

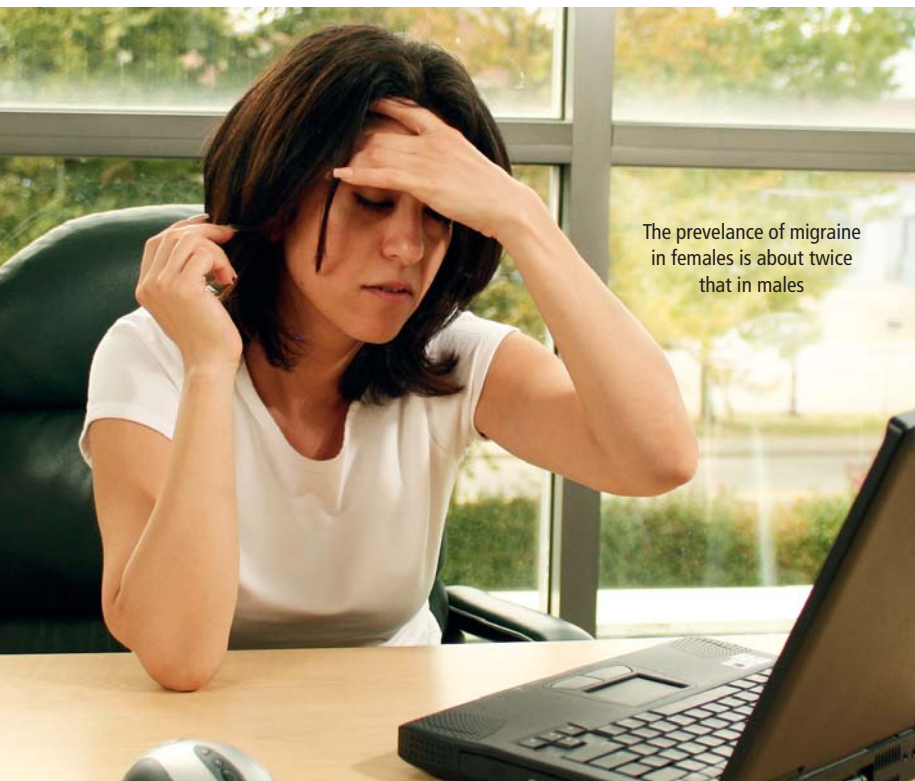


# Recommendations for the Management of Migraine

The Multidisciplinary Panel on Neuropathic Pain

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Migraine headache is a common and often undertreated condition in the Asia-Pacific region. The Multidisciplinary Panel on Neuropathic Pain has come out with recommendations for the management of migraine. The recommendations highlight the epidemiology of the condition as well as various approaches for the diagnosis and treatment of migraine.



The prevalence of migraine in females is about twice that in males

## I. Epidemiology, Classification and Pathophysiology

Migraine is a recurrent, often debilitating headache disorder that causes significant impairment to the patient's quality of life.<sup>1</sup> The International Headache Society (IHS) has classified migraine into six subtypes<sup>2</sup>:

- migraine without aura
- migraine with aura
- childhood periodic syndromes that are commonly precursors of migraine
- retinal migraine
- complications of migraine
- probable migraine

Each of these subtypes is characterized by specific features and associated symptoms. These recommendations focus on the first two subtypes: migraine with and without aura. The main difference between these two subtypes is the presence of focal neurological symptoms in migraine with aura.<sup>2</sup> These symptoms generally precede or accompany the headache.

The prevalence of migraine in females (12%–17%) is about twice that in males (6%–8%); while migraine attacks may commence at any age, the highest incidence is between 35 and 45 years.<sup>1,3-6</sup> In some studies, the lifetime prevalence in females has been estimated to be as high as 24%.<sup>5</sup> Epidemiological studies have estimated the median frequency of migraine attacks to be 1–1.5 a month.<sup>1,3</sup> A survey in Hong Kong in 1998 revealed that the estimated prevalence of migraine is 12.5%, similar to that reported in Western populations, with a greater preponderance in females.<sup>7</sup>

More patients have migraine without aura than migraine with aura.<sup>1,5</sup> Migraine sufferers often have lower health-related quality of life than non-migraineurs.<sup>8</sup> The impact of migraine extends beyond the patient's personal life, affecting work, family and social activities.<sup>9</sup> In the United States, costs attributed to migraine amount to US \$13 million annually due to missed workdays and impaired work function.<sup>10</sup>

A number of clinical and community-based studies have demonstrated that patients with migraine are also likely to suffer from certain comorbid psychiatric disorders, such as depression, generalized anxiety disorder, panic disorder and bipolar

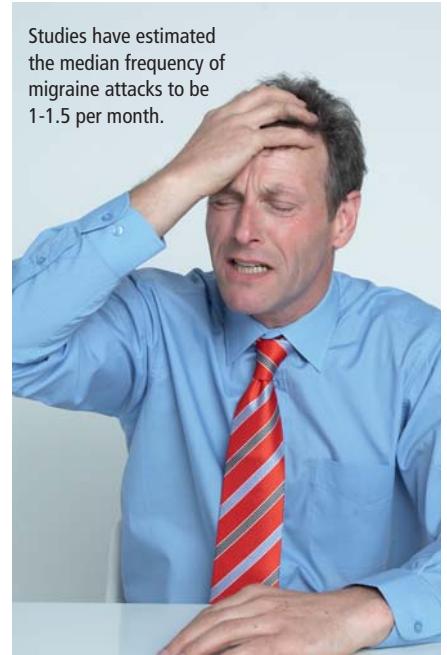
**"Migraine is a complex disease and the mechanisms underlying the pathogenesis of migraine are not fully understood"**

disorder.<sup>8,11,12</sup> Migraine may also be a risk factor for ischaemic stroke.<sup>13</sup> A meta-analysis of 14 observational studies found that the pooled relative risk of developing stroke was 2.16 (95% CI 1.89–2.48) in patients with migraine; the risk was higher in women who used oral contraceptives.<sup>13</sup> However, further studies need to be done to assess the increased risk of stroke in migraine sufferers, and other contributing factors, such as obesity, hypertension and smoking, may also need to be present.

Migraine is a complex disease and the mechanisms underlying the pathogenesis of migraine are not fully understood. Migraine is considered a primary disorder of the brain.<sup>3</sup> It is considered a type of neurovascular headache, where neural events cause dilation of blood vessels resulting in pain and further nerve activation. Migraine is believed to involve a dysfunction of brainstem pathways that normally modulate sensory input.<sup>3</sup> Based on the sensory disturbances experienced during migraine auras, the cortical spreading depression (CSD) theory has been proposed as a plausible mechanism.<sup>14</sup> The CSD theory involves both vascular and neuronal components and is associated with disturbances in nerve cell metabolism and reduced blood flow in the brain.

## II. Diagnosis

Migraine without aura typically presents as a unilateral and pulsating headache of moderate to severe intensity, usually lasting 4–72 hours. Routine physical activities such as walking or climbing stairs may aggravate the condition. Other associated symptoms include nausea and/or sensitivity to light and sound.<sup>2</sup> Migraine with aura is charac-



Studies have estimated the median frequency of migraine attacks to be 1-1.5 per month.

terized by reversible focal neurological (visual and/or sensory and/or speech) symptoms that gradually develop over 5–20 minutes and are sustained for less than 60 minutes. Usually, following the development of aura symptoms, headache with features similar to migraine without aura develops.<sup>2</sup>

Migraine is diagnosed mainly on the basis of a detailed patient history and a normal neurological examination.<sup>1</sup> In migraine patients with atypical headache patterns, it may be necessary to perform neuroimaging to rule out secondary headache disorders, which may suggest a potentially serious underlying pathological cause.<sup>15</sup> In particular, magnetic resonance imaging of the brain is recommended if<sup>1</sup>:

- neurological examination is abnormal
- onset of migraine attacks is after the age of 40 years
- the frequency or intensity of migraine attacks progressively increases

**Table 1. Diagnostic criteria for migraine with and without aura<sup>2</sup>**

**Migraine without aura**

- A. At least five attacks fulfilling criteria B, C and D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache with at least two of the following characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache, at least one of the following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- E. Not attributed to another disorder

**Migraine with aura**

- A. At least two attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6\*
- C. Not attributed to another disorder

\* Specific diagnostic criteria for each of the subforms of migraine with aura (1.2.1. typical aura with migraine headache, 1.2.2. typical aura with non-migraine headache, 1.2.3. typical aura without headache, 1.2.4. familial hemiplegic migraine, 1.2.5. sporadic hemiplegic migraine and 1.2.6. basilar-type migraine) can be found in the International Classification of Headache Disorders, 2nd edition (ICHD-2).<sup>2</sup>

- there is a change in symptoms associated with migraine
- new psychiatric symptoms accompany migraine attacks

The IHS has developed specific diagnostic criteria for migraine headaches with and without aura (Table 1).<sup>2</sup>

Patients with migraine often exhibit symptoms that fulfill the criteria for multiple subtypes. These patients should receive appropriate multiple headache diagnoses according to their symptoms.<sup>2</sup>

This recommendation focuses on the management of migraine in adults, for the treatment of acute attacks and for the prophylaxis of migraine. The pharmacological treatments for

migraine included in this recommendation are based on the published guideline from the European Federation of Neurological Societies (EFNS).<sup>1</sup> However, some agents included in this recommendation may not be approved for use in migraine headache disorders. Full prescribing information should be consulted before initiating drug therapy.

**III. Evidence for the Acute Treatment of Migraine**

Effective management of migraine is challenging because of the complexity of the condition and the variation of symptoms. Treatments for acute attacks should be rapid, with treatment

initiated as soon as an attack is recognized, and consistent to prevent recurrence, enable patients to regain their ability to function, and reduce the need for backup and rescue medications.<sup>3,16</sup> Generally, pharmacological treatment is the mainstay of management of acute attacks (Figure 1).

**Pharmacological Management**

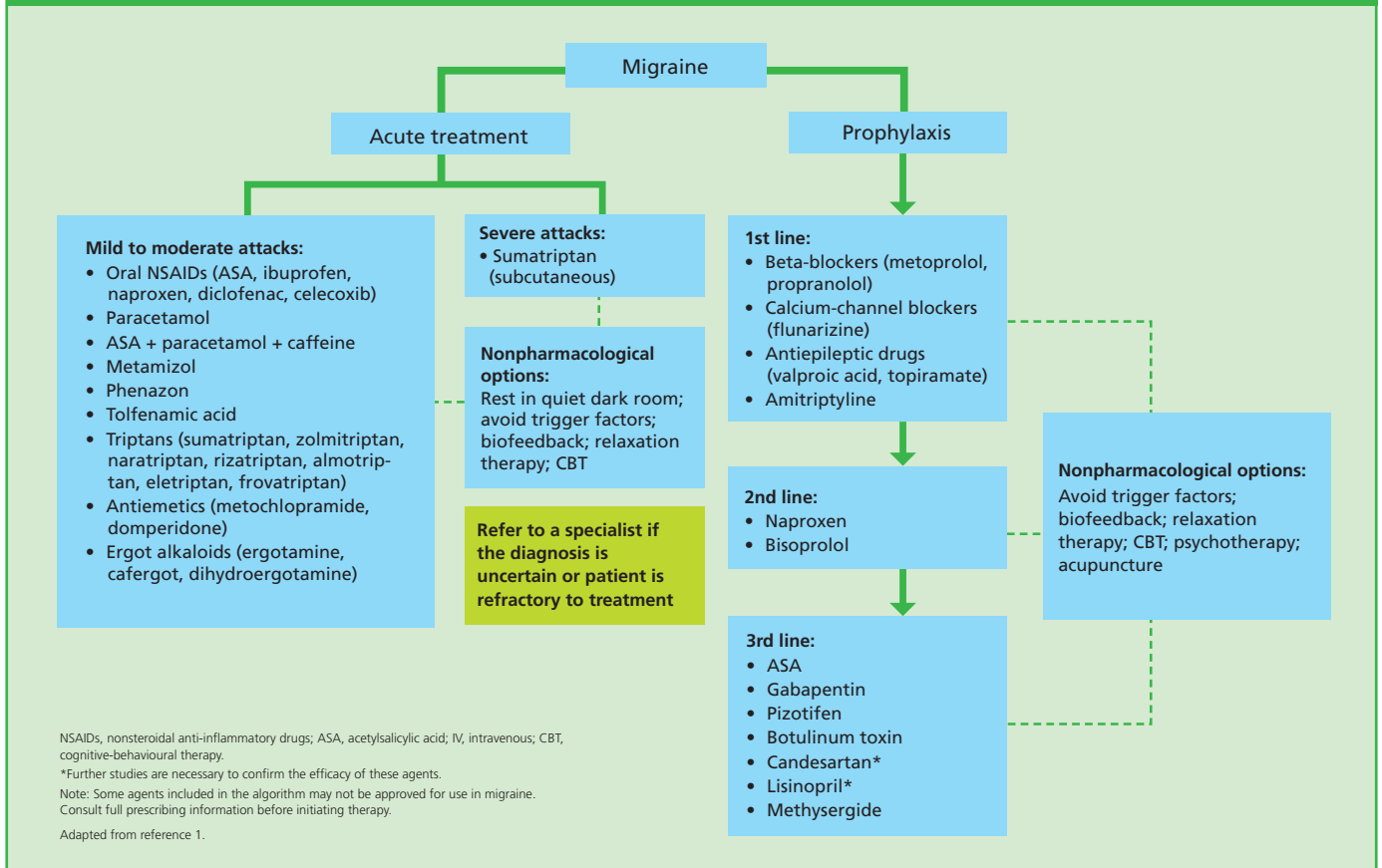
**Analgesics**

The first-line treatment for mild to moderate attacks of migraine are analgesics, mainly oral nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>1,16</sup> For very severe attacks, the EFNS guideline recommends intravenous acetylsalicylic acid (ASA);<sup>1</sup> however, this formulation is unavailable in Hong Kong. NSAIDs are believed to relieve pain by both central and peripheral mechanisms, primarily through the inhibition of cyclooxygenase activity and prostaglandin synthesis.<sup>17</sup>

Several double-blind, placebo-controlled trials have demonstrated the efficacy of oral NSAIDs, such as ASA,<sup>18-20</sup> ibuprofen<sup>19,20</sup> and diclofenac.<sup>21,22</sup> In one trial, ASA 1,000 mg was as effective as ibuprofen 400 mg, reducing headache severity from moderate or severe to mild or no pain in 52% of patients compared with 60% of patients treated with ibuprofen.<sup>20</sup> NSAIDs are usually well tolerated by most patients; the most frequent side effects include gastrointestinal symptoms and bleeding.<sup>1,23</sup>

A randomized, open-label trial of celecoxib versus naproxen for the treatment of acute migraine was published recently.<sup>24</sup> Patients were randomized to celecoxib 400 mg (n=30) or naproxen (n=30) and took the study medication for the first acute migraine episode that occurred during the study period. Fifty-two

Figure 1. Proposed treatment algorithm for migraine



patients suffered a migraine episode during the study period, with patients in each group reporting significant improvements in pain severity; there was no significant difference in the magnitude of improvement between groups.<sup>24</sup> The incidence of gastric pain was significantly lower in the celecoxib than in the naproxen group (p=0.029).

Other analgesics with demonstrated efficacy in treating acute migraine attacks include phenazon, metamizole, tolfenamic acid and paracetamol.<sup>1</sup> A fixed combination of ASA, paracetamol and caffeine was shown to be more effective than each drug taken separately.<sup>25</sup>

One possible complication with

the overuse of analgesics in migraine therapy is medication overuse headaches (MOH).<sup>16,23</sup> To prevent this, it is recommended that simple analgesics should not be taken for more than 15 days/month and combined analgesics for not more than 10 days/month.<sup>1</sup> Patients should be cautioned about the possibility of MOH even when taking analgesics less frequently.

**Triptans**

Triptans (5-HT<sub>1</sub> receptor-specific agonists) are widely prescribed, migraine-specific medications with well-established efficacy. Commonly used triptans include sumatriptan,

zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan.<sup>1</sup> Usually, these drugs are used to treat moderate to severe migraine or mild to moderate migraine that is unresponsive to analgesics.<sup>23</sup> Triptans

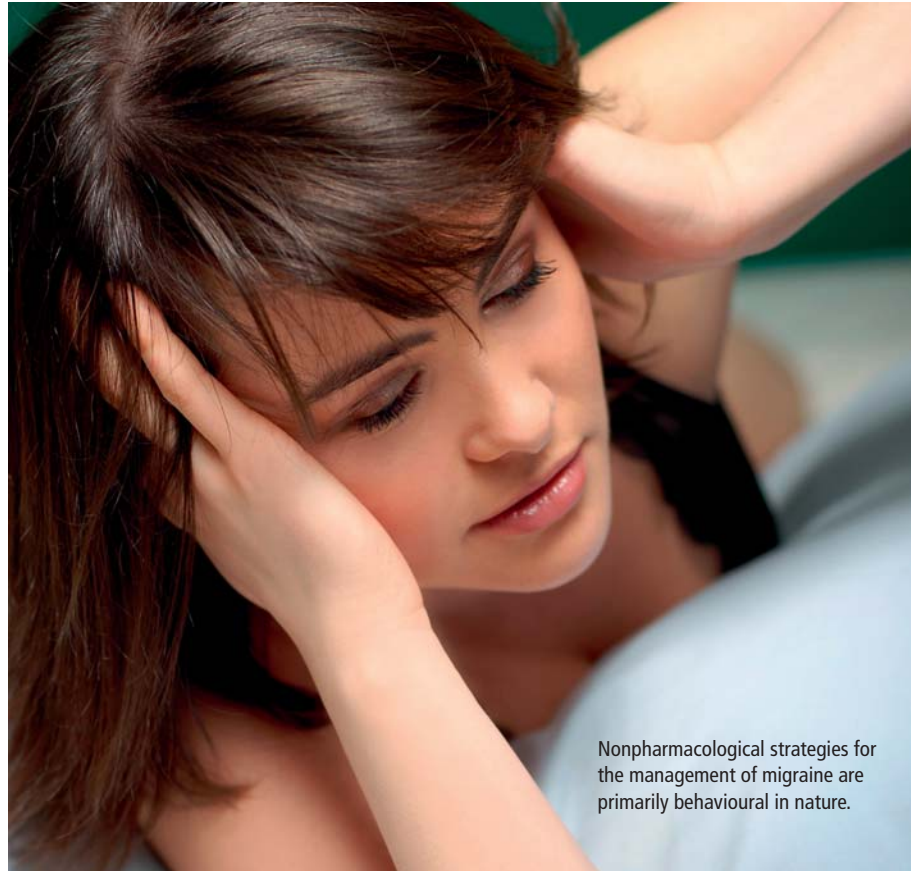
**"The precise mechanism of action of triptans in migraine is not well understood"**

are effective in about 60% of non-responders to NSAIDs.<sup>26</sup> For severe attacks, subcutaneously injectable sumatriptan can be administered as it can reach peak blood concentrations in only 15 minutes, faster than any other migraine-specific drug.<sup>23</sup> In one study, up to 80% of patients experienced pain relief 2 hours following subcutaneous administration of sumatriptan.<sup>27</sup> Non-oral forms of triptans are suitable options for patients who experience nausea and/or vomiting.

The precise mechanism of action of triptans in migraine is not well understood. Triptans act on the receptors located in meningeal arteries (5-HT<sub>1B</sub>) and trigeminovascular fibre endings (5-HT<sub>1D</sub>), resulting in vasoconstriction of cerebral blood vessels, inhibition of the release of vasoactive neuropeptides and inhibition of nociceptive neurotransmission.<sup>28</sup>

Early intake of triptans (within 1 hour of headache onset) improves efficacy.<sup>29</sup> However, caution should be exercised as this can lead to frequent drug intake, which may ultimately result in MOH.<sup>1,23,30</sup> Triptan use should be restricted to a maximum of 10 days/month.<sup>1</sup> Another concern with triptan use is headache recurrence, which occurs in about 15%–40% of patients.<sup>1</sup> Subcutaneous sumatriptan has the highest recurrence rate, while naratriptan and frovatriptan have the lowest. Patients who experience headache recurrence may benefit from a second dose of the same triptan.<sup>1</sup>

Triptan administration is not recommended during the aura phase of migraine, mainly due to safety concerns and lack of efficacy when taken during this time.<sup>1</sup> Contraindications for triptans include untreated arterial hypertension, coronary heart disease, Raynaud's disease, history of ischaemic stroke, pregnancy, lactation and severe



Nonpharmacological strategies for the management of migraine are primarily behavioural in nature.

liver or renal failure.<sup>1</sup>

A meta-analysis of 53 randomized, active-controlled trials compared the efficacy and safety of six oral triptans (rizatriptan, sumatriptan, zolmitriptan, eletriptan, almotriptan and naratriptan).<sup>31</sup> The key efficacy endpoints were headache relief at 2 hours, pain-free at 2 hours, sustained freedom from pain and consistency in migraine pain relief (headache relief in at least two of three treated attacks). Results indicated that all triptans were well tolerated. Rizatriptan 10 mg exhibited the greatest efficacy across all key endpoints. The authors concluded that rizatriptan 10 mg, eletriptan 80 mg and almotriptan 12.5 mg provide the highest likelihood of consistent success in the management of acute migraine

attacks.

A number of randomized, controlled clinical trials have been conducted to compare the efficacy of triptans with other migraine treatments; in general, triptans demonstrated comparable efficacy with analgesics, but were superior to ergotamines.<sup>1,20,22,32,33</sup> For example, oral sumatriptan 100 mg improved headache from severe or moderate to mild or none in 53% of patients, which was

**"A variety of supportive strategies may also help alleviate symptoms of migraine"**

comparable to the combination of ASA 900 mg and metoclopramide 10 mg (57% of patients).<sup>32</sup> In another study, significantly more patients receiving oral sumatriptan 100 mg experienced reduced intensity of headache (from severe or moderate to mild or none) by 2 hours after drug intake, than those receiving the combination of ergotamine tartrate 2 mg and caffeine 200 mg (66% vs 48%;  $p < 0.001$ ).<sup>33</sup>

### Antiemetics

Adjunctive therapy with antiemetics such as metoclopramide 20 mg or domperidone 20–30 mg is recommended for migraine-associated symptoms such as nausea and impaired gastric motility.<sup>1,23</sup> These drugs may be administered 20–30 minutes before, or concomitantly with, an analgesic or triptan.

### Ergot alkaloids

The ergot alkaloid ergotamine has been used in the treatment of migraine for many years.<sup>34</sup> It acts as an agonist on a variety of receptors, including  $\alpha$ -adrenoceptors, 5-HT<sub>1B/1D</sub> and dopamine D<sub>2</sub> receptors. Its major pharmacological action is vasoconstriction of large arteries, such as the pulmonary, cerebral, temporal and coronary arteries, which results in increased arterial blood pressure. Other available ergot alkaloid preparations include Cafergot® (caffeine and ergotamine) and dihydroergotamine.<sup>23</sup>

Ergotamine is associated with a number of side effects, including nausea, vomiting, paresthesia, weakness in the legs and ergotism.<sup>1,34</sup> It is contraindicated in the presence of cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, pregnancy and lactation. Ergotamine has a long half-life and is associated with a lower

recurrence rate.<sup>1</sup> As a result, it should be restricted to a selected group of migraine patients, specifically, those with prolonged attacks or regular recurrence.<sup>1,34</sup> Ergot alkaloids also have the potential to induce MOH and therefore their use should be limited to 10 days/month.<sup>1,23,30</sup>

### Nonpharmacological Management

The nonpharmacological treatment strategies for migraine are mainly behavioural in nature. They aim to decrease the emotional impact and disability from headaches and help patients to develop better pain-coping techniques. Most of these strategies are based on anecdotal evidence,<sup>35</sup> and very few have been evaluated in clinical studies.

- Biofeedback: Using a sensitive monitoring instrument, patients learn to detect and alter certain physiological processes at their own will.<sup>35</sup> Two useful common techniques are thermal control and blood volume pulse biofeedback.
- Relaxation therapy: Relaxation techniques, such as muscular relaxation, breathing exercises or direct imagery, are used. Although predominantly used for migraine prophylaxis, some patients find this technique helpful to abort a slowly evolving migraine.
- Cognitive-behavioural therapy (CBT): Patients learn to identify and modify their maladaptive responses to migraine attacks. This mainly involves stress-management training.

Other less established nonpharmacological approaches include hypnosis, chiropractic manipulations, transcutaneous electrical nerve stimulation (TENS), acupuncture and occipital

## "The most effective nonpharmacological strategy for preventing migraine is identification and avoidance of trigger factors"

or supraorbital nerve blockade with local anaesthetics.<sup>23,35</sup> Most of these techniques may be used alone or in combination. However, due to availability, cost, patient acceptance and time commitment involved, the use of these techniques in migraine patients may be limited.<sup>34</sup>

### General Supportive Measures

A variety of supportive strategies may also help alleviate symptoms of migraine. These include applying cold or pressure to the head, resting in a quiet, dark room, sleeping and avoiding potential triggers (eg, stress, dietary and environmental factors).<sup>1,35</sup>

### IV. Evidence for the Prophylaxis of Migraine

Both nonpharmacological and pharmacological treatments play a role in the prophylaxis of migraine attacks (Figure 1). Drug therapy for prophylactic treatment of migraine may be warranted in patients who experience frequent, severe attacks that cause significant disruption in their daily lives. Generally, preventive treatment for migraine is indicated when<sup>1</sup>:

- quality of life, attendance and/or productivity at school/work are severely impaired



Effective management of migraine can be challenging because of the complexity of the condition.

- two or more attacks occur each month
- acute drug treatment of migraine attacks is ineffective
- auras are frequent, very long or uncomfortable

Referral to a specialist may be necessary in special circumstances, such as when the diagnosis is uncertain or medications are ineffective in controlling symptoms within a reasonable time.

### Nonpharmacological Management

The most effective nonpharmacological strategy for preventing migraine is identification and avoidance of trigger factors.<sup>35</sup> A careful review of the patient's headache diary can help identify potential triggers, such as stress,

diet, behavioural changes (missed meals, too much or too little sleep) and environmental factors (loud noises, weather changes, strong odours).<sup>16,35</sup>

Other strategies include biofeedback, relaxation therapy, CBT and psychotherapy (in patients with comorbid psychiatric disorder).<sup>23,35</sup> There is conflicting evidence for the benefits of biofeedback in the prevention of migraine attacks. A meta-analysis of 25 controlled studies showed that biofeedback was as efficacious as pharmacotherapy in preventing migraine attacks.<sup>35</sup> In contrast, another published report challenged the value of biofeedback.<sup>35</sup>

There exist other nonpharmacological prophylaxes for migraine, which have not been evaluated for long-term safety and efficacy. These include aerobic training, chiropractic therapy,

osteopathy, naturopathy, homeopathy, TENS and acupuncture.<sup>23,35</sup>

Any benefit gained from these nonpharmacological therapies may largely be due to a placebo effect. Nevertheless, it is worth considering these as adjunctive treatments, mainly in patients who have failed to respond to conventional pharmacological treatment.

### Pharmacological Management

#### First-line Treatment

##### *Beta-blockers*

One of the first-line treatments for migraine prophylaxis is beta-blockers, specifically metoprolol and propranolol.<sup>1</sup> Several randomized, clinical trials have provided evidence for the therapeutic efficacy of these drugs. A systematic review of 58 randomized trials (n=5,072) involving propranolol (26 comparisons with placebo; 47 comparisons with other migraine drugs) found that propranolol (60–320 mg/day) reduced migraine frequency significantly more than placebo in the short term.<sup>36</sup> Due to lack of long-term follow-up studies, no firm conclusions could be made regarding the long-term efficacy of propranolol. Moreover, the small sample size of most trials prevented the detection of any difference in efficacy between propranolol and other migraine-preventing drugs. Another, similar meta-analysis (n=2,403) also came to the same conclusion about the short-term efficacy of propranolol.<sup>37</sup> On average, propranolol (about 160 mg/day) yielded a 44% reduction in migraine activity compared with a 14% reduction with placebo.<sup>37</sup> Generally, beta-blockers are well tolerated. Common adverse effects reported in clinical trials include fatigue, depression, nausea, dizziness and insomnia.<sup>12</sup>

*Calcium-channel blockers*

Another drug of first choice in migraine prophylactic therapy is the calcium-channel blocker flunarizine. Several controlled trials have demonstrated that flunarizine is superior to placebo and as efficacious as beta-blockers in migraine prevention.<sup>12</sup> Flunarizine is given at a dose of 5–10 mg/day.<sup>1,12</sup> The most common side effects include weight gain, somnolence, dry mouth, dizziness, hypotension, depression and extrapyramidal symptoms.<sup>12,16</sup>

*Antiepileptic drugs*

Antiepileptic drugs such as valproic acid and topiramate are also recommended as first-line prophylactic drugs for migraine.<sup>1</sup> Their efficacy rates are comparable with those of metoprolol, propranolol and flunarizine.<sup>1</sup> The efficacy of divalproex sodium (DVPX) was demonstrated in a randomized, double-blind, placebo-controlled, parallel-group study.<sup>38</sup> Forty-four to 45% of DVPX-treated patients compared with 21% of patients receiving placebo achieved 50% or more reduction in their migraine attack frequencies ( $p < 0.05$  vs placebo). This study was included in a systematic review, which evaluated the safety and efficacy of various anticonvulsant drugs in migraine prophylaxis.<sup>39</sup> Four placebo-controlled trials of DVPX involving 579 patients confirmed that, overall, DVPX was superior to placebo (OR 3.39; 95% CI 1.47–7.78).<sup>39</sup> One trial of sodium valproate (OR 4.67; 95% CI 1.54–14.14) and three trials of topiramate (OR 3.65; 95% CI 2.47–5.38) also demonstrated the superiority of active treatment to placebo.<sup>39</sup>

*Second-line Treatment*

Amitriptyline (50–150 mg) has been the only antidepressant with consistent evidence for efficacy in migraine pre-

vention.<sup>1,12,16</sup> In one randomized, placebo-controlled, crossover study comparing amitriptyline and propranolol, amitriptyline significantly reduced the severity, frequency and duration of headache attacks, while propranolol only reduced the severity of attacks.<sup>40</sup> Due to central side effects, amitriptyline is recommended as a second-line treatment in the EFNS guideline.<sup>1</sup> However, in Hong Kong, amitriptyline is one of the most widely prescribed drugs for migraine prophylaxis and has been included in the treatment algorithm (Figure 1) as an alternative first-line agent. Amitriptyline may be useful in younger patients who may also have tension-type headache; it should be used with caution in the elderly.

Other drugs recommended as second choice for migraine prophylaxis include naproxen 1,000 mg and bisoprolol 5 mg.<sup>1,41,42</sup>

*Third-line Treatment*

Two large cohort trials have shown that ASA 200–300 mg is effective in reducing migraine frequency.<sup>43,44</sup> However, the use of ASA in migraine prophylaxis is limited, as frequent use of ASA can lead to MOH.<sup>1,12</sup> In a double-blind, placebo-controlled trial, gabapentin 2,400 mg was shown to be superior to placebo on several headache indices, including reduction in median 4-week migraine rate ( $p = 0.006$ ), percentage of patients achieving 50% reduction in 4-week migraine rate ( $p = 0.008$ ), average number of days per 4 weeks with migraine ( $p = 0.006$ ) and median change in 4-week headache rate ( $p = 0.013$ ).<sup>45</sup> Gabapentin was generally well tolerated, with mild to moderate dizziness and somnolence being the most common side effects.<sup>45</sup> Pizotifen is another agent with documented efficacy in migraine prophylaxis, but

may be associated with side effects such as weight gain and drowsiness.<sup>16</sup>

In recent years, there has been increased interest in botulinum toxin for migraine prophylaxis. Scalp injections of botulinum toxin type A (25 U) significantly reduced migraine frequency, migraine severity, acute medication usage and migraine-related vomiting compared with placebo during a 90-day follow-up period.<sup>46</sup> Candesartan<sup>47</sup> and lisinopril<sup>48</sup> have also shown efficacy in migraine prophylaxis in one placebo-controlled trial each. However, their use is controversial and further randomized, controlled trials are needed to establish the therapeutic efficacy of these agents.

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