

Approach to headache disorders and the management of migraine: consensus guidelines from the Headache Society of Singapore, first edition (2023)

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Abstract

Headache disorders, particularly migraine, are one of the most common and disabling neurological disorders. There is a need for high-quality, accessible care for patients with headache disorders across all levels of the healthcare system in Singapore. The role of the Headache Society of Singapore is to increase awareness and advance the understanding of these disorders and to advocate for the needs of affected patients. In this first edition of local consensus guidelines, we focus on treatment approaches for headaches and provide consensus recommendations for the management of migraine in adults. The recommendations in these guidelines can be used as a practical tool in routine clinical practice by primary care physicians, neurologists and other healthcare professionals who have a common interest in headache disorders.

Keywords: Consensus recommendations, headache, headache disorders, migraine, Singapore

INTRODUCTION

Headache disorders, such as migraine and tension-type headache (TTH), are common disabling neurological disorders that affect individuals who are in the most productive phase of their lives.^[1] Migraine constitutes 88% of the burden of headache disorders, whereas TTH accounts for 11.8% of this burden.^[1] The global prevalence of migraine is approximately 15%, affecting one in every seven people worldwide.^[2] Migraine is highly prevalent among women, students and urban residents.^[3] In Asia, the prevalence of migraine is 10.1%^[3] and ranges from 11.3% to 14.4% in women to 3.6% to 6.7% in men. According to the latest Global Burden of Disease study, the prevalence, incidence and years lost due to disability (YLD) of migraine in all ages in 2019 were 1.1 billion, 87.6 million and 42.1 million, respectively.^[1] Migraine patients who experience 15 or more migraine days per month for at least 3 months are diagnosed with chronic migraine (CM).^[4] CM is a highly disabling primary headache disorder that affects approximately 2% of the population and

is associated with reduced quality of life and increased risk of anxiety, depression and chronic pain, which increases the utilisation of healthcare resources.^[5,6] Approximately half of CM patients also have medication overuse headache (MOH);^[7] moreover, the prevalence and YLD for MOH due to migraine are 83 million and 0.9 million, respectively.^[8]

Several international and regional recommendations have been published for the management of various headache disorders. However, it is imperative that these guidelines are interpreted and implemented appropriately to match the regulatory and

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Received: 21 Oct 2022 **Accepted:** 09 Mar 2023 **Published:** 19 Sep 2023

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How to cite this article: Zhao YJ, Idu Jion YB, Ho KH, Wong PS, Lo YL, Chan YC, *et al.* Approach to headache disorders and the management of migraine: consensus guidelines from the Headache Society of Singapore, first edition (2023). Singapore Med J 2026;67:345-60.

Access this article online

Quick Response Code:



Website:
<https://journals.lww.com/SMJ>

DOI:
10.4103/singaporemedj.SMJ-2022-195

clinical requirements in Singapore. In Singapore, patients with headaches can seek treatment in the primary care setting first. Subsequently, those with more challenging conditions are referred to neurologists, neurologists with a special interest in headache disorders and pain physicians in tertiary care settings. Thus, there is an increasing need to standardise the treatment approaches available in Singapore, particularly with the rapidly expanding armamentarium of therapeutic options. Hence, the Headache Society of Singapore (HSS) commissioned a working committee to develop a set of guidelines for the approach to headache disorders and to harmonise the management of migraine among adults in Singapore.

METHODOLOGY

A working committee was convened by the HSS to review the literature pertinent to migraine and other headache disorders in Singapore. The committee comprised neurologists, anaesthesiologists, pharmacists and family practitioners.

This set of recommendations was collectively generated by members of the working committee and was based on clinical experience and feedback from stakeholders.

Literature review

A literature search was performed for research articles in the English language on migraine that involved the use of triptans, ergotamine, dihydroergotamine, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and antiemetics. Only prospective, randomised trials, meta-analyses, established clinical guidelines^[9-15] and observational studies published between 1998 and 2019 were selected. After reviewing the literature, consensus-based decisions were established by the working committee. Evidence and draft recommendations were reviewed collectively, and consensus (defined as at least 90% agreement) was obtained for recommendations that were not supported by sufficient evidence in the literature.

The working committee adopted the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) working group principles for grading the level of evidence and recommendations [Section 1, Supplemental Digital Appendix].^[16-18]

Expert recommendations versus consensus

The recommendations formulated in these guidelines are based on available evidence from literature at the time of manuscript preparation. To avoid confusion, when nonrandomised studies and expert opinions form the basis for a conclusion regarding how patients in specific clinical situations should be managed, the suggestions are labelled ‘expert consensus’ rather than a recommendation. The term ‘recommendation’ is reserved for advice based on evidence from randomised, double-blind, controlled clinical trials.

Advisory on medication

This set of guidelines reviewed only therapeutic options

that were available in Singapore at the time of manuscript preparation. The document does not include comprehensive details of side effects, adverse events, contraindications or drug interactions. Clinicians are advised to consult standard resources and product information sheets when making therapeutic decisions. In addition, clinicians should note that while certain treatment options are supported by clinical data, not all have received specific approval for the treatment of a particular headache disorder.

EVALUATION OF HEADACHE DISORDERS

Based on the International Classification of Headache Disorders, third edition (ICHD-3), 2018, headache disorders can be classified into primary and secondary headaches.^[4] The majority of headaches are primary headaches such as migraine and TTH. However, it is important to identify secondary headaches, which are those that are precipitated by another condition or disorder, as the management of the two greatly varies.

History taking for headaches

The most crucial step in the clinical evaluation of headaches is to take a comprehensive history because diagnostic investigations are unhelpful in most primary headache disorders, and these comprise the great majority of headaches that are presented. Several factors need to be considered in patients presenting with a headache for the first time or in those presenting with a change in headache pattern. The speed of onset, location of pain, associated symptomatology, precipitating factors, severity, impact on work and family, acute and preventive medication usage, and the presence of comorbidities that might influence the treatment strategy should be explored in detail. Coexisting medical problems and other associated systemic complaints/features should also be uncovered during history taking. A visual analogue scale may aid in quantifying the intensity of pain.^[19,20] Table 1 presents the main elements of an adequate headache history.

Physical examination

Apart from history taking, a comprehensive physical examination can provide further clues for diagnosis and prompt the need for further investigation(s). The presence of abnormal neurological signs raises the suspicion of a secondary headache. The physical examination should include a neurological assessment and/or assessment of other targeted areas depending on the clinical judgement [Table 2].^[12]

Secondary headaches

A secondary headache is defined as “a headache that occurs in close temporal relationship to another disorder known to cause a headache”.^[2] These causative conditions need to be identified for early intervention. The following headache ‘red flags’ (use the mnemonic SNNOOP to aid recall) should prompt further exclusion of a secondary headache through additional investigation(s) [Table 3].

Table 1. Useful questions to ask during history taking for headache.^[10,12]

Factors to consider	Useful questions to ask
Time course of headache	- When did you first notice the headache?/What was the age of onset of headache? - What is the frequency of the headache (episodic or daily, number of days per month)? - Is the headache pain intensity maximum at onset? - How long does each attack last (seconds/minutes/hours/days)? - Has there been a change in the intensity and frequency of the headache? - What has prompted you to seek medical attention now?
Characteristics of headache	- How severe is the pain intensity (mild/moderate/severe)? - Can you describe the quality of pain (pressing, pulsating, stabbing, etc.)? - Where do you feel the pain? Does it radiate to any other location? - What are the other symptoms experienced during a headache (e.g., nausea/vomiting, photophobia, phonophobia, hyperlacrimation and conjunctival injection)? - Evaluation of the presence of aura if the diagnosis of migraine is suspected, including the type of aura, duration and accompaniment with headache attacks
Reasons	- What are the triggers for your headache? - What are the aggravating or relieving factors? - Is there a family history of headaches?
Medication	- Are you taking any medication, both prescribed and over the counter? If yes, what are those and what is the dose? - Do you use drugs for pain relief (analgesics, triptans, NSAIDs, etc.), and how often per month (number of days per month)? - Did you use preventive treatment? If yes, please specify the drugs used for preventive treatment and the duration of treatment for each drug - Do you use oral contraceptive pills? (if relevant) - Do you use any traditional medications?

NSAID: nonsteroidal anti-inflammatory drug

Table 2. Recommended physical examination in the assessment of headache.^[12]

Neurological assessment	Targeted assessment
General inspection and mental status	Vital parameters (blood pressure, heart rate)
Motor power examination	Fundoscopy for papilloedema
Sensory system examination	Assessment of jaw opening
Cerebellar system examination	Palpation of muscles of mastication for tender points
Cranial nerve examination	Sinus percussion
Gait assessment	Palpation of the temporal artery for tenderness
	Examination of the neck for stiffness
	Body mass index assessment

Neuroimaging for headache

Neuroimaging may not be necessary for patients with clinical features suggestive of a primary headache disorder. In the context of a normal neurological examination and the absence of red flags on assessment, the likelihood of finding a serious secondary pathology in such patients is almost identical to that in people who do not have a headache.^[23] While neuroimaging can relieve anxiety in certain patients presenting with headaches, unwarranted neuroimaging may also uncover incidental findings that can cause undue anxiety.^[24] Thus, physicians should balance the risks and benefits of neuroimaging, and discuss them with their patients. The type of investigations to be pursued should be directed by clinical suspicion, especially if the history and/or examination suggest a secondary aetiology. Where neuroimaging is indicated, magnetic resonance imaging of the brain is the modality of choice, if it is easily accessible. Investigations such as sinus X-rays, cervical X-rays, electroencephalograms and lumbar punctures are not routinely recommended for the assessment of headaches unless specific secondary headache disorders are suspected.

MIGRAINE

Epidemiology

In Singapore, migraine is the second leading cause of disease burden, affecting up to 10% of the population.^[25] The lifetime prevalence of migraine in Singapore is 8.2%, with a mean age of onset of 26.4 years.^[26] Approximately 90% of migraine patients experience their first attack before 40 years of age.^[27]

Clinical features and diagnosis

Migraine without aura phenotype is characterised by recurrent episodes of moderate-to-severe headaches, which are usually unilateral (but can be bilateral) and frequently have a throbbing quality. There may be associated nausea, vomiting, and light, noise and/or movement sensitivity. Attacks can last for 4–72 h with freedom from symptoms in between and can vary in frequency from one per year to a few times per month.^[4] The most sensitive and specific features of migraine are nausea, disability (activities or routines affected) and photophobia.

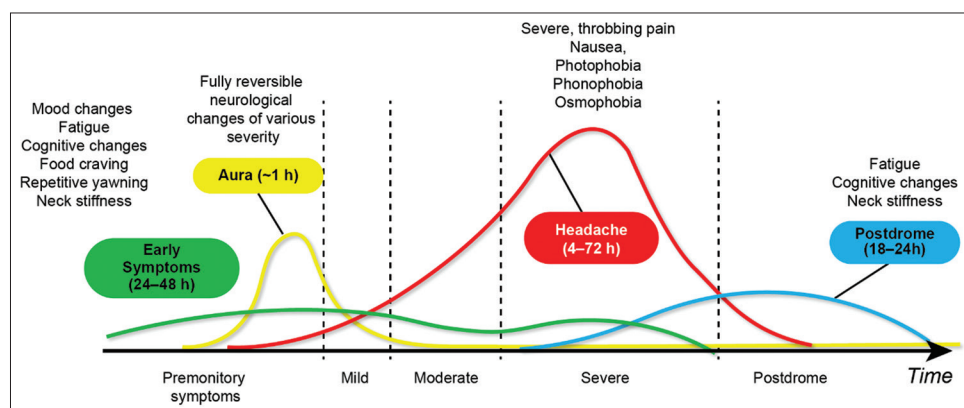
Approximately one-third of patients with migraine have migraine with aura.^[28] The aura phase consists of reversible focal neurological disturbances that may be visual, sensory, motor and/or other subtypes. Typically, symptoms develop gradually over minutes, with each aura symptom lasting 5–60 min.^[4] Supplementary Tables 3 and 4 [Section 2, Supplemental Digital Appendix] present the diagnostic criteria of migraine with and without aura, respectively, based on ICHD-3.^[4]

Phases of migraine

Migraine can be arbitrarily divided into different

Table 3. SNNOP for secondary headaches.^[21,22]

Symptoms	Features and possible aetiology
Systemic symptoms and other secondary risk factors	Fever, history of an immunocompromised state and significant weight loss
Neoplasm	History of malignancy, metastasis
Neurological deficit(s)	Focal deficits, altered mental status
Older age (after 50 years)	New-onset headache and change in characteristics of the headache at an older age
Onset of headache	Thunderclap characteristics may suggest subarachnoid haemorrhage, headache due to intracranial haemorrhage, reversible cerebral vasoconstriction syndrome and cranial or other cervical vascular disorders
Pattern change or recent onset of headache	A change in the phenotype of previous baseline headache(s) should prompt further investigations to exclude a secondary headache
Papilloedema	Papilloedema noted on fundoscopy suggests raised intracranial pressure, also associated with headaches due to neoplasm of the brain, metastasis to the brain and idiopathic intracranial hypertension
Painful eye with autonomic features	Painful red eyes, increased lacrimation, rhinorrhoea and ptosis, which can suggest headaches due to ophthalmological causes (e.g., glaucoma), lesions in the pituitary and Tolosa–Hunt syndrome
Painkiller overuse	Frequent usage of analgesics increases the risk of developing medication overuse headache
Positional headaches	Headaches worse on lying supine may be suggestive of a raised intracranial pressure. Headaches precipitated by assuming a supine or sitting position may suggest intracranial hypotension
Posttraumatic headaches	New onset of headache after traumatic injury to the head, which can be present in postconcussion syndrome, intracranial haemorrhage and cervical artery dissection
Precipitating activity	Headaches precipitated by sneezing, coughing or exercise, suggestive of headaches due to raised intracranial pressure
Pregnancy or puerperium	Headaches occurring for the first time peripartum may suggest cerebral venous sinus thrombosis, hypertension-related disorders (e.g., preeclampsia/eclampsia) or other cranial or cervical vascular disorders

**Figure 1:** Diagram shows the phases of migraine.^[29-32]

phases [Figure 1]. In the premonitory phase, patients frequently experience a varying spectrum of symptoms such as stiff neck, photophobia, phonophobia, food cravings, irritability, difficulty concentrating and fatigue (72%).^[29-32] Aura affects around one-third of migraine patients^[33] and typically consists of fully reversible visual, sensory and/or speech symptoms evolving over minutes, with the manifestation of each aura having a total duration of up to 60 min.^[4] When multiple aura symptoms occur in succession, the acceptable maximal duration may be more than 60 min. Motor symptoms may last up to 72 h. Aura may occur without headache, particularly in older patients.^[29] Aura usually precedes but may occur during or after the headache, and it may also occur in other forms of primary headaches. After the attack, in the postdrome phase, patients often experience symptoms of nature similar to the premonitory phase.^[34]

In recent times, there have been considerable advancements in the understanding of migraine neurobiology. It is postulated that migraine is most likely a neurovascular disease in which the underlying genetic predisposition makes the brain of a migraine patient more susceptible to a variety of endogenous and exogenous triggers. Migraine aura is a transient, slow-spreading neurological disease associated with decreased neuronal metabolism, typically spreading slowly from the occipital lobes (cortical-spreading depression). Migraine probably arises from the activation of nociceptors in the meninges and cerebral blood vessels and secondarily from increased pain sensitivity in the central nervous system.^[35]

DISTINGUISHING COMMON PRIMARY HEADACHES

Migraine can be clinically differentiated from other primary headache disorders such as TTH and cluster headache [Table 4].

Table 4. Distinguishing features among the common primary headaches (adapted from ICHD-3, 2018).^[4]

Migraine	Tension-type headache	Cluster headache (a trigeminal autonomic cephalgia)
Unilateral (may be bilateral as well)	Bilateral	Unilateral (never bilateral)
Pulsating (throbbing/pounding)	Pressing, tightening, nonpulsating	Red-hot poker sensation
Moderate or severe	Mild or moderate, but not disabling	Very severe
Aggravated by, or causes avoidance of, routine physical activity	No aggravation by, or avoidance of, routine physical activity	Restlessness/agitation No aggravation by physical activity
Nausea and/or vomiting Photophobia Phonophobia	May have mild nausea, but no vomiting, photophobia or phonophobia	Ipsilateral to pain, and there may be the following: Conjunctival injection Lacrimation Nasal congestion Rhinorrhoea Eyelid swelling/drooping
Attacks last from hours to days (usually 4–72 h)	Attacks last from hours to days (30 h to 7 days)	Attacks last from 15 min to 3 h
Variable frequency	The majority of the cases are intermittent and do not interfere with work or normal lifespan	Frequency: One to three attacks per day (up to eight) and usually occur daily for 2–3 months at a stretch
Chronic migraine: At least 15 headache days per month for >3 months, and fulfilling the diagnostic criteria for migraine, with at least 8 days of migraine headache days	Chronic tension-type headache: At least 15 headache days per month for >3 months and fulfilling the diagnostic criteria for tension-type headache	Chronic cluster headache: Attacks occurring for more than 1 year without remission, or remission periods lasting <3 months

ICHD-3: International Classification of Headache Disorders, third edition

MANAGEMENT PRINCIPLES OF MIGRAINE

The general principles of management are discussed subsequently.^[36]

Manage expectations

Patients may have unrealistic expectations of what is achievable. Clinicians should explain that migraine is a condition that can be effectively managed in the majority of cases but requires the patients to actively take charge of his/her condition with long-term lifestyle modifications.

Reassurance

Patients often do not have an underlying serious condition. Explaining the nature of the illness to the patients can be of therapeutic benefit.

Empower the patient to help promote self-management and identification of triggers

There are several common triggers for migraine attacks. It is good practice to give the patient a list of common triggers and to educate him/her on the importance of trigger avoidance [Table 5].

Headache diary

A headache diary [Section 3, Supplemental Digital Appendix] offers useful information about headaches, which can be used in routine clinical care.^[38] It can be useful for establishing the following:^[39] (a) frequency of headaches; (b) intensity of the pain; (c) status and pattern of medication usage; (d) degree of disability; and (e) trigger factor(s) and their correlation with the occurrence of attacks. The use of a headache diary or calendar is recommended for recording symptoms and temporal patterns of headaches, which helps with the diagnosis

Table 5. Triggers of migraine attacks.^[37]

Type of trigger	Common trigger factors
Hormonal	Menstrual cycles, ovulation
Dietary	Alcohol, caffeine, monosodium glutamate, processed meat
Behavioural/psychological	Irregular mealtimes/skipping of meals, sleep deprivation, excess of sleep, stress, over strenuous exercise/physical activity
Environmental	Bright/flashing lights, abrupt weather change, strong odour, loud noise
Medication related	Oral contraceptives, hormonal replacement therapy, nitroglycerin, histamine

and treatment of migraine. It is useful to record usage patterns of medication and potential overuse, encourage compliance with preventive medications and provide insights on treatment outcomes. It can also reveal any potential association of headaches with menstrual cycles and other triggers. Several studies have reported favourable outcomes with the use of electronic diaries. Strong test–retest reliability was observed for headache frequency, peak intensity, average intensity, duration and medication usage. Furthermore, electronic diaries were found to be easier to use, resulting in better recording compliance.^[40–42]

Headache disability assessment

Several validated questionnaires have been developed for use in the care of patients with headache disorders.

Migraine disability assessment is a questionnaire-based scale that assesses the impact of headaches on patients.^[43,44] This tool is highly reliable and valid, and correlates with clinical judgements regarding the need for medical care.^[44]

Headache impact test-6 is a validated global measure of the impact of headaches and correlates with headache severity and quality of life of patients.^[45]

Physicians caring for patients with migraine are encouraged to use these tools to objectively monitor the impact and disability of headaches, especially after commencing a treatment strategy.

Migraine can be associated with depression and anxiety. Results from the second Singapore Mental Health Study included migraine as one of the comorbidities for general anxiety disorder.^[46] Patients with migraine are 2.7 times more likely to be depressed compared to those without migraine.^[47] In a hospital-based study, more than half of migraine patients had anxiety–depression symptoms.^[48] Hence, it is important to assess both depression and anxiety levels, in addition to measures of disability, when treatment is planned. The hospital anxiety and depression scale^[49] and a patient health questionnaire^[50] are some useful tools to quantify anxiety–depression symptoms, which can indicate the need for further attention.

Nonpharmacological treatment strategies

Patients should be encouraged to adopt a healthy lifestyle (regular eating habits, good sleep hygiene and regular exercise).^[51] Although these measures appear simple, they can be very effective in the long-term management of migraine. It is important to identify and reduce predisposing factors, such as stress, depression or anxiety, as much as possible. Patients should identify and eliminate triggers such as irregular lifestyle habits (e.g., poor or irregular sleep patterns). Dietary items such as red wine, dark chocolate and certain cheeses have been reported to be migraine triggers, although this does not apply to all migraine patients.

Behavioural therapies

Relaxation techniques and cognitive behavioural therapy, including stress management, biofeedback, pacing and self-monitoring skills, are behavioural therapies that may be beneficial for patients. They can be used along with medication.^[52–54]

Acupuncture

Acupuncture, in addition to acute migraine treatment, has been demonstrated to reduce the number of headache days to an extent comparable to conventional preventive treatment. However, only a small difference was observed compared to sham acupuncture.^[55]

Individualised treatment strategies

The medication used for the treatment of migraine can be divided into two broad categories: symptomatic or acute medication and preventive medication.^[56] The prescriptions of these medications should be individualised, taking into consideration the patient's preferences, lifestyle, concomitant medical problems, existing medication and future plans (e.g., pregnancy or travel). If the response to the first agent is not optimal, other pharmacological

options can be tried to determine the most suitable medication, balancing efficacy and tolerability.^[57–59]

PRINCIPLES OF ACUTE TREATMENT OF MIGRAINE

The goals of acute migraine treatment are to rapidly relieve pain and the associated symptoms of migraine consistently across attacks, with minimal or no adverse events. Furthermore, migraine-related disabilities should be alleviated, so that the patient can quickly return to normal functioning.^[60]

Acute treatment approaches for migraine attacks can be generally classified into two broad strategies. One strategy is the stepped approach. Treatment is always started with simple analgesics (e.g., paracetamol or NSAIDs with or without an antiemetic), and if this proves ineffective within or across attacks, a triptan is started.^[37] Another strategy is the stratified approach. Initial treatment is selected based on attack severity or pain intensity, with less-severe cases being treated with simple analgesics and more severe cases being given triptans. The 'stratified care' approach has been shown to result in better clinical outcomes and to be cost-effective.^[61,62]

Early treatment of attacks

The majority of patients should be encouraged to take their acute medication as early as possible after the onset of the headache and while the pain is still mild. This maximises the effectiveness of the administered acute medication.^[56,63] An effective acute treatment is associated with a significant beneficial response within 2 h from the time of administration, confers a sustained pain-free response over 24 h and reduces disability quickly during attacks.^[64]

Antiemetics

The addition of an antiemetic (e.g., metoclopramide and domperidone) to any acute treatment improves the efficacy of that medication by improving gastric motility and, therefore, drug absorption.^[65]

Choose the most appropriate available formulation

For migraine attacks that build up very rapidly and/or are characterised by early vomiting and for attacks that present with full-blown symptoms upon awakening, a parenteral formulation (e.g., subcutaneous sumatriptan) is preferred.^[66,67] In patients with nausea, which is exacerbated by drinking water, or where water may not be readily available to swallow conventional tablets, orally disintegrating tablets may be useful.^[68]

Medication overuse

Potential issues of medication overuse, such as the impact on headache and side effects, should be discussed with patients. Patients should understand that frequent usage of acute medication may be linked to the development of MOH. Opioids are the least preferred medication class for the treatment of acute migraines as they are not significantly effective and may increase the risk of MOH and development of withdrawal

symptoms when discontinued.^[10,36] Patients taking different acute medications on different days should be counselled to limit their total use of acute medications to 9 days a month if one of their medications is a triptan, a combination analgesic, an ergotamine or an opioid [Section 4, Supplemental Digital Appendix].

Expert consensus: Migraine acute treatment

- 1 The goal of acute migraine treatment is to achieve rapid relief of headache, and acute medications should be taken as early as possible after the onset of headache.
- 2 When choosing an acute migraine medication, consideration should be given to the clinical features of the attack and other patient characteristics.
- 3 Although a single acute medication may relieve migraine attacks for most patients, others may benefit from taking more than one medication simultaneously (e.g., an antiemetic in combination with an NSAID or triptan).
- 4 When initiating acute treatment, patients should be counselled about MOH.
- 5 Patients should avoid the use of aspirin, NSAIDs and paracetamol for more than 14 days per month, and use of triptans, ergots, opioids or combination analgesics for more than 9 days a month. Patients taking different acute medications on different days should limit their total use of acute medications to 9 days a month if one of their medications is a triptan, a combination analgesic, an ergotamine or an opioid.
- 6 Patients should be advised to record their acute medication usage pattern in a headache diary.
- 7 Preventive treatment should be considered for patients with frequent migraine attacks who may be at risk of medication overuse.

Acute treatment options

Treatment for acute migraine attacks may be divided into two broad types: migraine specific and nonspecific. Specific treatment comprises ergot alkaloids and triptans, whereas the latter group includes antiemetics, NSAIDs, sympathomimetics and other miscellaneous agents.^[36,56,69]

Simple analgesics and antiemetics

Drugs (simple analgesics and antiemetics) are most commonly used for the treatment of mild-to-moderate migraine attacks as they are easily accessible and less expensive. They are also useful choices for patients who cannot take ergots or triptans due to cardiovascular or other contraindications. For mild-to-moderate attacks associated with significant nausea or vomiting, the intake of antiemetics such as metoclopramide or domperidone, administered before NSAIDs, improves oral absorption and the gastrointestinal symptoms of migraine.^[10,70,71] The efficacy of paracetamol, acetylsalicylic acid and various NSAIDs in the treatment of migraine attacks has been demonstrated.^[72] The dosing

Table 6. Dosing of simple analgesics and antiemetics for the acute treatment of migraine.^[10,70,71]

Medication	Recommended dose (mg)	Maximum daily dose (mg)
Simple analgesics		
Aspirin	500	4,000
Diclofenac	50, 100	150
Ibuprofen	200, 400	2,400
Ketoprofen	100	300
Naproxen/naproxen sodium	500/550	1,250
Paracetamol	1,000	4,000
Antiemetics		
Domperidone	10	30
Metoclopramide	10	30
Prochlorperazine	10	40

of various NSAIDs and antiemetics available for the acute treatment of migraine is detailed in Table 6. The use of simple analgesics should be limited to a maximum of 14 days per month to avoid MOH.

Expert recommendations: Acute medication for migraine

- 1 Naproxen sodium is recommended for the acute treatment of migraine attacks of all severities.
(Strong recommendation, high-quality evidence)
- 2 Diclofenac potassium is recommended for the acute treatment of migraine attacks of all severities.
(Strong recommendation, high-quality evidence)
- 3 Aspirin is recommended for the acute treatment of migraine attacks of all severities.
(Strong recommendation, high-quality evidence)
- 4 Paracetamol is recommended for the acute treatment of mild or moderate migraine attacks.
(Strong recommendation, high-quality evidence)
- 5 Ibuprofen is recommended for the acute treatment of migraine attacks of all severities.
(Strong recommendation, moderate-quality evidence)
- 6 Ketoprofen is recommended for the acute treatment of migraine attacks of all severities.
(Strong recommendation, moderate-quality evidence)

Expert recommendations: Antiemetics

- 1 Metoclopramide is recommended for use with acute migraine medications to relieve nausea.
(Strong recommendation, moderate-quality evidence)
- 2 Domperidone is recommended for use with acute migraine medications to relieve nausea.
(Strong recommendation, low-quality evidence)

Triptans

Since their introduction, triptans have revolutionised the acute treatment of migraine. At the time of manuscript preparation,

three triptans, namely, eletriptan, sumatriptan and zolmitriptan, were easily accessible for clinical use in Singapore.^[73,74] The dosing of various triptans available for migraine is given in Table 7.^[70] Triptans should be taken early in the course of an attack when the pain intensity is mild,^[75] but generally not during the aura phase in patients with migraine with aura.^[76] For moderate-to-severe migraine attacks without vomiting or severe nausea, triptans are most effective when taken early at the onset of the headache and less likely to be effective if taken during the preceding aura.^[71,76] The lack of response to one triptan does not predict the response to other triptans. After treatment failure with a particular triptan, a trial with an alternative triptan should be attempted.^[77] Therefore, the choice of a triptan needs to be individualised.

Subcutaneous route is considered to be the most rapid and effective route for pain relief with sumatriptan 6 mg. However, it is associated with a higher risk of adverse events compared to other formulations.^[67] The coadministration of a triptan and an NSAID with a long half-life, such as naproxen, exhibits a superior effect than monotherapy^[78] and can be considered for rescue therapy. Common side effects of triptans include a sensation of pressure on the chest, nausea, distal paraesthesia and fatigue. Contraindications to triptans include cerebrovascular or cardiovascular disease, uncontrolled hypertension and gastrointestinal ischaemia.^[79] Oral triptans may, in case of nausea/vomiting, be combined with the antiemetic metoclopramide^[80] or domperidone. Triptans have not been systematically tested in patients with hemiplegic migraine or migraine with brainstem aura and are not recommended for use in these patients. However, some studies involving patients with these conditions have not confirmed the risk of using triptans.^[81,82] If these patients do not have a previous history of stroke, uncontrolled hypertension, ischaemic heart disease or peripheral vascular disease, triptans may be used. Of note, experimental studies in humans have shown that sumatriptan does not constrict intracerebral blood vessels.^[83,84]

Approximately 20%–50% of patients experience a recurrence of migraine within 48 h after the first dose of a triptan. An additional dose of triptan is usually effective in these cases. Recurrence of migraine may also be treated with NSAIDs in such circumstances. Triptans should be used for a maximum of 9 days per month to avoid an MOH.

Expert recommendations: Triptans

- 1 Triptans are recommended for the acute treatment of migraine attacks that are likely to become moderate or severe.
(Strong recommendation, high-quality evidence)
- 2 If the response of migraine to sumatriptan is inadequate, consider the coadministration of naproxen sodium with a triptan.
(Strong recommendation, high-quality evidence)

- 3 Patients with migraine attacks that are usually moderate or severe in intensity should be advised to take triptans early during their migraine attacks, when the pain is mild, to improve the efficacy of the medication administered.

(Strong recommendation, high-quality evidence)

- 4 If a patient does not respond well or has poor tolerance to one triptan, the use of different triptans should be attempted in subsequent attacks.

(Strong recommendation, moderate-quality evidence)

- 5 If the response of migraine to other triptans (other than sumatriptan) is inadequate, consider the coadministration of an NSAID (e.g., naproxen sodium) with the triptan.

(Strong recommendation, low-quality evidence)

Table 7. Dosing of triptans for acute migraine.^[70]

Triptans ^a	Formulation	Strength (mg)	Single dose (mg)	Max/24 h (mg)
Eletriptan	Tablet	40	40	80
Sumatriptan	Tablet/ subcutaneous injection	50/6	50–100/ 6	300/ 12
Zolmitriptan	Tablet	2.5/5	5	10

^aAt the time of manuscript preparation, almotriptan, frovatriptan, naratriptan and rizatriptan were not easily accessible in Singapore.

Opioids

Oral opioid combinations should not be routinely prescribed for acute migraines.^[10,85] They may occasionally be considered for use in acute migraine in cases when sedation will not put the patient at risk, the risk for abuse has been addressed or when the patient is intolerant or allergic to alternative agents.^[85]

Expert recommendations: Opioids

Oral opioids, including codeine and tramadol, are not recommended for routine use in migraine due to a lack of evidence of superiority to standard drugs (NSAIDs and triptans), risk of dependence/abuse, high potential for the development of MOH and the possibility of a withdrawal syndrome following discontinuation.

(Strong recommendation, low-quality evidence)

Ergots and cyclooxygenase-2 inhibitors

The ergot alkaloids that are used in the treatment of migraines are ergotamine and dihydroergotamine. Although these agents have been used extensively, they are now slowly being replaced by triptans due to their adverse side effects, low bioavailability and high potential for abuse.^[86]

In patients who are unable to tolerate nonspecific cyclooxygenase (COX) inhibitors, COX-2 inhibitors may be the drug of choice.^[87]

Expert consensus : COX-2 inhibitors

Clinicians may consider ergots and COX-2 inhibitors when they are clinically appropriate, but patients should be cautioned against adverse events. An individualised approach should be followed.

PREVENTIVE TREATMENT OF MIGRAINE**General principles****Individualised treatment strategy**

In choosing a preventive medication, the following should be considered:^[56,61] (a) efficacy; (b) tolerability and side effect profile; (c) coexisting medical and/or psychiatric disorders; and (d) patient preference.

Dose escalation, duration of treatment and withdrawal

Preventive medication for migraine should be titrated slowly to an effective or maximum tolerable dose and continued for at least 4–8 weeks to adequately assess its beneficial effects.^[56]

Gradual withdrawal may be considered after 6–12 months of effective preventive treatment.^[88] The decision to withdraw treatment needs to be individualised and can be better guided with the help of a headache diary.^[56,71,88]

Effective preventive treatment^[56,71,88]

An effective migraine preventive medication does the following: (a) decreases monthly migraine days by at least 50% over a period of 3 months while on the medication; it is important to counsel patients that the expected outcome is a reduction, and not elimination, of attacks; (b) decreases the reliance on acute medication; (c) improves the response to acute medication; and (d) reduces disability during attacks and improves the quality of life.

Indication for preventive treatment

The objective of preventive treatment of migraine is to reduce the frequency and severity of attacks. It should be considered in patients who have four or more migraine days per month, and whose attacks have a substantial impact on their lives despite the appropriate use of acute medication, or where the frequency of migraine attacks is such that reliance on acute medication places them at risk of MOH. Although the frequency of attacks helps to determine the indication for preventive treatment, the decision to start preventive treatment should be individualised. All aspects of the patient's migraine syndrome, including the risk of acute medication overuse, need to be considered. Preventive therapy may also be considered in patients who have severe or prolonged auras, even if the attacks are relatively infrequent.^[56] Thorough education about the rationale, side effects and realistic expectations associated with the treatment is important and should be routinely provided to the patient. Consider discontinuation of preventive medication after 6–12 months and reassess if there is still a need for the medication. The lack of effect of one type of preventive medication does not preclude the effect of other types of medication. The factors influencing the choice of the initial migraine preventive medication depend on the patient's profile, preferences and circumstances.

Expert consensus: Migraine preventive treatment

- 1 Prescribing decisions for migraine preventive treatment should be individualised, considering the patient's preferences, socioeconomic status, occupation, habits, concomitant medical problems, side effect/tolerability profile, previous treatment(s) and their future plans (e.g., pregnancy or travel).
- 2 Migraine preventive treatment should be considered for patients with a frequency of four or more headache days a month, or if the headache consistently results in severe disability.
- 3 To optimise the success of any preventive medication, any underlying acute medication overuse should be addressed beforehand.
- 4 An adequate trial of migraine prevention should consist of an optimal or maximum tolerated dose for at least 2 months before the drug is considered ineffective.
- 5 Preventive medication is usually considered effective if the migraine attack frequency or the number of headache days per month is reduced by 50% or more.
- 6 In addition to a reduction in migraine attack frequency or the number of headache days per month, a reduction in headache intensity and migraine-related disability needs to be considered when judging the effectiveness of migraine preventive treatment.
- 7 A periodic review to monitor potential side effects and efficacy is necessary. The use of a headache diary is encouraged for this purpose.
- 8 The failure of one preventive medication does not predict the failure of others.
- 9 After 6–12 months of successful preventive treatment, consider tapering the dose to wean the drug off completely. If the headache frequency increases as the preventive drug dosage is reduced, the medication can be recommenced, and the dosage may be titrated upwards again to an effective level.

Preventive treatment options**Beta-blockers**

Beta-blockers are commonly prescribed as the first-line preventive drugs. Evidence for the efficacy of propranolol and metoprolol is robust.^[89] There is some evidence for the efficacy of bisoprolol, timolol and atenolol.^[90] Side effects include fatigue, dizziness, reduced physical ability and cold extremities.

Angiotensin II receptor antagonists

Candesartan has a good tolerability and safety profile and has been shown to be comparable to beta-blockers in terms of efficacy.^[91]

Antidepressants

Amitriptyline and nortriptyline are commonly used in migraine preventive treatment and are particularly useful if the patient experiences frequent TTH.^[90] These medications are usually

given 1–2 h before bedtime. Extended-release venlafaxine can also be considered as an option, especially in patients with significant psychiatric conditions.^[92-94]

Antiepileptics

Topiramate and sodium valproate have comparable efficacies to beta-blockers, but are generally associated with more potential side effects.^[95-97] The side effects of topiramate include paraesthesia, sedation, dizziness, weight loss, kidney stones and reduced cognition.^[98] The side effects of sodium valproate include dyspepsia, hand tremors, weight gain, transaminitis, thrombocytopaenia and foetal malformations. It should not be prescribed to women of childbearing potential.^[98]

Calcium channel blockers

The effect of flunarizine is comparable to that of beta-blockers, but it is generally associated with more potential side effects.^[99] Commonly noted side effects include drowsiness, fatigue, increase in weight, depression and unmasking of latent Parkinson's disease.^[100,101]

Expert recommendations: Migraine preventive treatment

Amitriptyline

- 1 We recommend amitriptyline for migraine prevention in eligible patients.

(Strong recommendation, high-quality evidence)

Sodium valproate

- 2 Although there is high-quality evidence that sodium valproate is effective for migraine prevention, a weak recommendation was made based on the risk–benefit profile of this medication for many patients. This medication often promotes weight gain and may cause reversible tremors and hair loss.

(Weak recommendation, high-quality evidence)

Topiramate

- 3 Topiramate can be considered for migraine prevention in eligible patients. There is high-quality evidence that topiramate provides a reduction in migraine frequency, although side effects from treatment are common.

(Strong recommendation, high-quality evidence)

- 4 We recommend propranolol, metoprolol or atenolol for eligible patients for migraine prevention.

(Strong recommendation, high-quality evidence)

- 5 Although there is high-quality evidence that flunarizine 10 mg/day is effective for migraine prophylaxis, a weak recommendation was made because treatment is often limited by side effects such as depression and weight gain. Flunarizine is particularly useful for migraines with prominent vertigo.

(Weak recommendation, high-quality evidence)

- 6 Sodium valproate, as well as candesartan and valsartan, should be avoided in women of childbearing age unless pregnancy can be avoided.

(Strong recommendation, high-quality evidence)

Nutraceuticals

Nutraceuticals are food or dietary supplements that can provide a therapeutic benefit for migraine. The most common nutraceuticals include riboflavin, coenzyme Q10 and magnesium.^[102] According to some studies, riboflavin and coenzyme Q10 have been found to help regulate the imbalance of energy metabolism in the brain caused due to mitochondrial dysfunction.^[102,103] Magnesium at adequate levels can inhibit glutamate, an excitatory neurotransmitter, thus decreasing the threshold for migraine attacks.^[104,105] The dosing recommendations of various treatments available for preventive migraine are presented in Table 8.

Calcitonin gene-related peptide monoclonal antibodies

Drugs acting against the calcitonin gene-related peptide (CGRP) pathway (either the ligand or the receptor) are recent preventive treatments that have been specifically developed for migraine.^[115-117] These are monoclonal antibodies that are administered subcutaneously or via intravenous infusion at monthly or three-monthly intervals. Erenumab blocks the CGRP receptor, whereas the three other antibodies (fremanezumab, galcanezumab and eptinezumab) bind to the CGRP ligand.

Candesartan

- 7 We recommend candesartan for eligible patients for migraine prophylaxis. Although the evidence for candesartan facilitating a reduction in migraine frequency is limited, two randomised trials support its use and report minimal associated side effects.

(Weak recommendation, moderate-quality evidence)

Riboflavin

- 8 We recommend riboflavin for migraine prevention in eligible patients. There is some evidence supporting its benefit; side effects are minimal.

(Strong recommendation, low-quality evidence)

Lisinopril

- 9 Although lisinopril is generally well tolerated, the evidence for its efficacy is limited and the magnitude of its benefits in migraine prevention appears minimal.

(Weak recommendation, low-quality evidence)

Coenzyme Q10

- 10 We recommend coenzyme Q10 for eligible patients for migraine prevention.

(Strong recommendation, low-quality evidence)

Magnesium

- 11 We recommend elemental magnesium (oxide/chloride) for migraine prevention. There is some evidence of its benefit with minimal side effects.

(Strong recommendation, low-quality evidence)

Venlafaxine

- 12 We recommend venlafaxine for migraine prevention in patients with concomitant significant psychopathy.

(Weak recommendation, low-quality evidence)

Table 8. Recommended preventive medications for episodic and chronic migraine.^[87,93,106–114]

Drug	Starting dose	Suggested titration/increment	Dose ranges reported in clinical studies	Comments
Amitriptyline	10 mg ON (at bedtime)	10 mg/week	10–150 mg at bedtime	Consider if the patient has depression, anxiety, insomnia or TTH
Nortriptyline	10 mg ON (at bedtime)	10 mg/week	10–75 mg at bedtime	Reasonable alternative if amitriptyline is not tolerated
Venlafaxine (extended release)	75 mg	37.5 mg/week	150 mg once a day	Consider if the patient has significant psychopathy
ARBs/ACE inhibitors				
Candesartan	4 mg OD	2 mg	16 mg/day	
Lisinopril	10 mg OD	10 mg	20 mg/day	
Beta-blockers				
Propranolol	20 mg BD	20 mg/week	80–240 mg/day	Avoid in asthma/COPD
Metoprolol	50 mg BD	50 mg/week	47.5–200 mg/day	Avoid in asthma/COPD; use the short-acting form (tartrate) in two divided doses; use the long-acting form (succinate) once daily
Nadolol	40 mg/day	20 mg/week	80–160 mg/day	Avoid in asthma/COPD
Atenolol	50 mg/day	50 mg/week	100 mg/day	Avoid in asthma/COPD
Anticonvulsants				
Topiramate	25 mg daily	25 mg/week	50–200 mg/day	Consider if the patient is overweight; higher incidence of adverse effects and withdrawal seen with 200 mg/day
Sodium valproate	250 mg daily	250 mg/week	400–1500 mg/day divided into two doses	Avoid in pregnancy or when pregnancy is possible
Calcium channel blockers				
Flunarizine	5 mg ON (at bedtime)	5 mg/week	10 mg/day	Avoid in patients with depression
Nutraceuticals				
Coenzyme Q10	100 mg TDS	No titration needed	100 mg TDS	
Magnesium	200–300 mg BD	No titration needed	300 mg BD	Drug of choice in pregnancy or if the patient prefers nonprescription medications
Riboflavin	100–200 mg BD	No titration needed	200 mg BD	

ACE: angiotensin-converting enzyme, ARBs: angiotensin II receptor blockers, BD: twice daily, COPD: chronic obstructive pulmonary disease, OD: every day, ON: every night, TDS: thrice daily, TTH: tension-type headache

Table 9. CGRP monoclonal antibodies for migraine preventive treatment.^[97–99]

Drug (route)	Dosage
Erenumab (SC)	70–140 mg every month
Eptinezumab (IV)	100 mg every 3 months
Fremanezumab (SC)	225 mg every month or 675 mg every 3 months
Galcanezumab (SC)	240 mg loading dose (first month) followed by 120 mg every month

CGRP: calcitonin gene-related peptide, IV: intravenous, SC: subcutaneous

Current evidence indicates that treatment with these agents results in a significant decrease in the frequency of migraine attacks, with both episodic and CM patients experiencing fewer migraine days per month. Notably, no significant safety or tolerability concerns have been identified.^[118–121] The dosing of various CGRP monoclonal antibody options available for migraine prevention is summarised in Table 9.

Expert consensus: CGRP monoclonal antibodies

- 1 In patients with episodic migraine (EM) or CM who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, eptinezumab, fremanezumab or galcanezumab.
- 2 In patients with EM or CM, we suggest weaning off treatment with erenumab, eptinezumab, fremanezumab or galcanezumab after 6–12 months of effective treatment.
- 3 In view of inadequate safety data to date, avoid anti-CGRP monoclonal antibodies in patients who are pregnant or breastfeeding, in individuals with alcohol or drug abuse, and where there is a history of cardiovascular or cerebrovascular disease.

Onabotulinumtoxin A

Botulinum type A toxin (Botox) is approved for the preventive treatment of CM in patients who have shown insufficient response or intolerance to other migraine preventive drugs. The efficacy and safety of onabotulinumtoxin A for the preventive treatment of CM have been demonstrated in the Phase III Research Evaluating Migraine Prophylaxis Therapy clinical programme. Botox is administered at a dosage of 155–195 IU once every 12 weeks across 31 injection sites.^[122,123]

MANAGING HEADACHE AT PRIMARY CARE LEVEL

Guidance on the referral to tertiary centres

Primary headaches can generally be managed at the primary care level. A specialist referral can be initiated when the following consideration(s) apply:^[20] (a) diagnostic uncertainty; (b) persistent management or treatment failure; (c) inadequate response to two successive preventive treatments (for migraine); (d) frequent clinic attendance by a patient; (e) unresolved disability due to headache; (f) persisting aura or motor weakness after the resolution of headache pain; (g) red flags and possible indicators (warning signs) of secondary headache; these patients need urgent or emergent review; and (h) clinical features suggestive of a trigeminal autonomic cephalalgia, e.g. cluster headache.

SUMMARY GUIDE

A suggested guide is provided in Box 1. Figure 2 provides an algorithm illustrating the approach, treatment and management of headache disorders.

FUTURE DIRECTIONS AND CONCLUSION

Several new and exciting therapies exist for the treatment of migraine. In Singapore, the following two new treatment options may soon become available.^[124] The gepants (oral CGRP antagonists such as rimegepant and ubrogepant) are an attractive option for individuals who cannot use triptans for medical reasons (e.g., uncontrolled hypertension or coronary artery disease) or to those who do not tolerate or respond to triptans. Noninvasive neuromodulation represents a nonpharmacological modality of treatment. It modulates the pain experienced by migraine patients, but without any of the side effects associated with taking medication in acute and preventive migraine therapy. Single-pulse transcranial magnetic stimulation has been approved by the US Food and Drug Administration and the National Institute for Health and Care Excellence in the UK for acute and preventive treatment of migraine with and without aura.

The management of migraine is multifaceted, which includes a strategy that comprises acute and preventive treatment complemented by other modalities such as lifestyle/behavioural modification and trigger factor(s) avoidance.

Expert recommendations: Onabotulinumtoxin A

- 1 We recommend botulinum toxin type A as an option for the preventive treatment of CM in patients with 15 or more headache days per month, who have failed two or more oral preventive medications.
(*Strong recommendation, high-quality evidence*)
- 2 We recommend against providing botulinum toxin type A for the preventive treatment of EM in patients with less than 15 headache days per month.
(*Strong recommendation, high-quality evidence*)

Box 1. Factors influencing the choice of migraine preventive treatment.

- For patients who have not had preventive treatment before:
- Beta-blocker strategy: Propranolol, metoprolol
- Tricyclic strategy: Amitriptyline, nortriptyline
- Low side effect strategies:
- Candesartan, lisinopril, elemental magnesium, riboflavin, coenzyme Q10
- For patients with obesity: Topiramate
- For patients with hypertension: Propranolol, metoprolol, candesartan, lisinopril
- For patients with depression/anxiety: Amitriptyline, venlafaxine (extended release)
- Second-level monotherapy drug strategies: CGRP monoclonal antibodies, topiramate, sodium valproate, flunarizine
- Refractory patient strategy: Concomitant use of two drugs
- Strategy for migraine during pregnancy: Drug avoidance, if possible
When necessary and after discussing with the patient, magnesium, riboflavin (vitamin B2), propranolol, metoprolol, amitriptyline and nortriptyline may be considered
- Strategy for migraine during lactation: Drug avoidance, if possible.
When necessary and after discussing with the patient, magnesium, riboflavin (vitamin B2), propranolol, metoprolol, amitriptyline and nortriptyline are considered compatible with breastfeeding [Section 5, Supplemental Digital Appendix]

CGRP: calcitonin gene-related peptide

New treatments are in the horizon with the promise of meeting current unmet therapeutic needs. This is indeed an era of development and an age of hope for both patients and physicians.

Acknowledgement

We would like to thank BioQuest Solutions for the editorial support. In addition, we would like to thank Novartis (Singapore) and Allergan (Singapore) for providing an educational grant.

Financial support and sponsorship

Nil.

Conflicts of interest

Ho KH – Honoraria: Eisai, Novartis, Schwabe Pharma, Teva; advisory boards: Eisai, Eli Lilly, Lundbeck, Novartis, Pfizer, Teva.

Ong JY – Honoraria and advisory boards: Novartis, Teva, Lundbeck, DKSH, AbbVie.

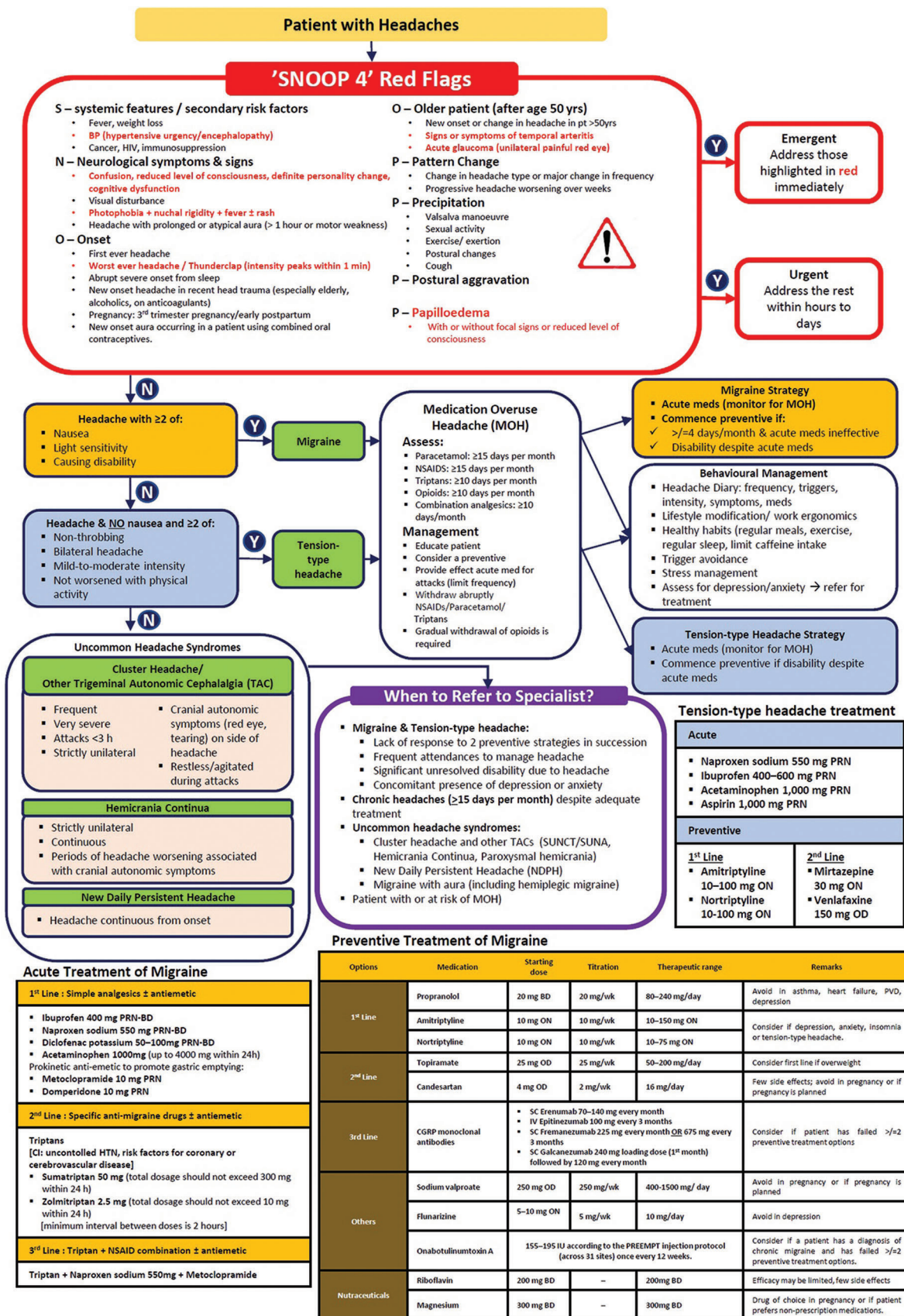


Figure 2: Algorithm for approach, treatment and management of headache disorders. BD: twice daily, NSAID: nonsteroidal anti-inflammatory drug, OD: every day, ON: every night, PRN: as necessary

Supplemental digital content

Appendix at <http://links.lww.com/SGMJ/A332>

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