Management of Migraine

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Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

Migraine is a complex neurovascular disease characterised by episodic attacks of severe headache accompanied by autonomic and neurological symptoms. Two types of migraine have been identified: (1) common migraine, or migraine without aura, occurring in about 70% of migraine patients (migraineurs); (2) classic migraine, or migraine with aura. In the latter case, aura symptoms are usually manifested as visual hallucinations such as flashing lights, zig-zag lines or blind spots, although sensory and motor dysfunction may also occasionally occur.

Migraineurs are defined as those individuals who have had at least two attacks of classic migraine, or at least five attacks of common migraine. Thus, any individual can suffer an isolated migraine attack without being a migraine patient. On the other hand, patients suffering from at least one attack during the previous year are termed active migraineurs. The epidemiology of migraine is similar across western countries and is highly dependent on age and gender. About 10% of the general population are active sufferers. However, several studies have shown that migraine is two to three times more prevalent in adult females than it is in adult males, with females in their 40's having the highest incidence. In active migraineurs, the median attack frequency is 1.5 per month and the median duration of attacks is just under one day although attacks lasting several days are known to occur. Thus, there is enormous variation from patient to patient as well as from attack to attack.

Migraine attacks can have profound effects on the day-to-day life and the well-being of the sufferer. Migraineurs suffering from frequent, debilitating attacks may have to absent themselves from work, or may experience reduced productivity even when attempting to perform normal daily activities. In addition, the impact of migraine stretches beyond the time of the actual attack, since some patients may have to curtail their activities to avoid situations that may trigger an attack. Reduction in the burden of migraine may be achieved through accurate diagnosis, assessment of the disability experienced by the individual and appropriate, well-executed treatment strategies. Moreover, the goal of the treatment should be not only to relieve pain, but to restore the patient's ability to function normally as rapidly as possible.

Diagnosis

Migraine is a common clinical disorder that continues to be highly under-recognized. Diagnosis is difficult because it is hard to elicit precise information from a patient who is trying to translate symptoms into words, the symptoms are somewhat similar to those of tension headaches, and the manifestation of attacks exhibits considerable inter- and intra-patient variability. The situation is further complicated by the fact that there are no biological markers to confirm diagnosis.

Based on the recommendations of the International Headache Society, a number of diagnostic criteria for migraine have been put forward (Table 1). These guidelines should all be taken into account when formulating a patient interview with the aim to obtain an accurate headache history of the sufferer. Such history-taking plays a key role in migraine diagnosis and should thoroughly address all the relevant criteria. During the interview, it is important to look out for and recognise certain patterns that are typical of migraine attacks. Thus, the patient should be questioned about:

- Family history of migraine
- Abatement of the headache with sleep
- Perimenstrual or periovulation timing of migraine attacks
- Stimulation of attack by sustained exertion
- Consistent precipitation of headaches by reliable triggers (Table 2).

Patient interview alone is not always sufficient to make a definite diagnosis of migraine. In such cases, it is essential for the patient to undergo a physical examination in order to eliminate the possibility that there is a more serious underlying cause of the headaches. Features which raise concern and which require immediate referral include:

1) a first severe headache of rapid onset
2) a marked change from a previously stable long-standing headache pattern

Table 1: Diagnostic criteria for Migraine

I. Migraine without aura

1) At least five attacks fulfilling criteria (2) to (4)
2) Headache attacks, untreated or unsuccessfully treated, lasting 4 to 72 hours
3) At least two of the following headache characteristics:
   a) unilateral location
   b) pulsation
   c) moderate to severe pain intensity (interferes with or prohibits daily activities)
   d) aggravation by motion (e.g. walking up stairs or similar routine activity)
4) At least one of the following associated symptoms:
   a) nausea and /or vomiting
   b) photophobia
   c) phonophobia
   d) osmophobia (aversion to odours)
5) No evidence of related organic disease

II. Migraine with aura

1) At least two attacks fulfilling criteria (2) to (5)
2) One or more fully reversible aura symptoms (usually manifested as visual disturbances)
3) At least one aura symptom develops gradually over > 4 minutes, or two or more symptoms develop in rapid succession
4) Duration of aura symptoms is 4 to 60 minutes
5) Headache follows aura within one hour, or begins before or simultaneously with aura

3) a new onset of headache after age 50

4) the precipitation of severe head pain by bending down, exertion or coughing

5) the presence of systemic symptoms such as fever, malaise, myalgia or weight loss.

Pharmacological Management of Migraine

Traditionally, the pharmacological management of migraine has focussed on two major approaches: symptomatic treatment and prophylactic therapy.

Symptomatic treatment

The objective of symptomatic treatment is to reduce the intensity and duration of pain and its associated symptoms, whilst optimising the patient's ability to function normally. Treatment of attacks generally involves the use of one or a combination of the following classes of drugs: simple analgesics, nonsteroidal anti-inflammatory drugs, antiemetics, narcotic analgesics, ergot derivatives and serotonin(1)-agonists. The choice of the medication depends on a number of patient factors (Table 3), and on the treatment strategy selected.

There are two major strategies for the treatment of migraine: step-care and stratified care. In step-care, all patients begin at the bottom of the therapeutic pyramid, starting with an inexpensive simple analgesic. After an appropriate trial, if treatment is unsuccessful, therapy is escalated until patients get the treatment that is successful. In stratified-care, the treatment of the patient is immediately matched with the severity of the condition. Thus, the patient's treatment needs must be identified by assessing the degree of disability experienced by the patient. In mild attacks, the patient can proceed with daily activities with only very minimal disruption; in moderate attacks, the patient experiences moderate impairment in normal activities; in severe attacks, the patient is unable to proceed with daily activities and experiences impaired efficiency in any capacity due severe discomfort; in ultra-severe cases, there is prolonged inability to function in any capacity.

Table 4 summarises the various drugs commonly used to treat mild and moderate attacks of migraine, and gives the initial dose that is generally used to treat migraine attacks in adult patients. Milder migraine headaches often respond to paracetamol or aspirin, but since peristalsis is often reduced during attacks the medications may fail to be sufficiently absorbed to be effective. Therefore, effervescent or dispersible formulations are preferable. Other non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, mefenamic acid and tolfenamic acid have been used in the treatment of moderate migraine attacks, but their use may be restricted by their gastrointestinal side effects. In addition, oral anti-emetics, such as metoclopramide or prochlorperazine, are usually required as adjunctive therapy in order to relieve the symptoms of nausea associated with migraine. If vomiting is a problem,

Table 2: Precipitating factors of migraine attacks.

- Stress/strain/emotional disturbances
- Light stimulation/glare
- Lack of sleep, fatigue
- Excessive sleep
- Menstrual periods
- Fasting
- Alcohol
- Specific foods, such as chocolate, caffeine, aged cheeses
- Medications, such as oral contraceptives, nitroglycerine

Table 3: Factors influencing the choice of medication for acute migrane attacks

1) Severity of the attack (mild, moderate, severe)
2) Presence or absence of vomiting
3) Time from onset of pain to peak pain level
4) Comorbid medical conditions
5) Concomitant use of other medications
6) Adverse effects of the drug

domperidone or prochlorperazine may be administered rectally. Oral analgesic preparations containing metoclopramide constitute a convenient therapeutic alternative. Combination medications containing paracetamol or aspirin with codeine and/or caffeine may be used in patients who do not respond to simple analgesic therapy. However, such products should be used intermittantly and on a short-term basis in order to preclude rebound headache.

Oral ergotamine has been used in the management of migraine for many years. However, its use is limited by a number of factors. Firstly, it is associated with variable bioavailability due to erratic absorption. It has to be taken early during an attack to prevent vomiting and may actually sometimes cause nausea, vomiting, abdominal pain and muscular cramps as side effects. In addition, it cannot be prescribed in conjunction with commonly used prophylactic migraine treatments such as beta-blockers. To avoid habituation, the frequency of administration of ergotamine should be limited to no more than twice a month, treatment should not be repeated at intervals of less than four days and it should not be given prophylactically.

The newer triptan drugs, mainly sumatriptan and zolmitriptan, have today become the drugs of choice for the treatment of moderate migraine attacks which are unresponsive to NSAID therapy. These agents are highly selective serotonin 5HT1B/1D receptor agonists inhibiting cranial vasodilation and neurogenic inflammation. Zolmitriptan, which has improved oral bioavailability relative to sumatriptan, also crosses the blood brain barrier and has central effects, inhibiting the transmission of pain impulses. Unlike ergotamine, both sumatriptan and zolmitriptan are effective whether taken early or late after the onset of headache; however, sumatriptan is not effective during the aura phase preceding headache onset. Another advantage of the triptans over ergotamine is that they can be prescribed concomitantly with beta-blockers. However, the triptans should not be co-administered with ergotamine because of increased risk of vasospasm; in fact, ergotamine should be avoided for at least six hours after administration of either of the triptans, while sumatripan and zolmitriptan should be avoided for 24 hours and 6 hours respectively following the use of ergotamine. Side-effects associated with the triptans include nausea, dizziness, drowsiness, heat sensations, tingling, weakness, transient increases in blood pressure and heaviness, tightness or pressure in the neck, throat limbs or chest. Thus, these agents are contra-indicated in patients suffering from cardiac diseases or uncontrolled hypertension. Also, like ergotamine, they are contraindicated during pregnancy.

Severe migraine attacks may require parenteral administration of dihydroergotamine or triptan drugs, as well as adjunctive parenteral medications. Hence the patient should be referred to a physician's clinic or, in ultra-severe cases, to the hospital emergency department.

Prophylactic treatment

The main objective of prophylactic therapy is the reduction of the frequency, duration and intensity of attacks by at least 50% using the least amount of medication with the fewest side effects. Such therapy should be considered for patients suffering from two or more attacks per month, which do not respond to symptomatic treatment. When selecting a medication for prophylaxis, it is important to take into account the possible presence of co-morbid conditions and the drugs' side-effects. Agents used include:

1) beta-blockers without instrinsic sympathomimetic activity, such as atenolol, propranolol and metoprolol but not pindolol (contraindicated in patients with asthma, chronic obstructive pulmonary disease, peripheral vascular disease, heart failure and diabetes mellitus and in pregnancy)
2) tricyclic antidepressants, such as amitriptylene (contraindicated in patients with glaucoma and cardiac, kidney, liver, prostate or thyroid disease)
3) calcium-channel blockers, such as verapamil, nifedipine and flunarizine (contraindicated in

Table 4: Commonly used medications for the treatment of migraine of different severity.

Drug	Proprietary name	Initial Oral Adult Dose
I. Mild attacks		
Paracetamol	Panadol® (Sterling Health)	1000 mg
Aspirin	Aspro® (Roche)	500-1000 mg
Ibuprofen	Nurofen® (Crookes Healthcare)	400 mg
Naproxen sodium	Naprosyn® (Roche)	500 mg
Metoclopramide	Maxolon® (SmithKline Beecham)	10 mg
Domperidone	Motilium® (Janssen)	20 mg
Dimenhydrinate	Dramamine® (Searle)	100 mg
II. Moderate attacks		
Ibuprofen	Nurofen® (Crookes Healthcare)	400 mg
Naproxen sodium	Naprosyn® (Roche)	500mg
Mefenamic acid	Ponstan® (Parke-Davies)	500 mg
Tolfenamic acid	Clotam® (GEA Ltd.)	200 mg
Ergotamine	Migril ® (GlaxoWellcome)	1-2 mg
Sumatriptan	Imigran® (GlaxoWellcome)	50-100 mg
Zolmitriptan	Zomig® (Zeneca)	2.5-5 mg
Combination drugs:		
Paracetamol+ codeine+caffeine	Solpadeine® (Smithkline Beecham)	2 tablets
Paracetamol+codeine	Migraleve® (Pfizer)	2 tablets
Aspirin+codeine	Codis® (Reckitt & Colman)	2 tablets

pregnancy, and in patients with hypotension, arrhythmias, congestive heart failure)

4) pizotifen, which however may cause fatigue, drowsiness and weight gain

5) sodium valproate, which however has occasionally been associated with severe hepatic and pancreatic toxicity

6) NSAIDs, which however should only be used intermittently, for example to prevent perimenstrual attacks, in view of their gastrointestinal side effects.

Except in the most resistant cases, it is recommendable to use only a single prophylactic agent at any time. Prophylactic therapy should not be expected to work immediately and may take several weeks before an effect is observed. Treatment should be started at a low dose, and the dosage subsequently increased to the maximally effective tolerable dose. The therapy should be continued for an adequate period, and then withdrawn gradually to minimise the risk of rebound headaches.

Conclusion

Pharmacists are in an excellent position to educate patients on the nature of migraine and its management and hence improve patient compliance. They may help patients to understand the actions of their medications and the possible adverse effects, drug interactions and contraindications (e.g. pregnancy) associated with their therapy. They may assess the degree of patient compliance to prescribed prophylactic medications. Pharmacists may also offer advice to patients on non-drug therapies such as relaxation techniques. Another important area is the identification and avoidance of triggering factors including specific foods, and hence the provision of dietary advice.

These factors make the pharmacist a key role-player in the provision of pharmaceutical care in the prevention and treatment of migraine. ✶

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Bibliography

Deleu, D., Hanssens, F., and Worthing, E. (1998) Symptomatic and prophylactic treatment of migraine - a critical reappraisal. Clinical Neuropharmacology, 21: 267-279.

Doughty, M., and Lyle, W. (1995) Medications used to prevent migraine headaches and their potential ocular adverse effects. Optometry and Vision Science, 72: 879-891.

Ferrari, M. (1998) Migraine. The Lancet, 351: 1043-1051.

Goadsby, P., and Olesen, J. (1997) Increasing the options for effective migraine management. Neuralgia, 48: S1-S3.

Headache Classification Committee of the International Headache Society. (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain. Neuralgia, 8: 1-96.

Lipton, R., and Stewart, W. (1997) Clinical applications of zolmitriptan (Zomig™, 311C90). Cephalgia, 17: 53-59.

Maizels, M. (1998) The clinician's approach to the management of headache. Western Journal of Medicine, 168: 203-212.

Pryse-phillips, W., Dodick, D., Edmeads, J., Gawel, M., Nelson, R., Purdy, A., Robinson, G., Stirling, D., and Worthington I. (1997) Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Medical Association Journal, 156: 1273-1287.

Zagami, A. (1997) 311C90: Long-term efficacy and tolerability profile for the acute treatment of migraine. Neuralgia, 48: S1-S3.

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Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

Assessment Questions:

1. Which of the following symptoms is not normally associated with migraine?
   a) headache
   b) nausea
   c) vomiting
   d) diarrhoea

2. In migraine, head pain is not accompanied by:
   a) photophobia
   b) phonophobia
   c) xenophobia
   d) osmophobia

3. Migraineurs are defined as those individuals who have had at least
   a) two
   b) three
   c) four
   d) five
   attacks of common migraine.

4. The highest incidence of migraine occurs in
   a) young boys
   b) young girls
   c) adult females
   d) adult males

5. What is the normal initial dose of zolmitriptan in the treatment of migraine in adults?
   a) 0.25 mg
   b) 2.5 mg
   c) 25 mg
   d) 250 mg

6. What is the normal initial dose of sumatriptan in the treatment of migraine in adults?
   a) 0.1 mg
   b) 1 mg
   c) 10 mg
   d) 100 mg

7. Which of the following drugs is used in the prevention of migraine attacks?
   a) amitriptylene
   b) propranolol
   c) pizotifen
   d) all of the above

8. Which of the following beta-blockers cannot used as a migraine prophylactic agent?
   a) atenolol
   b) pindolol
   c) propranolol
   d) metoprolol

9. Which of the following drugs can be used concomitantly with beta-blockers?
   a) zolmitriptan
   b) ergotamine
   c) verapamil
   d) dihydroergotamine

10. Which of the following foods is known to be a migraine triggering factor?
    a) carrots
    b) cheese
    c) potato
    d) rice

11. A migraine attack may be triggered by:
    a) stress
    b) excessive sleep
    c) insufficient sleep
    d) all of the above

12. Which of the following anti-emetics is generally administered rectally in migraine patients experiencing vomiting?
    a) metoclopramide
    b) domperidone
    c) dimenhydrinate
    d) none of the above

13. Which of the following drugs is used in the treatment of migraine attacks?
    a) nalidixic acid
    b) tolfenamic acid
    c) ascorbic acid
    d) none of the above

14. Which of the following drugs would be preferable in the first-line treatment of a mild migraine attack in an asthmatic individual?
    a) ibuprofen
    b) paracetamol
    c) atenolol
    d) naproxen

15. Which of the following drugs can be used to treat migraine in pregnant women?
    a) sumatriptan
    b) ergotamine
    c) zolmitriptan
    d) none of the above

16. Which of the following factors should be taken into account when selecting the appropriate antimigraine therapy for a patient?
    a) severity of the attack
    b) presence or absence of vomiting
    c) presence of concomitant medical conditions
    d) all of the above

17. What is the main reason for combination products containing NSAIDs to be used only intermittantly?
    a) prolonged use may give rise to rebound headache
    b) the patient may become tolerant to the medication
    c) the patient may develop an allergic reaction to the drug
    d) the high cost associated with continuous use of such products

18. Which of the following classes of drugs are not used in the management of migraine?
    a) beta-receptor blocking agents
    b) histamine-receptor agonists
    c) serotonin(1)-receptor agonists
    d) none of the above

19. Which of the following symptoms is not a common adverse effect associated with the triptan drugs?
    a) drowsiness
    b) warm sensation
    c) nausea
    d) skin rash

20. Amitriptylene should not be used to prevent migraine in patients with
    a) cardiac disease
    b) thyroid disease
    c) glaucoma
    d) all of the above