Guidelines for the diagnosis and management of migraine in clinical practice

Evidence

Études

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Abstract

Objective: To provide physicians and allied health care professionals with guidelines for the diagnosis and management of migraine in clinical practice.

Options: The full range and quality of diagnostic and therapeutic methods available for the management of migraine.

Outcomes: Improvement in the diagnosis and treatment of migraine, which will lead to a reduction in suffering, increased productivity and decreased economic burden.

Evidence and values: The creation of the guidelines followed a needs assessment by members of the Canadian Headache Society and included a statement of objectives; development of guidelines by multidisciplinary working groups using information from literature reviews and other resources; comparison of alternative clinical pathways and description of how published data were analysed; definition of the level of evidence for data in each case; evaluation and revision of the guidelines at a consensus conference held in Ottawa on Oct. 27–29, 1995; redrafting and insertion of tables showing key variables and data from various studies and tables of data with recommendations; and reassessment by all conference participants.

Benefits, harms and costs: Accuracy in diagnosis is a major factor in improving therapeutic effectiveness. Improvement in the precise diagnosis of migraine, coupled with a rational plan for the treatment of acute attacks and for prophylactic therapy, is likely to lead to substantial benefits in both human and economic terms.

Recommendations: The diagnosis of migraine can be improved by using modified criteria of the International Headache Society as well as a semistructured patient interview technique. Appropriate treatment of symptoms should take into account the severity of the migraine attack, since most patients will have attacks of differing severity and can learn to use medication appropriate for each attack. When headaches are frequent or particularly severe, prophylactic therapy should be considered. Both the avoidance of migraine trigger factors and the application of nonpharmacological therapies play important roles in overall migraine management and will be addressed at a later date.

Validation: The guidelines are based on consensus of Canadian experts in neurology, emergency medicine, psychiatry, psychology, family medicine and pharmacology, and consumers. Previous guidelines did not exist. Field testing of the guidelines is in progress.

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Résumé

Objectif : Fournir aux médecins et aux membres des professions paramédicales des lignes directrices sur le diagnostic et la prise en charge de la migraine en pratique clinique.

Options : L'éventail complet et la qualité des méthodes de diagnostic et de traitement disponibles pour la prise en charge de la migraine.

Résultats : Amélioration du diagnostic et du traitement de la migraine qui débouchera sur une atténuation de la souffrance, une amélioration de la productivité et une réduction du fardeau financier.

Preuves et valeurs : La création des lignes directrices a suivi une évaluation des besoins effectuée par des membres de la Canadian Headache Society et a comporté les mesures suivantes : énoncé d'objectifs, élaboration de lignes directrices par des groupes de travail multidisciplinaires qui ont utilisé des renseignements tirés de recensions des écrits et d'autres sources, comparaison d'autres moyens cliniques et description de la façon dont on a analysé des données publiées, définition du niveau des données probantes dans chaque cas, évaluation et révision des lignes directrices au cours d'une conférence consensuelle qui a eu lieu à Ottawa du 27 au 29 oct. 1995, rédaction d'une nouvelle version à laquelle on a ajouté des tableaux indiquant des variables clés et des données tirées de diverses études, ainsi que des tableaux de données et des recommandations, et réévaluation par tous les participants à la conférence.

Avantages, préjudices et coûts : L'exactitude du diagnostic joue un rôle important dans l'amélioration de l'efficacité du traitement. L'amélioration du diagnostic précis de la migraine, conjuguée à un plan rationnel de traitement des crises aiguës et de prophylaxie, devrait entraîner d'importants avantages sur les plans humain et financier.

Recommandations : Il est possible d'améliorer le diagnostic de la migraine en utilisant des critères modifiés de l'International Headache Society, ainsi que des entrevues semi-structurées auprès des patients. Le traitement approprié des symptômes devrait tenir compte de la gravité de la crise de migraine, car la plupart des patients sont victimes de crises dont la gravité diffère et peuvent apprendre à utiliser les médicaments qui conviennent à chaque type de crise. Lorsque les maux de tête sont fréquents ou particulièrement graves, il faudrait envisager une thérapie prophylactique. L'évitement des facteurs déclenchants de la migraine et le recours à des traitements non pharmacologiques jouent des rôles importants dans le traitement global de la migraine et cette question sera abordée ultérieurement.

Validation : Les lignes directrices sont fondées sur le consensus d'experts canadiens en neurologie, en médecine d'urgence, en psychiatrie, en psychologie, en médecine familiale et en pharmacologie, ainsi que de consommateurs. Il n'y avait pas de lignes directrices auparavant. L'essai terrain des lignes directrices est en cours.

Commanditaires : La conférence consensuelle a bénéficié d'une subvention de recherche sans restriction de Glaxo Wellcome Inc. La coordination rédactionnelle a été assurée par Medical Education Programs Canada Inc.

Population-based studies have consistently shown that about 5% of men and 15%–17% of women suffer migraine attacks.[1,2] Over 80% of these people suffer some degree of headache-related disability.[3] In the United States the estimated annual cost, including costs of direct medical care and lost productivity, exceeds $17 billion.[4]

However common, migraine is still underrecognized and undertreated,[2,5–8] perhaps in part because there are no biological markers to confirm the diagnosis. The need for a reliable diagnostic tool led to the publication of the International Headache Society (IHS) criteria.[9,10] All of these criteria tend to have high levels of either specificity or sensitivity, but not both. Validation of the IHS criteria is ongoing.[11] Although imperfect, these criteria are being increasingly accepted as an aid in diagnosis.

Clinical practice guidelines aim to state general principles for the improvement of clinical effectiveness and quality of care and to allow informed decision-making by both physicians and patients.[12] It is anticipated that effective guidelines for the diagnosis and treatment of migraine will improve symptom relief, increase quality of life and reduce the economic burden of this condition. We know of no similar management criteria published previously.

Formulation of the guidelines

The creation of the guidelines followed a needs assessment by members of the Canadian Headache Society and included the statement of objectives; the development of guidelines by multidisciplinary working groups using, among other resources, literature reviews of the subject; the comparison of alternative clinical pathways and the description of how published data were analysed; the definition of the level of evidence for data in each case; the evaluation and revision of guidelines (at a consensus conference involving neurologists, specialists in emergency medicine, psychologists, psychiatrists, primary care physicians, pharmacists and consumers); the redrafting and insertion of tables showing key variables and data from various studies, and tables of data with recommendations; the reassessment by all conference participants; and field testing by neurologists, specialists in emergency medicine and primary care physicians.

MEDLINE was searched for articles published from 1966 to 1996 on the management of migraine using the terms "migraine," "human," "English," "therapy," "sumatriptan" and "clinical trial." The most informative, statistically appropriate references identified were reviewed. Standard texts on headache were also reviewed. The search did not focus on single case reports unless there was no other evidence available. Studies were chosen according their level of evidence, in the following sequence: randomized controlled trials, randomized trials (not controlled), cohort studies, case–control studies, and case series. The definitions of levels of evidence and classes of recommendations used[13] are shown in Appendix 1.

The formulation of the guidelines was supported by an unrestricted educational grant from Glaxo Wellcome Inc. Neither in the conference setting nor in the activities of the writing groups after the conclusion of the conference were representatives of the sponsor invited or available to influence the content of the guidelines. Medical Education Programs Canada Inc. was responsible for editorial coordination in preparing this article for submission and had no involvement with content.

The Canadian Headache Society hopes that these guidelines will achieve the same level of recognition as other standards and will be acceptable to the Canadian medical community. The guidelines are designed to be noncontroversial and to reflect current clinical practice in Canada. It is accepted that no clinical practice guidelines can cover all situations. Although scientifically validated and set at national levels, the guidelines are suggested as appropriate first steps. Modifications may be necessary for local use.

Diagnosis

Migraines are difficult to diagnose because it is hard to elicit precise information from a patient who is trying to translate symptoms into words, the symptoms are similar to those of tension headaches, and the manifestation of individual migraine attacks varies considerably between and among individuals. To improve the reliability of the diagnosis, the methods used to elicit information and the interpretation of the individual diagnostic criteria and patient responses must be orderly and consistent.[14]

History-taking

We recommend the use of a semistructured interview technique and slightly modified IHS diagnostic criteria.

Criteria for diagnosing migraine without aura

The following criteria have been modified from those of the IHS Headache Classification Committee (level III evidence).[9]

A. At least 5 attacks fulfilling criteria B–D.
B. Each attack, untreated or unsuccessfully treated, lasts 2–72 hours.
C. The attack has at least 2 of the following characteristics:
   - Unilateral location: Migraines are most commonly unilateral; however, they can be bilateral in 30%–40% of cases,[15] and sometimes the pain begins on one side and later spreads to the other. Location should therefore be characterized at different phases of the attack, and early or mild attacks should be differentiated from full-blown attacks. Useful questions to ask the patient include Do you feel pain on one or both sides? If one-sided, is it always on the same side? If present on both sides, did the pain start on one side? Is it usually maximal on one side?
   - Pulsating quality: Over 50% of people who suffer migraines report nonthrobbing pain during some attacks, and 30% of patients with tension-type headaches may report pulsating pain.[16] Headache quality may also vary over the duration of the attack. If the pain is throbbing at any phase of the attack, it is recommended that, for consistency, the quality be considered as throbbing overall. Useful questions include What kind of pain is it — tightening, pressing, throbbing, pounding, pulsating, burning or other? Do different types of pain occur at different times in any one attack? If so, which types?
   - Moderate or severe intensity: The severity of the migraine inhibits or prohibits daily activity.
   - Pain is aggravated by walking up and down stairs or similar routine physical activity: Patients who

prefer not to move around should be considered as experiencing aggravation of pain by physical activity. Possibly useful questions about other, less equivocal aggravating factors include Do you avoid movement of even a minor nature (head movement or bending down) during an attack?

D. During an attack at least 1 of the following symptoms should be present.
   - Nausea or vomiting: It is important that nausea be differentiated from anorexia, which is common among patients with anxiety or tension-type headaches.
   - Photophobia, phonophobia and osmophobia: Although the IHS criteria mention only photophobia and phonophobia, we recommend that the presence of osmophobia (aversion to odours) also be determined, since this is a highly sensitive and specific feature of migraine.[17] Useful questions to ask the patient include During a headache, are you unusually sensitive to light, noise or odours? Do you take steps to avoid them?

   Because there is some degree of overlap of symptoms in D between migraine and tension-type headache, the severity of such symptoms should be graded as mild, moderate or severe,[18] as with pain severity.

E. There is no evidence from the patient's history or physical examination of any other disease that might cause headaches.

Criteria for diagnosing migraine with aura

These diagnostic criteria are the same as those for migraine without aura, bit they include symptoms of neurological dysfunction (including visual disturbance) occurring before or during the attack.

Additional questions

The patient should be questioned further in order to enhance the specificity and sensitivity of the above criteria, and to improve the "pattern recognition" of migraine (level III evidence, class A recommendation). Additional questions concerning other typical migraine characteristics should be asked to investigate the following:

- The regular or near-regular perimenstrual or periovulatory timing of attacks
- The gradual appearance of headache after sustained exertion
- Abatement of headache with sleep
- The presence of stereotyped prodromal symptoms such as irritability or other mood variations, hyperactivity, inability to think or concentrate, food cravings and hyperosmia
- The presence of a family history of migraine
- The consistent precipitation of headaches by food, odours, weather changes or stress
- The occurrence of headache at times of let-down, particularly after a high level of activity or stress

Features that should raise concern that a more serious underlying cause may be present, possibly indicating the need for further investigation, should be investigated (level III evidence, class A recommendation). The features include the following:

- The first or worst headache of the patient's life, particularly if the onset was rapid
- A change in the frequency, severity or clinical features of the attack from what the patient has commonly experienced (no longer conforms to the IHS criteria)
- The new onset of headache in middle-age or later, or a significant change in a long-standing headache pattern
- The occurrence of a new or progressive headache that persists for days
- The precipitation of head pain with the Valsalva manoeuvre (by coughing, sneezing or bending down)
- The presence of systemic symptoms such as myalgia, fever, malaise, weight loss, scalp tenderness or jaw claudication
- The presence of focal neurological symptoms, of any abnormalities found on neurological examination, or of confusion, seizures or any impairment in the level of consciousness

Physical examination

The general physical examination performed at the first consultation for headache problems should evaluate at least the following: vital signs (blood pressure and heart rate); cardiac status; extracranial structures (sinuses, scalp arteries, cervical paraspinal muscles and temporomandibular joints); and range of motion and the presence of pain in the cervical spine (level III evidence, class A recommendation).

A screening neurological examination capable of detecting most of the abnormal signs likely to occur in patients with headaches due to intracranial or systemic disease should be performed, including evaluation of neck flexion (for evidence of meningeal irritation) in certain cases; the presence of bruits over the cranium, orbits or neck; and the optic fundi, visual fields, pupillary reactions, sensory function of the fifth cranial nerve, corneal reflexes, motor power in the face and limbs, muscle stretch reflexes, plantar responses and gait (level III evidence, class A recommendation).

The presence of such abnormalities, unusual in uncomplicated migraine, suggest the need to consider further investigations.

Investigations

The Quality Standards Subcommittee of the American Academy of Neurology has developed practice parameters for neurologists for diagnostic procedures and treatment methods of a variety of clinical disorders.[19,20] On the basis of these parameters, and expert opinion, the following practice guidelines are proposed (level III evidence).

Electroencephalography

Electroencephalography is not useful in the routine evaluation of patients with headache. This does not exclude its use for the evaluation of headache with associated symptoms suggestive of a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness. Assuming that head-imaging equipment is readily available, electroencephalography is not recommended as a useful tool for the exclusion of a structural cause for headache (class D recommendation).[19]

CT and MRI

Neither CT scans nor MRI scans are warranted in adult patients whose headaches fit a broad definition of recurrent migraine and who have *not* demonstrated the following: any recent substantial change in headache pattern, a history of seizures or the presence of focal neurological symptoms or signs (class D recommendation).

There is insufficient evidence to define the role of CT and MRI in the evaluation of patients with headache that is not consistent with migraine (class C recommendation).[20]

Lumbar puncture

Lumbar puncture may have potential value in the following clinical situations (level III evidence, class B recommendation): the headache is the first or worst in the patient's life; a severe, recurrent headache of rapid onset; a progressive headache without signs of raised intracranial pressure; an atypical, chronic and intractable headache; and a headache associated with fever.

Lumbar puncture should be performed only if meningitis, encephalitis, subarachnoid hemorrhage or high- or low-pressure headache syndromes are considered clinically possible (class A recommendation).[21]

Symptomatic treatment

Patients respond to a variety of medications, and the medication of choice is often individual and idiosyncratic. The results of many studies of medications for acute migraine attacks are impossible to compare. Since 1989, standardization of clinical trials followed the publication of numerous multicentre studies of sumatriptan, making comparisons possible. Medications used to treat acute migraine attacks and the levels of evidence supporting their use are listed in Tables 1 to 3. The costs, benefits and hazards of the agents available should be considered as relevant factors in determining the most appropriate medication. The goals of therapy should be the relief of headache and associated symptoms and a return to normal functioning.[63]

Drug therapy is indicated if the headaches threaten to disrupt the patient's ability to function normally. In most cases migraine attacks are of different severity and have variable effects on a patient's functioning. In mild attacks the patient can continue his or her usual activities with only minimal disruption; in moderate attacks the patient's activities are moderately impaired; in severe attacks the patient is unable to continue his or her normal activities and can function in any capacity only with severe discomfort and impaired efficiency; in ultra-severe cases (includ-

Table 1: Medications recommended for mild migraine attacks[22–36]

Medication	Dosage*	Main side effect	Level of evidence
Acetylsalicylic acid (ASA), buffered or soluble tablet (not enteric coated)	650–1300 mg q4h × 2	GI§ upset	I
Ibuprofen	400–800 mg q6h × 2	GI upset	I
Naproxen sodium	275–550 mg PO q2–6h	GI upset	I
Acetaminophen†	650–1300 mg q4h × 2		III
Adjunctive medication			
Dimenhydrinate†	50–100 mg PO as needed	Drowsiness	III
Domperidone†	10–20 mg PO		III
Metoclopramide†‡	10 mg PO or IV		III

*PO = orally, IV = intravenously.
†Evidence for the drug's effectiveness is considered to be less convincing than that for ASA and ibuprofen.
‡In mild attacks with pronounced nausea, metoclopramide alone may relieve both the pain and the nausea.
§GI = gastrointestinal.

ing status migrainosus) there is prolonged (for more than 72 hours) inability to function in any useful capacity. Therefore, for each patient, appropriate therapy for attacks of differing severity should be made available. Treatment of some severe attacks will require a visit to a physician's clinic or to an emergency department.

Patients seldom suffer more than a few migraine attacks per month. Although these attacks may be incapacitating and require treatment, and because other types of headache may also occur, patients must be warned that frequent use of symptomatic treatments (analgesics and ergotamine in particular) can lead to medication-induced (rebound) headache and eventually to chronic daily headache. Without appropriate treatment, patients are more likely to consume increasing amounts of less effective compounds, which thus increases the risk of rebound headache. Asking the patient to keep a diary of headache symptoms and medication use may be valuable in preventing this situation.

Acute therapy

Mild attacks

Most medications suitable for treating mild attacks have some degree of anti-inflammatory activity (Table 1). Acetylsalicylic acid (ASA) (especially the buffered or soluble formulations), ibuprofen and naproxen have been studied in randomized placebo-controlled trials.[22,24–36] All 3 were shown to be more effective than placebo in alleviating mild attacks (level 1 evidence), but their tendency to induce gastrointestinal side effects should be considered. Although acetaminophen is widely used, no published studies have clearly demonstrated its efficacy when used alone in acute migraine, perhaps because subanalgesic doses have been used (level III evidence). Although dimenhydrinate and domperidone are often used in practice, there is inadequate evidence to recommend their use as adjunctive therapy (level III evidence, class C recommendation).

Moderate attacks

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in the treatment of many moderate attacks (Table 2) (level I evidence).[22,24–36,64]

Sumatriptan

The oral administration of sumatriptan, a selective 5-hydroxytriptamine 1 (5-HT_1) receptor agonist, has been shown to relieve up to 70% of migraine attacks at 1 hour,

Table 2: Medications recommended for moderate migraine attacks*

Medication†	Dosage‡	Main side effects	Level of evidence
NSAID§[22–36]			
Ibuprofen	400–800 mg PO q2–6h	GI upset	I
Naproxen sodium	275–550 mg PO q2–6h	GI upset	I
Mefenamic acid	250–500 mg PO q6h	GI upset	I
5-HT_1 receptor agonist			
Selective			
Sumatriptan[37–47]	50–100 mg PO (may be repeated twice within 24 h) 6 mg SC (may be repeated once within 24 h)	Chest tightness, tingling	I
Non-selective			
DHE‖[47–52]	0.5–1.0 mg SC, IM or IV (may be repeated at 1 h; maximum 4 doses within 24 h)	Chest tightness, tingling, nausea	I
Ergotamine¶[28–32,53]	1–2 mg PO q1h × 3 1 mg as suppository (maximum 3 doses within 24 h)	Chest pain, tingling, nausea	II
Combination drugs			
Acetaminophen + codeine	Varied according to formulation	CNS depression, drowsiness, habituation	III
ASA + codeine + caffeine			III
ASA + butalbital + caffeine			III

*For patients who do not respond to the initial choices, consider a combination medication or ergotamine. Combination medications with a high content of codeine (30 mg) should be used to minimize excessive intake of tablets.
†Use of the antinauseants listed in Table 1 is appropriate for moderate attacks. Metoclopramide alone may relieve all symptoms of the attack.
‡SC = subcutaneously, IM = intramuscularly.
§NSAID = nonsteroidal anti-inflammatory drug. Current evidence does not distinguish the relative efficacy of different NSAIDs.
‖DHE = dihydroergotamine.
¶Evidence suggests that oral ergot preparations are of limited efficacy and have excessive side effects.

as compared with less than 27% of cases with placebo.[35,37,38] Subcutaneous injection has been found to relieve symptoms in 77% of cases at 1 hour, as compared with less than 31% of cases with placebo.[36,39,41–45] A dose of 50 or 100 mg given orally (or 6 mg injected subcutaneously) should be given after the onset of an attack (level I evidence, class A recommendation);[35–45] If the 50-mg dose is ineffective, the 100-mg dose should be used subsequently (level III evidence, class B recommendation). Sumatriptan is effective when taken at any time during an attack, but in the case of migraine with aura it should not be taken during the aura phase, since the results of at least one study suggest that it is not effective at this stage (level II-2 evidence).[65] The same dose may be repeated once subcutaneously or twice orally within 24 hours if the headache was relieved but has recurred. Sumatriptan should not be taken within 24 hours of the administration of dihydroergotamine (DHE) or ergotamine (level III evidence, class A recommendation).[66]

Reported side effects of sumatriptan include sensations of heaviness or tightness in the chest, chest pain, pain in the throat, tingling in the head or limbs, nausea and, in the case of subcutaneous injection, local tingling at the injection site.[46] These side effects are usually self-limiting, but in some patients they may preclude the use of this medication. Patients with cardiac risk factors, cardiac disease or uncontrolled hypertension must not take sumatriptan.[67] According to the manufacturer, patients with hepatic problems should not take more than 50 mg orally. Sumatriptan is faster acting and is less apt to cause nausea than DHE; however, it has a higher rate of headache recurrence at 24 hours (44% v. 17% respectively).[47]

Dihydroergotamine

DHE, a nonselective 5-HT_1 receptor agonist, is effective in relieving headache when used subcutaneously, intramuscularly, intravenously or intranasally.[47–52] Its side effects are similar to those of sumatriptan except that DHE has a greater tendency to cause nausea and is less likely to induce chest pain. DHE has a longer duration of action than sumatriptan (level I evidence),[47] so headache recurrence rates are lower with its use.

Ergotamine

Ergotamine has been used for many years in oral, sublingual and suppository forms. Its side effects resemble

Table 3: Medications recommended for severe and ultra-severe migraine attacks

Medication*	Dosage	Main side effects	Level of evidence
Butorphanol[60,61]	1 spray (1 mg) in 1 nostril (may be repeated once in 3–5 h)	Nausea, dysphoria, tiredness	I
Chlorpromazine[54]	50 mg IM; or 0.1 mg/kg IV by drip over 20 min, repeated after 15 min (maximum 37.5 mg); pretreat with normal saline IV	Drowsiness, extrapyramidal reactions	I
Dexamethasone	12–20 mg IV		II-1
DHE[47–52]	0.5–1 mg q1h IM, SC or IV (maximum 3 times within 24 h)	Chest tightness, nausea, tingling	I
Ketorolac†[23,56–59]	30–60 mg IM (maximum 120 mg within 24 h)	Somnolence, nausea, dyspepsia	I
Meperidine[62]	50–100 mg IM or IV	Sedation, confusion, addiction	II
Metoclopramide[49,69]	10 mg IV (if not effective within 20 min follow with 0.5–1 mg of DHE IV, repeated up to 2 mg over 3 h)	Drowsiness, extrapyramidal reactions	I
Prochlorperazine[55]	25 mg by suppository (maximum 3 doses within 24 h), or 5–10 mg IV or IM	Drowsiness, extrapyramidal reactions	I
Sumatriptan[37–47]	50–100 mg PO (may be repeated twice within 24 h) 6 mg SC (may be repeated once within 24 h)	Chest tightness, tingling	I

*The use of antinauseants is recommended as adjunctive treatment (see Tables 1 and 2).
†Ketorolac is not approved in Canada for IV use.

those of DHE, but nausea is usually more severe.[28–32] A meta-analysis of studies of ergotamine has cast doubt on the utility of the drug and suggests that the side effects may outweigh the benefits.[53] However, some patients consider it to be useful, particularly if taken with an antiemetic (level III evidence, class C recommendation).

Combination medications

Combination medications such as acetaminophen with codeine, ASA with codeine and caffeine, and ASA with butalbital and caffeine (with or without codeine) can be used if patients do not respond to initial drug therapy or if vasoconstrictors are contraindicated (level III evidence, class C recommendation). However, overuse of such combination medications is considered to be one of the most prominent causes of rebound headache, which is the leading form of chronic daily headache.[68] In the long term, combination medications should be used only intermittently and for short periods (level III evidence).

Severe attacks

The recommended choices for the treatment of severe attacks are highlighted in Table 3. The first-line treatment should be with DHE given subcutaneously, intramuscularly or intravenously,[47,49] or sumatriptan given orally or subcutaneously[37–46] (level I evidence, class A recommendation). If an intravenous line is set up, 10 mg of metoclopramide should be given intravenously (level I evidence, class A recommendation).[49,69] If it is ineffective within 20 minutes, 0.5–1.0 mg of DHE may be added intravenously, repeated to a maximum of 2 mg over 3 hours (level I evidence, class A recommendation).[69]

Alternatively, chlorpromazine (0.1 mg/kg intravenously) can be given over 20 minutes and repeated after 15 minutes to a maximum dose of 37.5 mg (level I evidence).[54] The patient should first be given normal saline (5 mL/kg body weight) in order to prevent hypotension. Alternatively, an intramuscular dose of up to 50 mg may be used. Prochlorperazine (25 mg rectally, or 5–10 mg intravenously or intramuscularly) is another alternative (level I evidence).[55] If symptoms are not relieved with these treatments, ketorolac (30–60 mg intramuscularly) may be effective (level I evidence).[57–59] Dexamethasone (12–20 mg intravenously) has also been found to be effective in some resistant cases (level II-1 evidence).[70]

The role of butorphanol, a mixed opioid agonist-antagonist, in acute migraine management is still to be determined. Currently, butorphanol should be used for patients with infrequent but severe migraine attacks for whom the preceding treatments are either ineffective or inconvenient (level I evidence, class B recommendation).[60,61] Its side effects are prominent and include nausea and drowsiness. Habituation may occur. We suggest that meperidine (50 mg intravenously, or intramuscularly if an intravenous line is not in place),[62] along with 1 repeat dose if required, should be considered as a last resort (class D recommendation).

Ultra-severe attacks

The general principles for the treatment of ultra-severe attacks, including prolonged migraine (status migrainosus), are the same as those for the treatment of severe attacks. Patients who are vomiting with severe migraine attacks may be dehydrated, so rehydration is always an important first step. DHE is considered to be the drug of choice, but it may be necessary to give repeated doses of 0.5–1.0 mg intravenously every 8 hours for 24 hours or more, with each dose preceded by 10 mg of metoclopramide to prevent nausea. The addition of promethazine (50 mg intramuscularly), chlorpromazine (50 mg intramuscularly) or prochlorperazine (5 mg intramuscularly) has been recommended (level II-1 evidence).[71]

Other recommended medications, given alone or in combination, include the following:

- Prochlorperazine (10 mg intravenously) plus diphenhydramine (10 mg intravenously every 4 to 6 hours as needed) until symptoms are relieved[72] (level III evidence)
- Chlorpromazine (10.0–12.5 mg [0.1 mg/kg] intravenously) following an intravenous 500-mL bolus of normal saline (level II-1 evidence)[73]
- Dexamethasone (8–20 mg intramuscularly or intravenously) or methylprednisolone sodium succinate (100–250 mg intravenously) (level III evidence)[74]
- Dexamethasone (8 mg intramuscularly) plus meperidine (75–100 mg) plus promethazine (50 mg intramuscularly) (level III evidence)[70]

Other treatments

There is limited evidence to support the use of lidocaine intranasally (level I evidence, class B recommendation).[75]

Prophylactic treatment

Relatively few medications for prophylactic treatment have been subjected to adequate clinical trial.[10,14,63,76–144] Although current preventive agents can be expected to reduce the frequency and severity of migraine attacks, almost all patients will occasionally need abortive or symptomatic treatment. A "good" response to prophylactic treatment may be defined as a 50% re-

duction in the frequency or severity of migraines, or both.[78,79,86,87,89,91,93,95,99,102,105,117,119,122,123,128,130,131,145] Forty-one of the studies were randomized clinical trials, providing level I evidence.

The principle underlying a prophylactic treatment regimen is to use the least amount of the medication with the fewest side effects to gain control of the symptoms until the preventive treatment can be permanently stopped. When selecting a medication for prophylaxis, one should also take into account the presence of any comorbid conditions. Initiating and maintaining appropriate prophylaxis entails a major commitment by the patient.[63,132–135,137,140,144]

Discussion with the patient about the use of prophylactic treatment is indicated if (a) the migraine attacks are severe enough to impair the patient's quality of life or (b) the patient has 3 or more severe migraine attacks per month that fail to respond adequately to abortive or symptomatic therapy.[136,138,141,145]

Medications recommended for migraine prophylaxis are listed in Table 4. The drug and dosage must be considered on a patient-by-patient basis.

β-blockers

Exactly how β-blockers decrease the frequency of migraine attacks is not certain, but they may affect the central catecholaminergic system and brain serotonin (5-HT_2) receptors.

Not all β-blockers are effective. Those that are efficacious include atenolol, metoprolol, nadolol and propranolol, whereas those with intrinsic sympathomimetic activity (e.g., pindolol) are not (level I evidence).[76–78,82–86,89,91] β-blockers are contraindicated in patients with asthma, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, heart block or failure, or peripheral vascular disease. They are relatively contraindicated in pregnancy. Atenolol and nadolol are excreted by the kidneys and may cause fewer

Table 4: Medications recommended for migraine prophylaxis[10,14,63,74–141,157,158]

Medication	Dosage	Main side effects	Level of evidence
β-blockers[76–94]			
Atenolol	50–150 mg/d	Fatigue, bronchospasm, bradycardia, hypotension, congestive heart failure, depression, impotence, sleep disturbance	I
Metoprolol	100–200 mg/d		
Nadolol	20–160 mg/d		
Propranolol	40–240 mg/d		
Calcium-channel blockers[85–90,92–104]			
Flunarizine	5–10 mg/d	Fatigue, weight gain, depression (flunarizine), bradycardia, hypotension, constipation (verapamil), nausea, edema, headache, extrapyramidal side effects	I
Verapamil	240–320 mg/d		
Serotonin receptor antagonists[105–117]			
Methysergide	2 mg every night, gradually increased to tid (maximum 8 mg/d if needed) (usual dose 4–8 mg/d)	Retroperitoneal, cardiac and pulmonary fibrosis	I
Pizotyline (pizotifen)	0.5 mg every night, gradually increased to tid (maximum 3–6 mg/d if needed) (usual dose 1–6 mg/d); consider giving higher doses once every night	Weight gain, fatigue	I
Tricyclic analgesics[118,119]			
Amitriptyline	10–150 mg every night	Dry mouth, constipation, weight gain, drowsiness, reduced seizure threshold, cardiovascular effects	I
Nortriptyline	10–150 mg every night		I
Anti-epileptics[120–126]			
Divalproex	500–1500 mg/d	Nausea, tremor, weight gain, alopecia, increased liver enzyme levels	I
Sodium valproate	500–1500 mg/d		
Valproic acid	500–1500 mg/d		
NSAID[91,127–131,157,158]			
Naproxen sodium*	550 mg bid, for no longer than 1 wk per mo	GI upset, ulceration, rebound headache, renal dysfunction	I

*As prophylaxis for perimenstrual migraine attacks only.

side effects in the central nervous system than propranolol (level III evidence).[141,146,147] Failure with one β-blocker does not predict the response to another, so consecutive trials of different drugs in this class are appropriate (level III evidence).[141,146] When prescribing β-blockers, physicians should start with a low dose and titrate upward as required.

Once the migraine attacks are controlled, the medication should be tapered. Sudden withdrawal of β-blockers may cause rebound headaches and adrenergic side effects in some patients (level III evidence).[141,146,148,149]

Calcium-channel blockers

Calcium-channel blockers most likely work by modulating neurotransmitters rather than by causing vasodilatation and cytoprotection through the prevention of hypoxia and cellular influx of calcium ions (level III evidence).[136,150] The onset of effect of calcium-channel blockers is gradual, with maximum benefits possibly not seen for up to several months, and many side effects have been recorded.[136,141,148] Of the available agents, flunarizine and verapamil are most commonly used for migraine prophylaxis. Reduction in migraine frequency is the main benefit, and the overall efficacy of calcium-channel blockers is comparable to that of β-blockers (i.e., a reduction of about 50% in headache frequency) (level I evidence).[88,89,92,96–98,100–102]

Calcium-channel blockers are contraindicated in pregnant patients and in patients with hypotension, congestive heart failure or arrhythmias. They must be used with caution in patients with Parkinson disease and patients receiving β-blockers. Flunarizine is not recommended for patients with current or previous depressive illness, or for those with extrapyramidal symptoms (level I evidence, class A recommendation).[88,90,92,93,97]

Serotonin receptor antagonists

Pizotyline

Pizotyline (pizotifen) is a serotonin (5-HT_2) receptor antagonist with mild antihistaminic and anticholinergic properties. Although somewhat effective in migraine, providing relief in 50%–64% of cases, its side effects include weight gain and fatigue (level I evidence, class A recommendation).[105,106,151]

Methysergide

Methysergide, an ergot derivative, may be effective in migraine for several reasons: 5-HT_2-receptor antagonism, a carotid vasoconstrictor effect, an ability to inhibit perivascular neuronal peptide release, and an effect on 5-HT_2 and dopaminergic receptors through its active metabolite methylergometrine (level III evidence, class A recommendation).[136,141,152]

Methysergide is indicated for the prophylaxis of severe, recurrent migraine attacks unresponsive to other medications (level I evidence).[112–117] Contraindications include hypertension, cardiac, lung, liver, kidney and collagen diseases, thrombophlebitis, peptic ulcer disease and pregnancy. Side effects are numerous and include nausea, muscle cramps and aching, claudication, weight gain and hallucinations. Methysergide should not be used for more than 6 months without a break in treatment of 1–2 months to prevent retroperitoneal fibrosis. The dose should be decreased gradually before treatment is stopped (level III evidence).[109–111,138,141,145]

Tricyclic analgesics

Amitriptyline is useful in migraine,[118,119] especially in patients with associated tension-type headaches[149] (level III evidence, class B recommendation). The mechanism of action is unrelated to its antidepressant activity.[119] Amitriptyline modulates neurotransmitters, inhibiting both noradrenaline and serotonin reuptake and attenuating β-adrenergic and central serotonin receptor function.[119,141,147] The effective dosage varies, but 10 mg orally each night should be given at first, followed by an increase of 10 mg every week, up to 50 mg/d (level III evidence);[138,139,141,149] however, higher doses may be required in the presence of comorbid depression (level I evidence).[119]

Nortriptyline may produce a lesser degree of drowsiness and anticholinergic effects than amitriptyline (level III evidence).[147] Contraindications include severe cardiac, kidney, liver, prostate and thyroid disease, glaucoma, hypotension, seizure disorder and use of a monoamine oxidase inhibitor.[153] Tricyclic drugs should be used with caution in elderly patients because of anticholinergic side effects (level I evidence, class A recommendation).[118,119] Most often tricyclic drugs have been used for migraine prophylaxis also[137] (level III evidence, class C recommendation).

Selective serotonin reuptake inhibitors

To date, we know of no convincing evidence to support the use of selective serotonin reuptake inhibitors for migraine prophylaxis (level I evidence, class D recommendation),[118,154,155] despite the existence of some evidence of effect.[142]

Anti-epileptic drugs

Sodium valproate, valproic acid and divalproex sodium

have been found to be effective for migraine prophylaxis in randomized clinical trials (level I evidence, class A recommendation).[120–123,125] Such agents should be used cautiously in patients taking ASA or warfarin because they may also affect hemostasis and coagulation (level II-2 evidence, class B recommendation).[156,157] The side effects of these drugs include nausea, alopecia, tremor and weight gain,[120–126] and their use has been associated with hepatotoxicity, particularly in children.[158] They may also cause neural tube defects and should not be given to women who are pregnant or considering pregnancy.[158]

NSAIDs

The primary mode of action of NSAIDs involves cyclo-oxygenase inhibition with subsequent inhibition of prostaglandin biosynthesis and action.[131] These agents are somewhat useful in reducing migraine pain.[127,128,130] In particular, naproxen sodium has been shown to be effective in migraine prophylaxis (level I evidence, class A recommendation).[131] Both naproxen and naproxen sodium are useful in the prevention of perimenstrual attacks (level I evidence, class A recommendation).[159,160] NSAIDs should be used only for intermittent prophylaxis rather than continuously in cases of perimenstrual attacks because of the important gastrointestinal side effects (level III evidence).

Prophylactic management of migraine

Recommendations for health care professionals

- Ideally, the patient should be asked to keep a diary to record headache characteristics, use of medications and responses to therapy.
- The patient should be helped to understand the general nature of migraine, the action of the medications prescribed and their interactions, side effects and contraindications.
- Except in the most resistant cases, only 1 preventive agent should be used at a time.
- The dose should be low at first and then titrated upward to a maximally effective tolerable dose; adjustments may be necessary.
- The medication should be continued for an adequate period, usually several months, and withdrawn slowly to prevent rebound headaches.
- If the initial treatment is ineffective, several medications may be tried in sequence.
- If there is no response to a combination of prophylactic agents from different groups (e.g., propranolol plus amitriptyline) neurological consultation should be obtained.
- Prophylactic medications that are ineffective while patients are concurrently taking analgesics on a regular basis can become effective when the analgesics are withdrawn.
- The cost of medications should be considered in the choice of prophylactic agents.

Recommendations for patient education

The following points should be explained to patients in order to educate them about migraine prophylaxis (level III evidence, class A recommendation).

- Explain that the management of migraine is a team approach and that the patient is the most important member of the team.
- Ensure that the patient understands the diagnosis and nature of migraine.
- Ensure that the patient understands helpful "non-pill" therapy, such as the avoidance of triggers and the use of ice, which may be used along with their medication.
- Ensure that the patient understands the nature of the medication prescribed, as well as its possible side effects, interactions with other medications and any contraindications (e.g., pregnancy).
- Ask the patient to keep a diary in order to record medications used, dosages, responses to and evaluation of treatment, including side effects, and any over-the-counter or other medications being used. The patient should share this information with the physician.
- Explain that prophylactic medications should not be expected to work immediately; some take 1–2 months to work, especially calcium-channel blockers.
- Inform the patient that he or she should be prepared to expect some side effects, to take medication daily and to recognize that the physician may have to change the medication.
- Inform the patient that he or she should expect some migraine attacks, although they will probably be less severe or less frequent than previously experienced.
- Explain that prophylactic medications are designed to be used for a number of months and then discontinued. For the few patients with difficult headache problems, however, longer term use may be necessary.
- Instruct the patient not to use headache medications other than those prescribed, including over-the-counter headache medications; explain that the excessive use of other analgesics and over-the-counter medications may reduce the effectiveness of the prophylactic medications.
- Ask the patient to report if they become pregnant or are contemplating pregnancy.

Nonpharmacological treatment

In this article we have offered recommendations for the clinical and pharmacological management of migraine. We have purposefully not included all of the important nonpharmacological therapies. These include acupuncture, aromatherapy, biofeedback, chiropractic, dietary therapy, herbalism, homeopathy, hypnosis, osteopathy, reflexology, relaxation therapy, therapeutic massage and yoga. We consider such therapies to be of sufficient interest and therefore will be examining them separately at a later date.

Validation

The guidelines are based on consensus of Canadian experts in neurology, emergency medicine, psychiatry, psychology, family medicine and pharmacology, and consumers. Previous guidelines did not exist. Field testing of the utilization and value of these guidelines is in progress.

Summary

Migraine is a common clinical disorder that continues to be underdiagnosed and inadequately managed. The diagnosis of migraine can be improved with the use of modified IHS criteria and a semistructured interview technique. Appropriate symptomatic treatment should take into account the severity of the migraine attack, since most patients will have attacks of differing severity and can learn to use medication appropriate for each attack. The inappropriate use or overuse of certain medications should be avoided in order to reduce the risk of rebound headache. When attacks are frequent or particularly severe, prophylactic therapy should be considered. Persistence in trying a variety of prophylactic medications is usually rewarding. Both the avoidance of migraine trigger factors and the use of nonpharmacological therapies have important roles to play in managing migraine.

We have attempted to develop general principles to improve the quality of care and allow informed decision-making by both physicians and patients. Field testing of the utilization and value of these guidelines is in progress.

We expect that there will be a need for training in the use of these guidelines, monitoring of their acceptibility and identifying problems not anticipated during the design phase of the process. The guidelines must be flexible enough to allow updating as new clinical data emerge.

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Appendix 1: Definitions of levels of evidence and classes of recommendation used

Level of evidence	Definition
I	Evidence from at least 1 randomized controlled trial
II-1	Evidence from well-designed cohort or case–control studies, usually from more than 1 centre or research group
II-2	Evidence from well-designed controlled trials but without randomization
II-3	Dramatic results from uncontrolled experiments
III	Opinions of experts, findings from descriptive studies, or reports of expert committees

Class of recommendation	Definition
A	Good evidence to support procedure or treatment
B	Fair evidence to support procedure or treatment
C	Poor evidence to support procedure or treatment
D	Fair evidence that procedure or treatment should not be used
E	Good evidence that procedure or treatment should not be used