraine prevention
  - Cognitive-behavioral therapy,
  - Relaxation training,
  - Thermal or electromyographic biofeedback,
  - Mindfulness meditation.
- Layering behavioral and pharmacologic treatment
- Acupuncture

Neuromodulation

- Evidence for migraine prevention
  - The external trigeminal nerve stimulation device
  - The single-pulse transcranial magnetic stimulation device

Preventive treatment

- Who is candidate:
  - patients who are adversely affected by migraine on ≥2 days per month despite optimized acute treatment.
- first-line medications:
  - Use beta blockers (atenolol, bisoprolol, metoprolol or propranolol),
  - Topiramate or
  - Candesartan

Preventive treatment

- Second-line medications:
  - Flunarizine,
  - Amitriptyline or
  - (in men) sodium valproate
- Third-line medications:
  - CGRP monoclonal antibodies

Preventive treatment

- Neuromodulatory devices,
- Biobehavioural therapy and
- Acupuncture

Adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated

Managing migraine in special populations

- Older people
- Children and adolescents
- Pregnant and breastfeeding women

Recommendations

- Patients with apparent late-onset migraine: suspect an underlying cause
- Older people: consider the higher risks of
  - Secondary headache,
  - Comorbidities and
  - Adverse events with older age.

Recommendations

- Children and adolescents with migraine:
  - Bed rest alone might suffice;
  - If not,
    - Ibuprofen for acute treatment and
    - Propranolol, amitriptyline or topiramate for prevention.

Recommendations

- Pregnant or breastfeeding women,
  - Paracetamol for acute treatment
  - Avoid preventive medication whenever possible.
- Women with menstrual migraine:
  - Perimenstrual preventive therapy with a long-acting NSAID or triptan

Tension Type Headache

- Tension-type headache (TTH) most prevalent neurological disorder
- Recurrent headaches of mild to moderate pain intensity
- Headaches tend to be bilateral
  - Sometimes described as of a ‘hatband’-like pattern,
- Location: forehead, posterior head regions and neck
- Without accompanying symptoms such as photophobia, phonophobia and nausea

- TTH three subtypes based on headache frequency:
- infrequent episodic TTH (ETTH; headaches for 1 day/month on average
- Frequent ETTH <headaches for 1–14 days/month
- chronic TTH ≥15 days/month
- The ICHD-3 also subclassifies TTH as associated or not associated with pericranial tenderness
- Pericranial tenderness is the most common abnormal finding with CTTH

Acute treatment

- Simple analgesics:
- Acetaminophen
- Aspirin: acute treatment with level A recommendation
- NSAIDs:
  - Ibuprofen,
  - Ketoprofen
  - Naproxen and
  - Diclofenac

Preventive treatment

- Frequent ETTH
- CTTH
- duration of TTH prophylaxis:
  - Patients with excellent response (such as 50–75% reduction in monthly headache days) pausing the treatment after 3 or 6 months and monitoring for any recurrence of the headache is a widely used approach

- Amitriptyline:
  - First-choice: for the prevention of TTH in elderly and younger patients
- Mirtazapine:
  - Better tolerability profile than amitriptyline or other tricyclic antidepressants
  - Recommended in specific subpopulations: elderly patients
- Venlafaxine:
  - Evidence for efficacy: low

Box 3 | **Management of TTH in specific populations**

Children and adolescents

There is some evidence only for acetaminophen[267] in the acute treatment of tension-type headache (TTH) and amitriptyline[268,269] for prevention, whereas non-pharmacological and multidisciplinary interventions[216,270–272] have stronger evidence and should be preferable or used in combination with amitriptyline when needed.

Elderly individuals

First-choice treatment is non-pharmacological intervention (such as biofeedback or relaxation techniques) whenever accessible and accepted by patients. Acetaminophen is the drug of first choice for acute treatment (NSAIDs should be avoided) and amitriptyline for prevention of TTH, followed by venlafaxine and mirtazapine. Close monitoring is required owing to the risk of adverse effects[181,199,273]. Notably, TTH may be a risk factor for dementia[274].

Pregnancy and lactation

Pharmacological treatment should be offered and not be postponed when needed[275]. Acetaminophen is the first-choice drug for symptomatic treatment but combinations with caffeine or NSAIDs should be avoided[275]. Amitriptyline is preferred for the prevention of TTH, followed by venlafaxine and mirtazapine (same FDA classification as for pregnancy — C class)[275].